CHAPTER 21

Morphea and Lichen Sclerosus

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MORPHEA

Epidemiology

- **Age**
  - **Childhood** onset: **2–14 years. Linear type** > circumscribed plaque > generalized > deep
  - **Adult** onset: **40–50 years. Circumscribed plaque type** > generalized > linear
- **Sex**
  - F:M = 2.6:1 to 7:1 (more marked difference in adults)
  - Children: F:M = 1.5:1
  - **Adult pansclerotic morphea:** Males > Females

Classification

- Peterson et al.—most widely used. But contains some controversial non-morphea entities (lichen sclerosus, atrophoderma of Pasini and Pierini, and esoinophilic fasciitis) and does not include "mixed" morphea (2.6–23% cases in pediatric population).
- Rook's *Textbook of Dermatology*—more inclusive classification.

Table 21.1 provides both the classification systems and **Table 21.2** depicts the updated classification of morphea (as given in Rook's *Textbook of Dermatology*, 10th edn.).

Predisposing and Triggering Factors

- **Genetics:** Morphea patients show increased frequencies of class II HLA-DRB1*04:04, HLA-DQB1*02:01, DRB1*03:01, DQA1*03:00 (all only seen in morphea cases) and class I HLA-B*37, HLA-C*08, HLA-C*15 alleles, with HLA-DRB1*15 strongly associated with the generalised morphea subtype.
  The strongest associations were found with HLA-DRB1*04:04 and HLA-B*37 and one risk allele DRB*04:04 in common with SSc was identified.
- **Infections:** *Borrelia burgdorferi sensu stricto* (USA) and *B. afzelii*/*B. garinii* (Eurasia) have been reported. However, there is no conclusive evidence to prove causal association. Immune activation as a result of infection could act as a trigger for morphea in some cases. Other infectious triggers reported in the literature include hepatitis C, varicella, herpes zoster and SARS-CoV-2.
- **Trauma:** Accidental trauma/surgery/insect bite reactions/vaccinations/injections (more in linear and deep morphea, less in generalized)
  - **Vaccination**—hepatitis B, MMR, DPT, BCG, pneumococcal vaccine, and, more recently, COVID-19.

Table 21.1 Classification of morphea

Peterson et al.	Rook's *Textbook of Dermatology**
Plaque morphea • Morphea en plaque • Guttate morphea • Atrophoderma of Pasini–Pierini • Lichen sclerosus • Keloidal morphea	**Limited morphea** • Circumscribed plaque morphea • Guttate morphea • Atrophoderma of Pasini-Pierini
Generalized morphea (lesions at 3 or more anatomical sites)	**Generalized type plaque morphea** • Disseminated plaque (isomorphic and symmetric patterns)
Linear morphea • Linear morphea of limbs or trunk • En coup de sabre morphea • Progressive hemifacial atrophy/Parry-Romberg syndrome	**Linear morphea** • Head/neck variant – Morphea en coup de sabre – Progressive hemifacial atrophy/Parry-Romberg syndrome • Trunk/limb variant – Linear morphea – Linear atrophoderma of Moulin – Linear deep atrophic morphea • Multisite linear morphea
Pansclerotic morphea	Eosinophilic fasciitis
Bullous morphea	**Mixed types** (most commonly linear + plaque, more common in childhood onset)
Deep morphea (inflammation and sclerosis in deep dermis, subcutaneous fat, fascia, muscle) • Subcutaneous morphea • Morphea profunda • Eosinophilic fasciitis • Disabling pansclerotic morphea	**Lichen sclerosus with morphea**

*Based on Padua Consensus classification given by Laxer and Zulian

  - **Injections**—vitamin B_{12}, vitamin K, interferon beta-1b and enfuvirtide.
  - **Mechanical trauma**
    - **Isotopic** (morphea developing in same area as previously healed skin disease/injury within 6 months of trauma)—in 6% cases.
    - **Isomorphic** (morphea developing at sites of repeated trauma, like sites where clothing causes friction—Koebner's phenomenon)—in 9%.
- **Radiation and radiotherapy**—especially radiotherapy for breast cancer—1/500 breast Ca patients may develop morphea within 1–3 years of completion of radiotherapy, usually occurring in the field of radiotherapy, but in half of the cases, it may extend beyond it.
- **Drugs**—bleomycin, pentazocine, progestin, vitamin B_{12} vitamin K, cocaine, D-penicillamine, interferon-β1a, paclitaxel, methysergide, gemcitabine, bromocriptine, bisoprolol, L-hydroxytryptophan with carbidopa, ibuprofen, mitomycin C, immune checkpoint inhibitors including ipilimumab, nivolumab and pembrolizumab, mostly after 1–6 cycles; sclerosis is most rapid and extensive with pembrolizumab.

Q Describe triggers for morphea.

Pathogenesis

3 major components: Vascular damage, activated T cells, and altered connective tissue production by fibroblasts.

Prevalent autoantibodies—anti-fibrillin-1, anti-MMP-1, histone antibodies and ANA (18–68%, mostly speckled), and, less frequently, anti-topoisomerase and anti-centromere antibodies.

Immunological: There is also a role of **Th1/Th17 → Th2 shift** in the pathogenesis of morphea **(Figs 21.1 and 21.2)**, which seems to be the prevalent hypothesis.

Clinical Features

Classic Lesion of Morphea

- Begins with usually subtle, erythematous edematous inflammatory 'bruise-like' change in texture of skin.

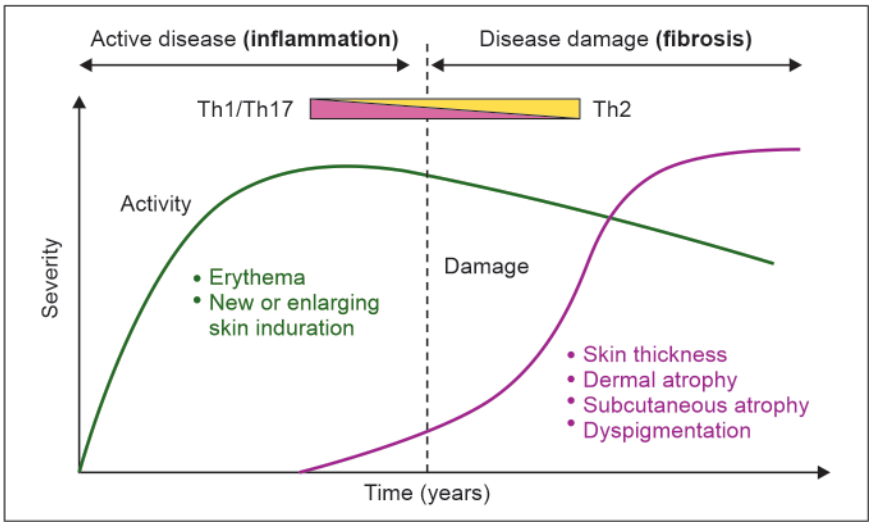


Fig. 21.1: Proposed conceptual model of morphea—transition from Th1/Th17 in the early stages to Th2 in the later stages

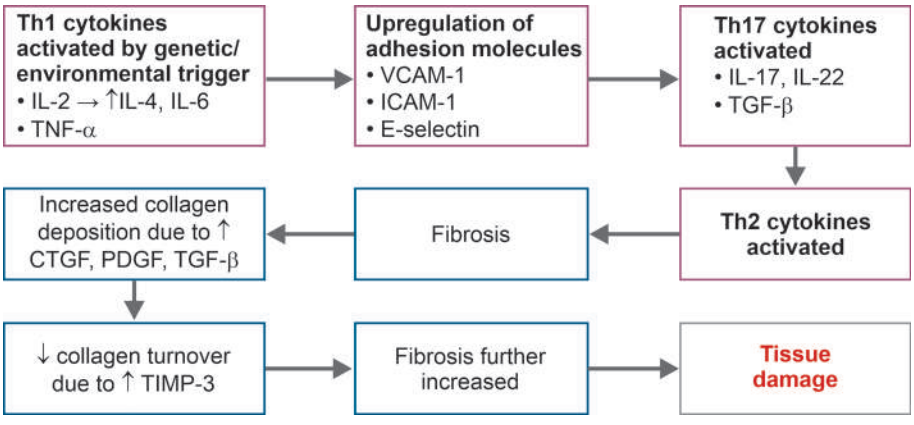


Fig. 21.2: Pathogenesis and role of Th cell subsets in morphea

Q Role of different T cell subsets in the pathogenesis of morphea.

- Followed by development of central sclerosis → skin becomes thickened waxy yellowish-white in center and surrounded by erythematous to violaceous 'lilac' ring +/– Loss of hair, loss of sweating **(Fig. 21.3a and b)**.
- Post-inflammatory hyperpigmentation often dominates over the white sclerosis as the lesions mature.
- Eventually, atrophic plaques with hypo- or hyper-pigmentation develop.
- Delay in diagnosis—more in plaque or generalized as linear morphea is more easily detected.

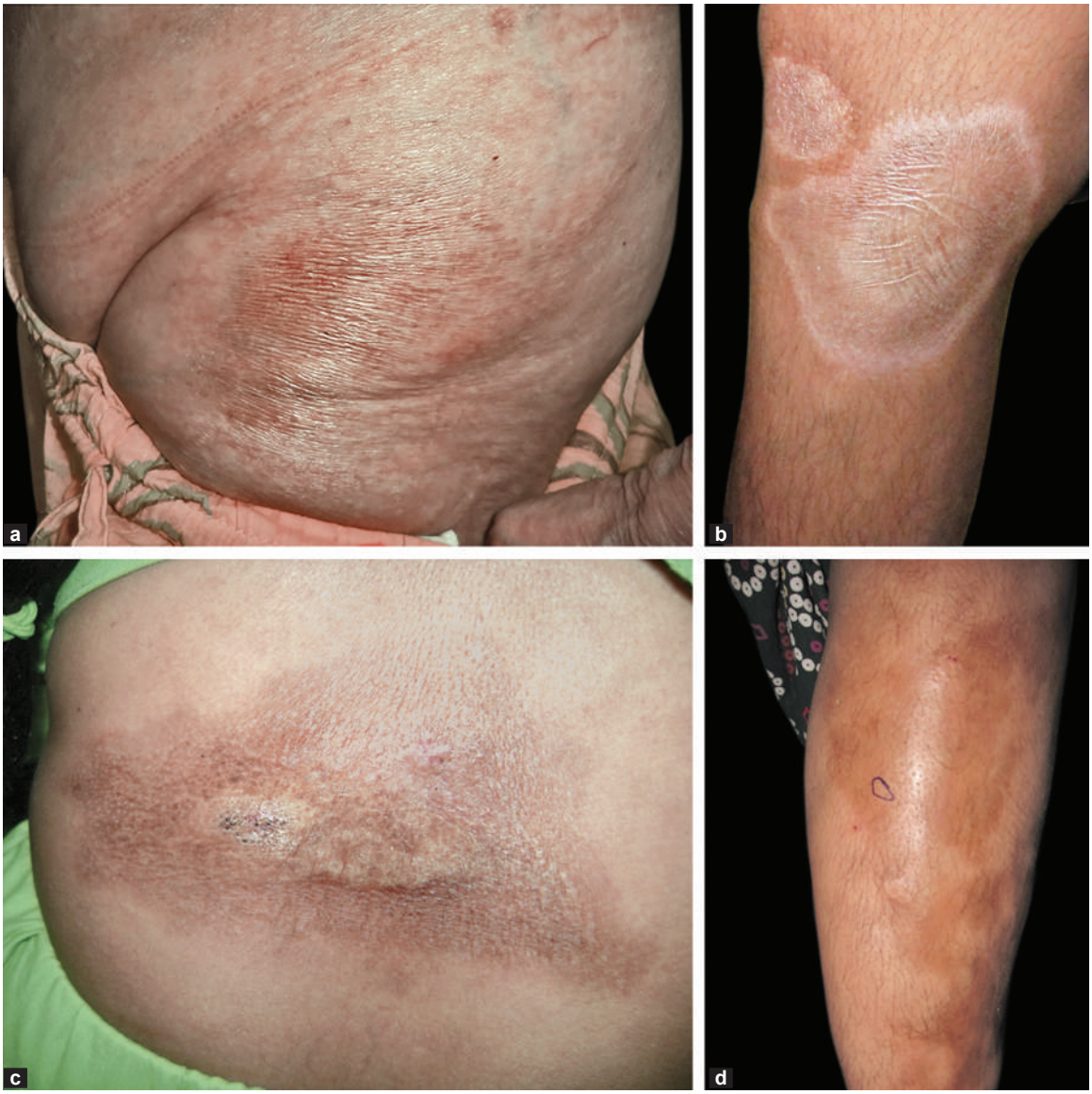


Fig. 21.3: (a) Plaque morphea; (b) Plaque morphea with central sclerosis, dry skin, loss of hair, peripheral lilac hue with a band of PIH; (c) Keloidal morphea with central raised firm lesion; (d) Limited deep morphea

Table 21.2 describes the various clinical types of morphea based on the Padua criteria (established by Laxer and Zulian in Padua, Italy) and the PReS classification proposed by the Pediatric Rheumatology European Society, along with some more modifications.

Certain "disease modifiers" (that are not separate entities and may occur across subtypes) have also been described as follows:

Deep: With involvement of deep dermis, subcutis and deeper structures, lesions are less well defined, thickened and bound down. Overlying skin may appear normal or puckered/cobblestoned/have a peau d'orange appearance **(Fig. 21.3d)**. Deep involvement leads to more functional impairment. Similar to the earlier description of "morphea profunda" (deep morphea).

Bullous: Tense subepidermal bullae overlying typical morphoea, usually in patients with active deep disease, most often on lower limbs.

Keloidal/nodular: Keloid-like or nodular lesions arising from normal or sclerodermatous skin, usually on the trunk, often at keloid prone sites **(Fig. 21.3c)**.

Table 21.2 Clinical features and differential diagnosis of morphea

Main type	Subtype	Characteristics	Differential diagnosis
Limited morphea	Circumscribed plaque morphea	• Single/multiple round/oval lesions >1 cm in up to 2 of 7 anatomical regions. • Usually epidermis and dermis, may involve deeper structures.	Granuloma annulare Extragenital LS Mycosis fungoides Necrobiosis lipoidica Pretibial myxedema Post-inflammatory hyperpigmentation Lipodystrophy Steroid-induced atrophy
	Guttate morphea	• Multiple small <1 cm erythematous to yellowish white, round/oval lesions, usually on trunk. • Involves dermis.	Extragenital LS
	Atrophoderma of Pasini-Pierini	• Multiple, round/oval, non-indurated, sharply demarcated, hyperpigmented depressed patches, 'cliff-drop' edge. • Involves the superficial reticular dermis.	Post-inflammatory hyperpigmentation Actinic LP Café-au-lait macule Post-FDE pigmentation
Generalised plaque morphea	≥4 indurated plaques that become confluent and involve at least 2 of 7 anatomical sites.		
	Isomorphic pattern	• Plaques coalesce at sites of repeated minor trauma from clothing. • Usually superficial and often coexists with LS.	
	Symmetric pattern	• Multiple individual plaques are distributed symmetrically about the midline on the trunk and limbs. Usually deep.	

(*Contd…*)

Q Describe the various clinical types of morphea.

Table 21.2	Clinical features and differential diagnosis of morphea (*Contd.*)		
Linear morphea (Also *see* Table 21.3)			
Trunk/Limb variant	Linear morphea **(Fig. 21.4b)**	• Blaschkoid linear induration of the limbs or trunk +/– dyspigmentation, +/– atrophy. • Involves dermis, subcutaneous tissue, muscle and bone	Post-traumatic atrophy
	Linear atrophoderma of Moulin	• Blaschkoid hyperpigmented linear atrophic limb/trunk lesions. • Superficial dermis	
	Linear deep atrophic morphea	• Linear atrophic lesions • Deep dermis and subcutis	
Head/neck variant	Morphea en coup de sabre **(Fig. 21.4a)**	Blaschkoid band of induration, +/– dyspigmentation, +/– atrophy over forehead, face and scalp, may involve muscle, bone, eye, oral cavity and brain.	Post-traumatic atrophy
	Progressive hemifacial atrophy/Parry-Romberg syndrome	Non-indurated skin with underlying atrophy on one side of the face. May involve the dermis, subcutaneous tissue, muscle, bone, eye, oral cavity and brain	Hemifacial microsomia (first and second branchial arch syndrome) and its variant Goldenhar syndrome (congenital non-progressive) Post-traumatic atrophy
Pansclerotic morphea		• Circumferential involvement, >85% of body surface area, sparing of fingers, toes and nipples. • Skin is thickened and may be bound down to underlying structures. Affects dermis, subcutis, fascia, muscle and/or bone. No internal organ fibrosis.	Systemic sclerosis Sclerodermoid GVHD Scleredema Scleromyxedema PCT Primary systemic amyloidosis Nephrogenic systemic fibrosis Carcinoid syndrome Drug-induced morphea Chemical induced sclerosis Occupational skin sclerosis
Eosinophilic fasciitis		• Symmetrical, extremities involved, sparing fingers and face. Painful, burning erythema and edema followed by progressive induration and thickening with guttering around vessels and tendons. • Skin is bound down. • Involves deep fascia, tendons and muscle. Dermis may be sclerotic or normal. • Concomitant plaque morphea in 20–40%.	(Same as for pansclerotic morphea)
Mixed type		A combination of two or more subtypes, most often linear and circumscribed plaque.	
Morphea – LS overlap (*see also* Table 21.4)		Most often in post-menopausal women with isomorphic generalized plaque morphea. Extragenital LS may occur at the same or different sites. Usually truncal but may be widespread. Increased prevalence of genital LS.	

Table 21.3 PHA versus ECDS	
PHA (progressive hemifacial atrophy)	**ECDS (en coup de sabre)**
Unilateral atrophy	Unilateral frontoparietal sclerotic band
Minimal/absent induration or previous inflammation	Usually preceded by skin induration
Cutaneous atrophy (but normal hair)	Scarring alopecia possible
Half face involved on one side	Usually does not go below eyebrow
Complications—enophthalmos, choroidal and retinal folding, hyperopia, uveitis, retinal vasculitis, glaucoma, third nerve palsy, headache, epilepsy, dental malocclusion and hemiatrophy of tongue	Neurological, ocular, auditory complications

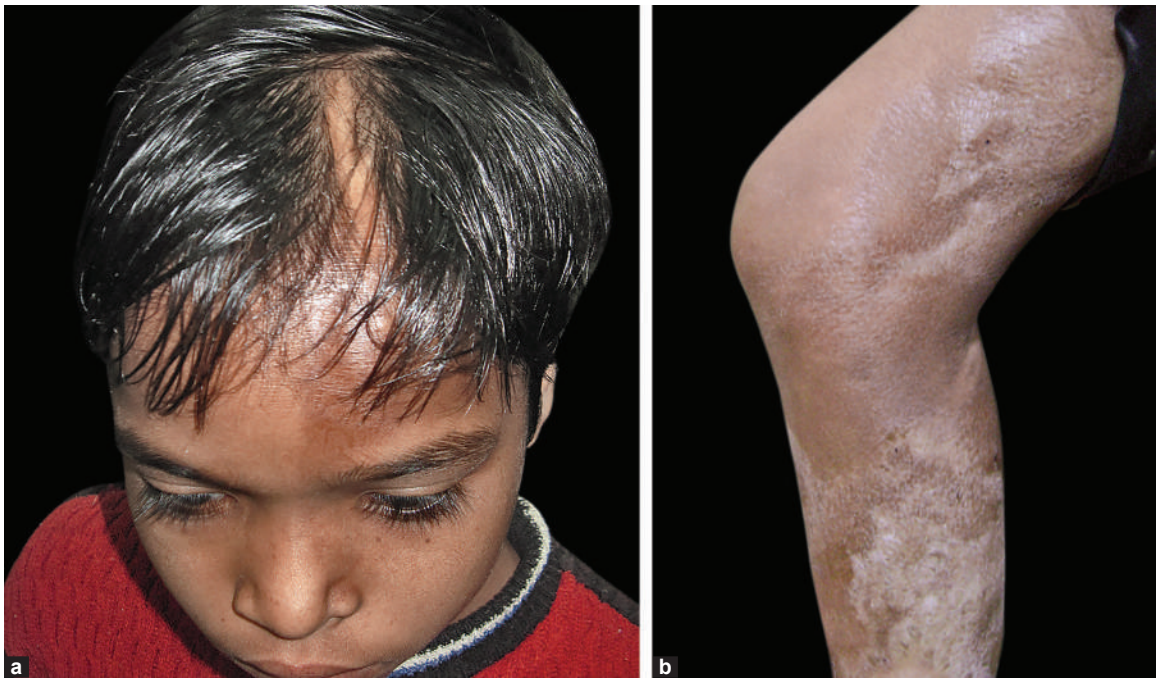


Fig. 21.4: (a) En coup de sabre; (b) Linear morphea

Table 21.4 Morphea versus LS		
	Morphea	**Lichen sclerosus**
Clinical appearance	• Thicker larger plaques with inflammatory/lilac border • Sclerosis more apparent	• Porcelain white papules/plaques with follicular plugging/telangiectasia purpura and atrophy • Sclerosis minimal
Histopathology	• Normal upper dermal elastic fibers more likely • Lichenoid infiltrate (–) • Basal layer vacuolization (–)	• Loss of elastic fibers • Lichenoid infiltrate (+) • Basal layer vacuolization (+)
Antibodies associated	• Antibodies to fibrillin-1 (also an extracellular matrix protein) likely	• Antibodies to extracellular matrix protein-1 (EMP-1)

Q Differentiate between en coup de sabre and hemiatrophy.

Extracutaneous manifestations: Musculoskeletal, neurological, ophthalmic, dental symptoms may be seen.

- In 20–25% of morphea patients:
  - **Linear (on the affected site)**
    - Neurological (31%)—headache, migraine, seizures.
    - Ophthalmological (8%)—episcleritis, anterior uveitis, keratitis.
    - Dental/oral—malocclusion, tongue hemiatrophy, TMJ involvement.
  - **Generalized**
    - Arthritis and joint limitations—most common
    - Vascular—Raynaud's phenomenon
    - Gastrointestinal—esophagitis, GERD. Rare. More likely due to skin immobility.
    - Respiratory—dyspnea. Rare. More likely due to severe skin immobility.

Associated Diseases

- **Autoimmune diseases**
  - Mostly with generalized morphea (45.9% prevalence compared to 9.6% with other types of morphea)
  - A family history of AICTDs or autoimmune diseases in first- and second-degree relatives is seen in 22% of children and 11% of adults with morphea.
  - Diseases:
    - AICTDs (autoimmune connective tissue diseases)—RA, SLE
    - AITD (autoimmune thyroid disorder)
    - Vitiligo, alopecia areata
    - Diabetes mellitus type I
    - Psoriasis
    - Multiple sclerosis
    - IBDs (inflammatory bowel diseases)

  The most frequently associated autoimmune diseases in a large study were Hashimoto thyroiditis, rheumatoid arthritis, alopecia areata and type 1 diabetes.
- **Lichen sclerosus** (also *see* **Table 21.2**). Morphea patients may have genital LS, predominantly in those with plaque type and generalized morphea.

  Extragenital LS lesions may occur with morphea and are usually asymptomatic, mostly at sites of friction.

  miR-155, TNF and IL-6 may play a role in overlap in morphea and LS.
- **Melanoma and NMSC**—reported to occur at higher incidence in morphea and SSc but this has been debated.

Investigations

Table 21.5 lists the important investigations in morphea while **Tables 21.6** and **21.7** give a histopathological comparison of early/late morphea and morphea/SSc, respectively.

Scoring

LoSCAT (localized scleroderma cutaneous assessment tool) can be utilized (shown in **Fig. 21.5**).

Modified Localized Scleroderma Skin Severity Index (mLoSSI)					Localized Scleroderma Damage Index (LoSDI)		
Site		*New/enlarge (within 1 mo)* 0 = None 3 = N/E	*Erythema* 0 = None 1 = Pink 2 = Red 3 = Dark red/ Violaceous	*Skin thickness* 0 = None 1 = Mild 2 = Moderate 3 = Marked	*Dermal atrophy* 0 = None 1 = Shiny 2 = Visible Vessel 3 = Obvious cliff drop	*Subcutaneous atrophy* 0 = None 1 = Flat 2 = Concave 3 = Marked atrophy	*Dyspigmentation (hypo/hyperpig.)* 0 = None 1 = Mild 2 = Moderate 3 = Marked
Scalp/face							
Neck							
Chest							
Abdomen							
Upper back							
Lower back							
RT	Arm						
	Forearm						
	Hand						
	Thigh						
	Leg						
	Foot						
LT	Arm						
	Forearm						
	Hand						
	Thigh						
	Leg						
	Foot						

Total score: mLoSSI (activity) _____ LoSDI (damage) _____

Please mark with a straight line:

Physician global assessment of disease activity

0 — 100
Inactive — Markedly active

Physician global assessment of disease damage

0 — 100
No damage — Markedly damage

Comment: _____

Fig. 21.5: Localized scleroderma cutaneous assessment tool

Histopathology

There are **five diagnostic "signs"** displayed in biopsy specimens from morphea lesions, four of which can be observed on scanning magnification. These are:

- **"Line"** sign, a straight/linear interface between the subcutis and the sclerotic reticular dermis–seen in the scanner view
- **"Cookie-cutter"** sign, straight and parallel lateral edges of a biopsy section
- **"Square biopsy"** sign, approximately 90° angles at the four corners of a biopsy section
- **"High"** eccrine glands, that is, located in the upper two-thirds of the dermis.
- The fifth sign, best seen at 40 × magnification, is the **presence of interstitial mucin**.

In a retrospective study of these signs, Jindal et al. found that the sensitivity is highest for "high" eccrine glands, whereas the "line" sign had the highest specificity but the lowest

Table 21.5 Investigations in morphea

Types of investigation	Finding
Dermoscopy	• Morphea— whitish fibrotic beams, linear branching vessels, structureless or network-like pigment structures, loss of hair follicles in the affected area • Lichen sclerosus—patchy white structureless areas, comedo-like openings, purpuric globules, scales, ice slivers and sparse, thin vessels
ESR, CRP, IgG, eosinophil count	• High in eosinophilic fasciitis
Imaging	• Cranial MRI—MRI of the brain with contrast is recommended in all patients with linear morphea affecting the face, head and neck area, regardless of the presence of characteristic neurological symptoms (headaches/migraine, seizures, hemiparesis) • CT—before surgery planned for unequal lengths of limbs • EEG—for head and neck morphea • USG: USG in the 20 MHz range, can be used to accurately assess the activity and damage of skin lesions in morphea, with results comparable to the clinical validated score localized scleroderma cutaneous assessment tool (LoSCAT)
Measurement of skin thickness	• Photography • Cutometer • Thermography • Computerized skin score • USG (15–20 MHz) • Durometer • Scanning laser Doppler
HPE	• Deep incisional ellipse (to include muscle and fascia) • From erythematous border if present/otherwise from central sclerosis area • Depth of involvement—variable in morphea. Best measured by deep tissue biopsy and MRI • Detailed histopathological comparison of morphea (early versus late) and morphea versus SSc is given in **Tables 21.6** and **21.7**.
Serology	Positive ANA titers are a/w a higher risk for extracutaneous, deeper involvement and disease relapse ANA (18–68%), ENA, RA factor, *Borrelia* serology (in areas with high prevalence), anti-single strand DNA (ssDNA)—topoisomerase IIα, phospholipid, fibrillin-1, MMP-1, and histone antibodies (AHA)
Scoring of severity	**LoSCAT score**
Referrals	ENT, ophthalmology, dental, orthopedics, plastic surgery, physiotherapy

Q Dermoscopic and histopathological features of morphea.

Table 21.6 Histopathological comparison of early and late morphea		
	Active inflammatory phase	**Late sclerotic phase**
Epidermis	Normal/flattened with loss of rete ridges/acanthotic	Flattened usually
Papillary dermis	Occasionally edema and infiltrate may be present	Fibrosis may extend into papillary dermis too
Reticular dermis	• Edema, dense perivascular infiltrate—lymphocytes, plasma cells, macrophages, occasional eosinophils • Swollen collagen bundles parallel to the skin surface	• Inflammation minimal • Collagen bundles—closely packed, horizontal, highly eosinophilic
Eccrine glands and hair follicles	Infiltrate may encompass them	Entrapped by collagen → appear higher up in dermis, eventually lost
Subcutaneous fat	Infiltrate may spill into fat Thickened newly formed wavy collagen bundles (type III collagen and fibrillin 1)	Replaced by collagen
Blood vessels of dermis and fat	Mild changes. Edema of walls and endothelial swelling	Fewer blood vessels, walls thickened
Fascia, striated muscles	Inflammation +/–	Fibrosis +

Table 21.7 Histopathological comparison of morphea and systemic sclerosis		
	Morphea	**Systemic sclerosis**
Inflammatory infiltrate	More intense	Less
Perineural inflammation	More likely	Less
Extent of fibrosis	More diffuse, may involve papillary and reticular dermis both	Less

sensitivity. High eccrine glands had the highest positive and negative predictive values for the diagnosis **(Fig. 21.6).**

The inflammatory cell infiltrate is composed of lymphocytes with some macrophages and plasma cells.

Patterns of inflammation (Walker et al., 2017)

- Top heavy—hyalinized collagen bundles exclusively in the papillary to superficial reticular dermis with absence of these changes in the lower layers.
- Bottom heavy—hyalinized collagen bundles in deep dermis and subcutaneous fat sparing the papillary through mid-dermis. Associated with higher functional impairment, pain and tightness.
- Full thickness— hyalinized collagen bundles throughout dermis.
- Severe inflammation—associated with pain and functional impairment

Types of lesions and patterns of inflammation (Walker et al., 2017)

- Linear/limited plaque: Top/bottom/full thickness
- Deep: Bottom/full

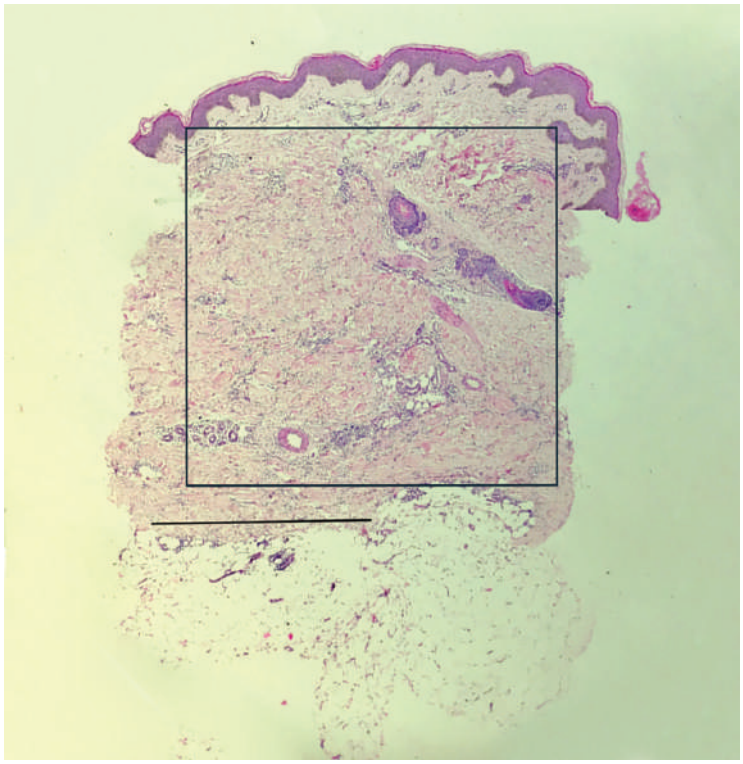


Fig. 21.6: A scanning image of morphea with "line" sign "square biopsy" sign and high eccrine glands (*Courtesy:* Dr Rashmi Jindal, MD)

- LS with morphea: Top
- Disseminated: Bottom, top

As in most cases, histology is used as a supportive investigation. It is useful to know the salient findings listed in **Table 21.6** which can help to differentiate early from late lesions.

Differential Diagnosis

Table 21.8 lists the disorders associated with skin sclerosis which may need to be differentiated from morphea on a few occasions.

Treatment (Flowcharts 21.1 and 21.2)

The therapy is based on various aspects and include general measures and pharmacotherapy. Initial evaluation of a patient with morphea should include assessment of the type, extent and activity of disease and extracutaneous involvement.

General measures include psychosocial support, physiotherapy, massage, lymphatic drainage, interdisciplinary consultations (rheumatology, physical medicine and rehabilitation, orthopedics, plastic and oral maxillofacial surgery) and surgery.

Pharmacotherapy is detailed below and is dependent on various aspects including type of morphea, age of patient, disease activity, extent, *depth, potential for permanent damage/ functional impairment, and impact on quality of life.* It is worthwhile to remember that reduction

Table 21.8 Disorders associated with skin sclerosis/sclerodermoid disorders	
Types of disorder	**Examples**
Autoimmune disorders	Systemic sclerosis, sclerodermoid GVHD
Metabolic disorders	PCT, PKU, muscle glycogenosis, hypothyroidism, carcinoid syndrome, diabetic cheiroarthropathy with skin thickening
Deposition disorders	Scleredema, scleromyxedema, primary systemic amyloidosis
Genetic disorders	GEMSS syndrome, Werner syndrome, progeria, acrogeria, poikilodermatous EB, melorheostosis, scleroatrophic Huriez syndrome
Associated with hematological diseases	POEMS syndrome, myeloma
Occupational causes	Vinyl chloride, perchloroethylene, trichloroethylene, organic solvents, pesticides, epoxy resins, silicone
Chemical induced	Eosinophilia myalgia syndrome (L-tryptophan), toxic oil syndrome (rapeseed oil), nephrogenic systemic fibrosis (gadolinium exposure in renal failure)
Drug induced	Bleomycin, pentazocine, progestin, vitamin B_{12} and vitamin K, cocaine, D-penicillamine, interferon-β1a, paclitaxel, methysergide, gemcitabine, bromocriptine, bisoprolol, L-hydroxytryptophan with carbidopa, ibuprofen, mitomycin C, balicatib (withdrawn), odanacatib (withdrawn), PD1 inhibitors (nivolumab, pembrolizumab), biologics (etanercept, adalimumab, golimumab, ustekinumab)

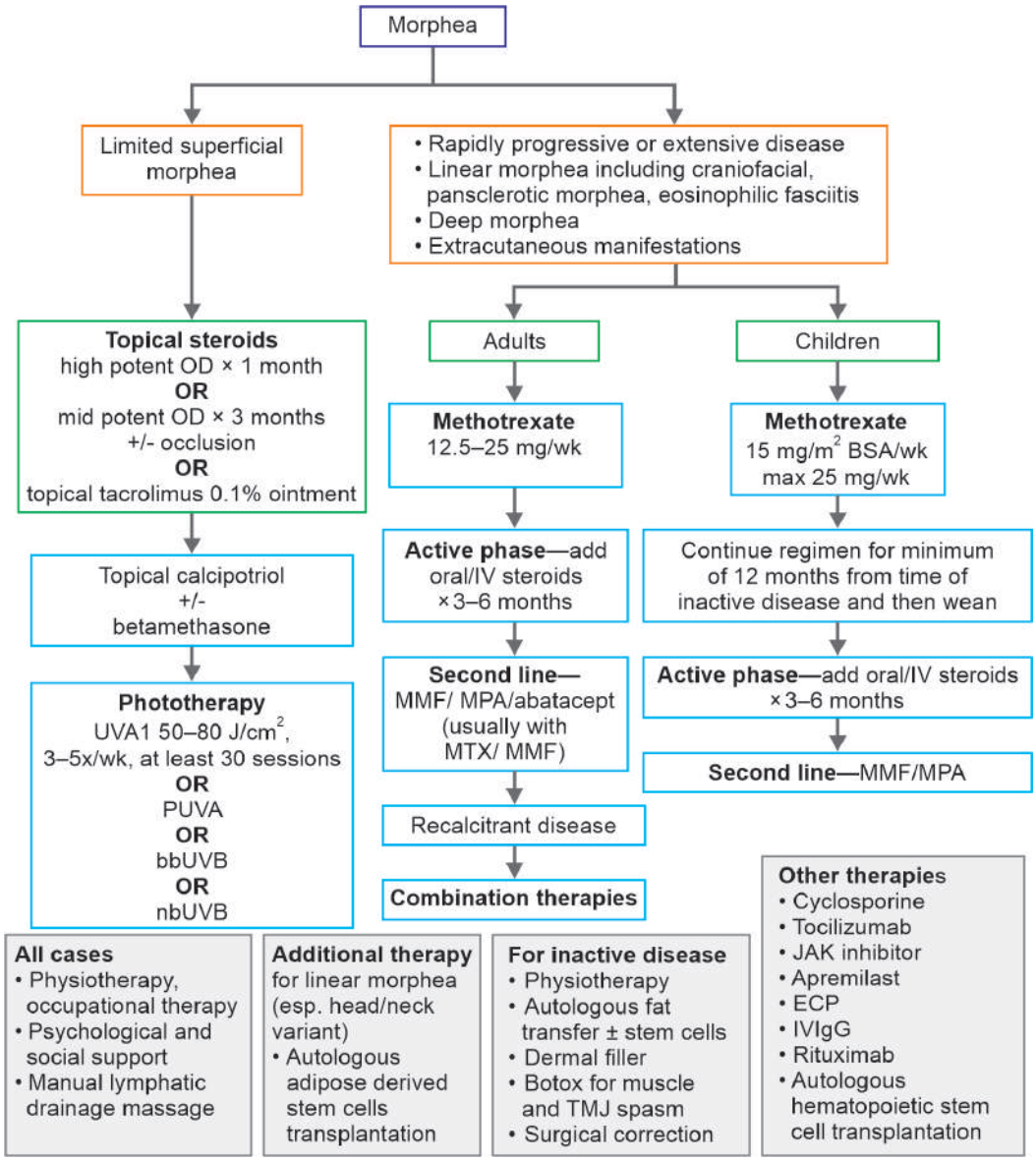
PCT, porphyria cutanea tarda; PKU, phenylketonuria; GEMSS syndrome, glaucoma, ectopia, microspherophakia, stiff joints, short stature; POEMS syndrome = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and sclerodermoid skin changes

of sclerosis typically takes at least **8–12 weeks**. While the level of evidence is detailed in Table 21.9, we will focus on type specific treatment.

1. **Treatment as per type of morphea**
   a. **Limited superficial:** Topical agents, topical tacrolimus 0.1%, 5% imiquimod cream (3–7 times weekly for 9-month period), calcipotriol/calcipotriene 0.005%, low-dose UVA-1 phototherapy (children) and topical and intralesional corticosteroids. Steroids are reserved for early inflammatory stages of disease or if there are pronounced epidermal changes.
   b. **Generalized:** Phototherapy, preferably UVA-1, but when this is not available, broadband UVA, narrowband UVB or topical psoralen and UVA (PUVA).
   Why phototherapy? UVA and UVB can induce MMPs such as collagenase, UVA-1 → upregulates antifibrotic haemoxygenase-1, causes T cell apoptosis, depletes dermal Langerhans and mast cells, induces interferon-γ (INF-γ), IL-1 and IL-6 production, ↓TGF-β production, ↑antifibrotic protein-decorin.
   Ideal light—UVA wavelength (320–400 nm) as it penetrates deeper and **UVA-1** (340–400 nm) is less erythemogenic and penetrates deeper than UVA-2 (320–340 nm).
   Dose: UVA-1 in low dose (10–20 J/cm^2), medium dose (20–70 J/cm^2) and high dose (70–130 J/cm^2), have all shown efficacy, significantly reducing skin thickness and stiffness in adults and children with all forms of morphea. It may be better to use **high doses** because of the lower cumulative UV exposure.
   Others: Broadband UVA, bath PUVA, cream PUVA and nbUVB.
   c. **Progressive and severe types:** Combinations of pulsed intravenous and/or oral steroids with methotrexate should be used as first line in patients with progressive disease despite topical therapy and/or phototherapy, and in patients with active disease and a moderate

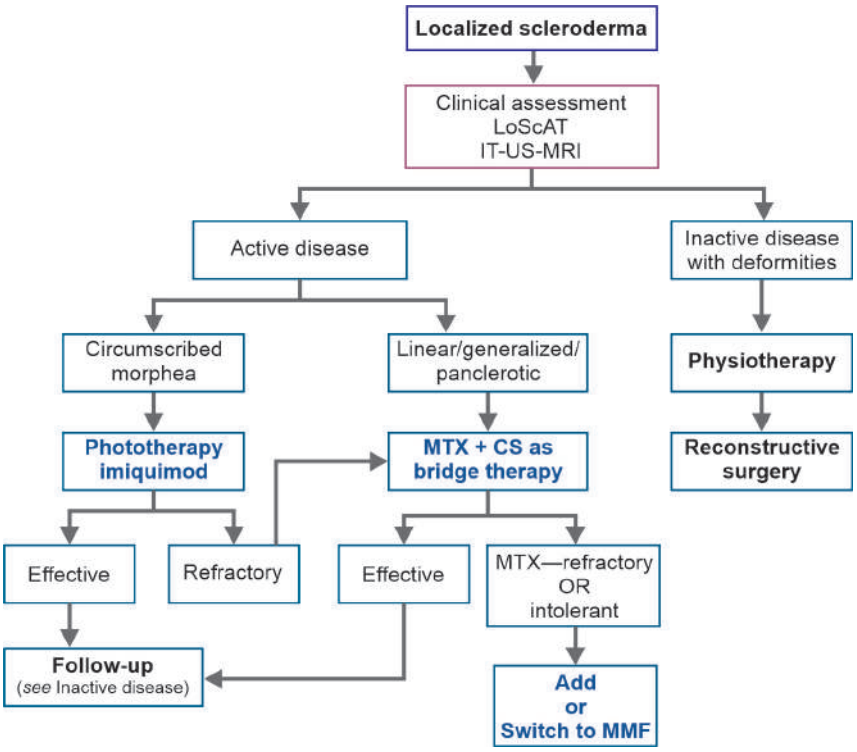
Q Discuss treatment of generalised morphea.

Flowchart 21.1: Treatment algorithm for morphea



Kreuter A, Moinzadeh P, Kinberger M, et al. S2k guideline: Diagnosis and therapy of localized scleroderma. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2024; 22: 605–620. https://doi.org/10.1111/ddg.15328

Flowchart 21.2: Treatment of newly diagnosed or refractory patients with *juvenile localized scleroderma* according to the clinical subtype (Zulian et al., 2019).



CS, corticosteroid; IT, infrared thermography; LoSCAT, localized scleroderma cutaneous assessment tool; MMF, mycophenolate mofetil; MTX, methotrexate; US, ultrasound.

Table 21.9 Levels of evidence of treatments for morphea

Type of morphea	First line treatments	Second line treatments	Third line treatments
Circumscribed plaque or superficial disease	• Tacrolimus 0.1% ointment BD (+/- occlusion) • Imiquimod 5% cream • Topical/intralesional steroids	• Calcipotriol – betamethasone (+/- occlusion) • Calcipotriol 0.005% BD under occlusion • Calcipotriol + low dose UVA1	• Phototherapy: UVA1, PUVA, bbUVA, nbUVB
Superficial generalized plaque	UVA1 phototherapy 3–5x/wk, 30–40 sessions	PUVA (bath or cream) BB-UVA nbUVB	Hydroxychloroquine
Pansclerotic/linear/deep disease/unresponsive disease/significant QoL impairment	• Methotrexate + IV steroids • Methotrexate + oral steroids	• MMF +/- IV/ oral steroids • Methotrexate + MMF +/– steroids • Abatacept	• Cyclosporine • Oral medication + phototherapy • Tocilizumab • JAK inhibitor • Apremilast • Infliximab • Extracorporeal photopheresis • IVIG

Q Discuss the treatment of morphea in a pediatric patient.

to high morbidity risk (linear, deep or disseminated forms of disease such as en coup de sabre, pansclerotic morphoea or eosinophilic fasciitis).

i. Steroids (0.5–1 mg/kg/day for 6 weeks then taper over a mean of 18 months).

ii. Methotrexate—ideal drug.

Action: ↓IL-8, ↑IL-1 receptor antagonist and soluble TNF receptor p75, ↓in serum IL-2, -4 and -6, ↓mast cell numbers and levels of tenascin. Dose = 0.3–0.6 mg/kg/week (15 mg/m^2/week) in children and 15–25 mg/week in adults.

Methotrexate treatment should be for at least 1 year before tapering as this leads to longer remission periods. The drug should be stopped only when the patient is in remission and off steroids for at least 1 year.

Combination: Pulse steroids + Methotrexate

iii. Other drugs: Mycophenolate mofetil, abatacept, infliximab. High dose intravenous immunoglobulin (IVIG) in resistant cases.

2. **Pediatric**

Zullian et al proposed an algorithm for treatment of morphea in pediatric patients **(Flowchart 21.2)**.

Emerging Therapies

i. Antifibrotic Drugs

Imatinib, a tyrosine kinase inhibitor that interferes with signaling pathways by blocking the activity of c-Abl, c-Kit and PDGF receptors, respectively, showed beneficial results in morphea patients in numerous case reports.

Connective tissue growth factor (CTGF) is a profibrotic peptide that acts downstream of TGF-β and is highly expressed in morphea lesional skin and **iloprost**, a prostaglandin analogue, which is already used in SSc patients for the treatment of severe Raynaud's syndrome, can suppress the secretion of CTGF by fibroblast.

Pirfenidone is a non-peptide synthetic chemical that inhibits the production of TGF-β1, TNF-α, PDGF, IL-1β, and collagen I and III, all of which have been linked to fibrosis. 8% pirfenidone gel three times daily for 6 months was shown to improve morphea based on localised scleroderma skin activity index (mLoSSI), durometer and histological assessment.

ii. Biologics and Oral Small Molecules

IL-6 plays a crucial role in the pathogenesis of morphea. It exerts both inflammatory and profibrotic effects by binding to its membrane receptor (IL-6R) and activating the downstream JAK-STAT signaling pathway. The latter leads to the stimulation of collagen and MMP production by fibroblasts, and the differentiation of naïve $CD4^+$ to pathogenic TH17 cells via the putative TGF-β axis. **Tocilizumab** is a potentially useful drug as it inhibits the IL-6 pathway. It has proven benefit in skin fibrosis and lung function in SSc and has also shown a reduction in mLoSSI and joint inflammation in patients with refractory morphea.

A more useful pathway is the **JAK-STAT** signaling pathway, which acts downstream of the central TGF-β axis. Thus JAK inhibitors can be used to block the TGF-β-driven skin fibrosis. **Tofacitinib**, a JAK1/3 inhibitor, has been shown to improve both clinical and histological skin thickness and also joint mobility in numerous cases of refractory, generalized morphea. Therapeutic response is seen in the first month, with a maximum response between 11 and 16 months [Papara C, et al., 2023]. **Abatacept** is a cytotoxic T-lymphocyte antigen 4 (CTLA4) IgG1 recombinant fusion protein that inhibits T-cell activation via competitive binding to CD80 or CD86. It has shown significant improvement in morphea.

Q What are the newer drugs for morphea? Describe their mechanisms of action.

Course and Prognosis

- In any patients, morphea progresses over 3–5 years, then stabilizes and eventually resolves spontaneously. However, this is not the rule.
- Residual atrophy and dyspigmentation may remain in those lesions that resolve.
- Recurrences may occur months—years after quiescent disease. Delayed initiation of systemic treatment is associated with longer disease activity, lower response rates, and higher relapse rates. Most relapses occur between 5 and 37 months after treatment cessation.
- Older age of initial onset and ANA positivity are potential markers for risk of relapse in pediatric patients.
- 30–50% linear morphea have osteoarticular complications.
- Juvenile morphea may behave more aggressively. The mean disease duration of childhood-onset morphea is twice as long as that for adult-onset disease (13.5 versus 5.8 years). Children with mixed morphea have a longer more complicated course, and relapse is more common in mixed, generalized, deep morphea.

  Linear morphea may stabilise but around 40% have functional limitations and frequent reactivations even after immunosuppressive therapy. Linear limb morphea has the highest chances of recurrence.
- Morphea → SSc rarely. It is noteworthy to stress that morphea does not usually transit to SSc.
- Linear morphea → SSc in 0.9–1.3%.

  Markers of disease activity are given in **Box 21.1**.

Box 21.1 Markers of disease activity

Clinical

1. New lesions in last 3 months (documented).
2. Expansion of pre-existing lesions in last 3 months (documented).
3. Moderate/severe erythema/skin lesions with erythematous/violaceous borders.
4. Tactile warmth.
5. Increased induration of border/abnormal skin texture—yellow, white, waxy, abnormally smooth/skin thickening/ mLoSSI >0.
6. Worsening of hair loss on scalp/eyebrow/eyelash.
7. Extracutaneous manifestations—deep tissue involvement, inflammatory arthritis, joint contractures, seizures, headaches or CNS vasculitis, uveitis or visual disturbance.

Investigations*

8. Progression to deeper tissue by MRI/USG.
9. Elevation of laboratory markers (CPK, aldolase, ANA).
10. Skin biopsy suggestive of active disease.

*Of the investigative measures, only the computerized skin score, ultrasonography and MRI have been validated.

LICHEN SCLEROSUS (LS) AND BALANITIS XEROTICA OBLITERANS

Epidemiology

- F >> M, whites >non-whites
- Any age, but has bimodal peaks:
  - Major peak = 40–50 years post-menopausal females
  - Second peak = Prepubertal girls (8–13 years)

- Associated with autoimmune diseases (especially in women)
  Most common: Autoimmune thyroid disease (15%)
  Others: Pernicious anemia, localized scleroderma/morphea (6%), psoriasis, and vitiligo
- **Autoantibodies:** Extracellular matrix protein-1 (ECM-1)
- **Site:** Most commonly affects male and female anogenital region (85%)
- Extragenital LS accounts for only 15%
- Extragenital sites—neck, shoulders, flexor surfaces of the wrists, and sites of physical trauma or continuous pressure.
- **Triggers:** Trauma, urine, infections (*Borrelia burgdorferi*, Mycoplasma), hormones, microbiome.
- Male penile involvement = Balanitis xerotica obliterans (BXO).

Clinical Features (Extragenital LS)

- Classic lesions: Sclerotic, ivory-white, atrophic, and flat-topped papules coalescing into plaques **(Fig. 21.7)**.
- Follicular plugging (follicular delling) more prominent in extragenital LS. The **Ink Test** is useful to highlight the follicular plugging, where marking ink is applied on the lesion, then cleaned with isopropyl alcohol, the ink remains in the follicular plugs and can be visualized by dermoscopy.
- Genital LS is usually symptomatic (itching, pain, and burning), whereas extragenital LS is typically asymptomatic.

Signs

- Hyperkeratosis (white thickened skin; hyperkeratosis on histology)
- Sclerosis (tight, yellowish white skin, for example, resulting in phimosis; dermal hyalinization on histology)
- Pallor (pale, whitish areas; the histological correlate is not described)

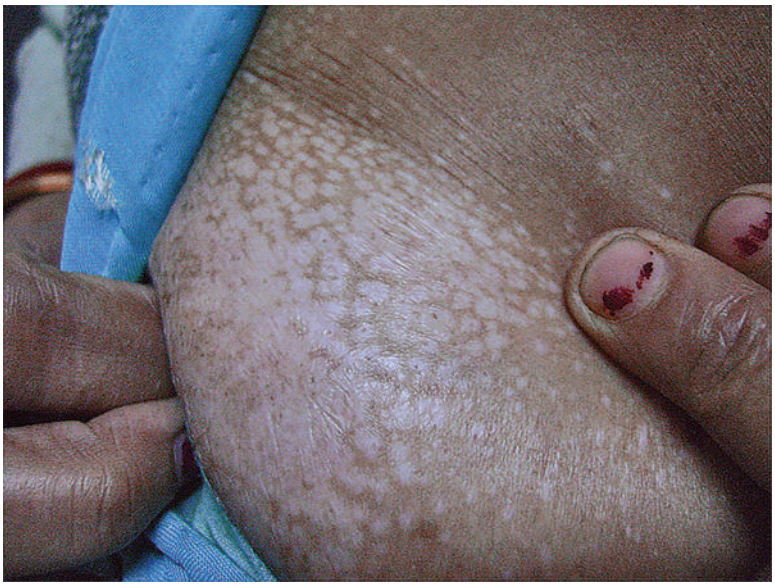


Fig. 21.7: Lichen sclerosus: Ivory-white lesions with follicular plugging

Q Differentiate LS and morphea.

- Atrophic skin (crinkly skin; epidermal atrophy on histology)
- Fissuring (skin fragility, loss of elasticity leading to splitting of skin)

Clinical Features (Genital LS)

Males

- Phimosis may be asymptomatic.
- Symptoms—itching, burning, bleeding, tearing, splitting, rash, hemorrhagic blisters, sexual dysfunction or dyspareunia, discomfort with urination and narrowing of the urinary stream.
- Signs—atrophic leukodermic patches or plaques, telangiectasia and sparse purpura, incomplete paraphimosis or 'waisting' due to a constrictive posthitis, signs of dysplasia, carcinoma *in situ* or of a frank cancer.
- Posthitis xerotica obliterans—prepuce damage, balanitis xerotica obliterans—glans penis.

Females

- Flat, atrophic, whitened epithelium, may become confluent, extending around the vulval and perianal skin in a 'figure-of-eight' configuration. Vaginal lesions do not occur, as LS seems to spare mucosal epithelium **(Fig. 21.8).**
- Symptoms—severe pruritus and soreness. Leading to dysuria, dyspareunia, or pain upon defecation (often manifesting as constipation in children). Scarring can lead to burying of the clitoris and fusion of the labia minora to the labia majora.

Complications

- Loss of self-esteem (e.g. concern about the genital appearance)
- Impaired quality of life
- Development of anogenital carcinoma (actual risk <5%)

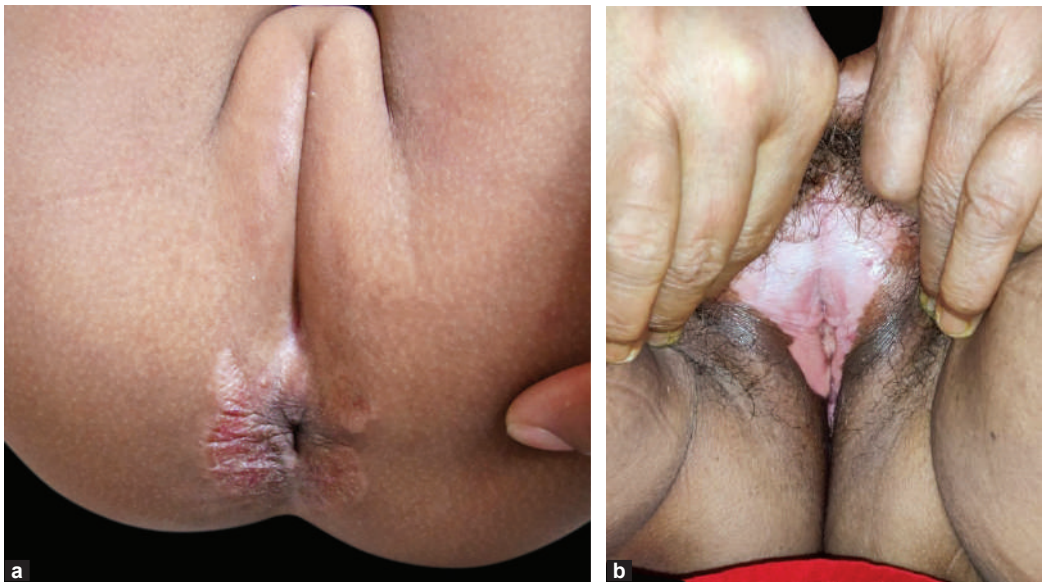


Fig. 21.8: Genital LS—atrophic wrinkled plaques with loss of appendages. Associated soreness and itching is pronounced

Q How would you differentiate genital vitiligo from genital lichen sclerosis?

- Development of clitoral pseudocyst
- Sexual dysfunction
- Urinary dysfunction
- Genital dysaesthesia

Differential Diagnosis

- Morphea (extragenital LS)
- Erosive lichen planus or erythroplasia of Queyrat (genital LS)
- Chronic GVHD
- SCC

Histopathology

- Epidermis is atrophic with basal cell hydropic degeneration.
- Papillary dermis shows homogenisation of collagen. Deep to the hyalinized zone is a band-like lymphohistiocytic infiltrate. Lymphocytes are noted between sclerotic collagen bundles in majority of the slides and is referred to as the "lymphocyte-peppered sclerotic collagen" [Yadav D, et al., 2021]. Dermal melanophages may be seen.
- **'Red, white, and blue sign'** **(Fig. 21.9)**
  A well-evolved lesion shows an atrophic epidermis with overlying orthokeratotic hyperkeratosis, vacuolar degeneration of basal keratinocytes and homogenization and hyalinization (sclerosis) and papillary dermal collagen jointly with edema. The lichenoid infiltrate is pushed down beneath this altered collagen.
  - Orthohyperkeratotic stratum corneum **(pink-red)**
  - Hyalinized/edematous papillary dermis **(pale-white)**
  - Band-like lymphocytic infiltrate **(blue)**

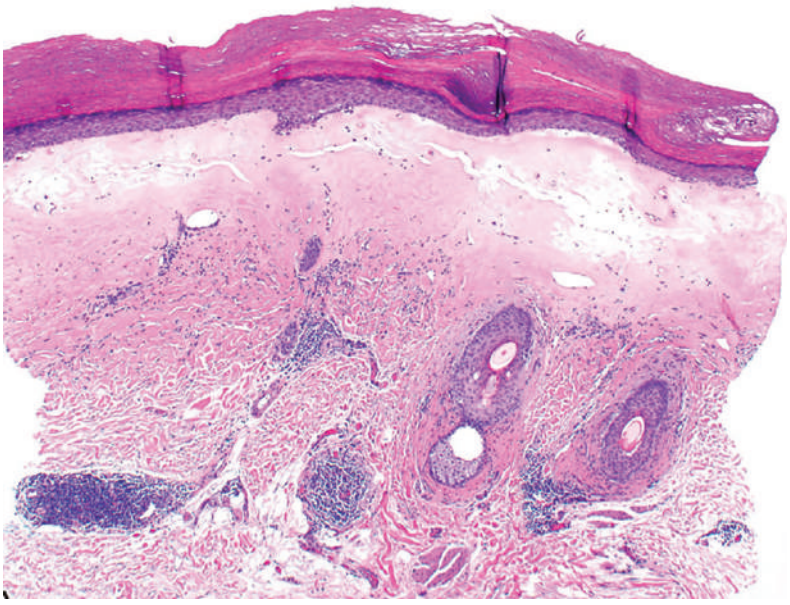


Fig. 21.9: Histopathological image of lichen sclerosus showing the "red, white and blue sign"

Use of topical steroids can lead to reduction in hyperkeratosis, subepithelial sclerosis and reduction of the lymphocytic infiltrate. Also use of topical antifungals (due to a mistaken diagnosis of Candida infection) may induce a hypersensitivity reaction leading to a psoriasiform reaction pattern of the skin.

Treatment (Table 21.10)

Principles of Treatment

1. Avoid synthetic clothes, use emollients, avoid excessive use of soaps, avoid scratching.
2. Minimise triggers—mechanical factors, including friction due to tight clothing, sexual abuse, surgery, radiotherapy or trauma, are known to be implicated in both development and maintenance of LS lesions, due to the Koebner phenomenon.
3. Topical emollients and steroids form the basis of treatment. Steroids have little side effects and a 30 gm tube should last for 1 year.
4. UVA1 therapy, if available, is useful.
5. Systemic agents like acitretin and methotrexate can be used.
6. Surgical treatment.

Only in case of **adult females**—de-adhesion/synechiolysis/perineoplasty can be advised when indicated.

In **males** circumcision or frenuplasty if medical treatment fails.

Table 21.10 Therapy of lichen sclerosus (Akel et al., 2018)

Extragenital lichen sclerosus

- UVA-1 (30–60 J/cm^2) phototherapy for 10 weeks
- Potent to ultrapotent topical steroids
- Tacrolimus ointment (0.1%) twice daily. Use of topical tacrolimus on its own for extragenital LS proved to be unsuccessful or inferior to topical corticosteroids
- Systemic acitretin/methotrexate

Genital LS

Female

- Clobetasol propionate (0.05% ointment—OD × 30 days; alternate day × 30 days, 2/week × 30 days. Maintenance 2/week) Efficacy—70%. Topical steroids can be applied in LS over years without significant adverse effects, provided the amount (by fingertip unit), frequency (2–3 per week) and site of application (affected area only) are carefully monitored.
- Resolution of skin thickening and ecchymosis, but not pallor, as pallor does not always resolve completely
- More effective than tacrolimus 0.1%, testosterone 2% in petrolatum, ultraviolet A1 home-based phototherapy
- As efficacious as mometasone furoate 0.1% ointment. Topical calcineurin inhibitors BD for at least 12 weeks have some effect in suppressing symptoms (pruritus, burning, dyspareunia) in LS; but LS is better treated by potent topical steroids.
- Treatment failure—poor compliance or coexistent vulvodynia, malignancy (SCC risk—5%)

Male

- Clobetasol propionate (0.05% ointment OD) for 1–3 months with an emollient soap substitute and barrier
- 50% of male patients with LS respond to CP
- Surgery—boys, complete circumcision is the treatment of choice, adult males may require surgery
- Treatment failure—tight phimosis, obesity and burying of the penis, SCC risk 0–12.5%

Q Discuss management of genital and extragenital LS.

Acknowledgement

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CHAPTER 1

Acne Vulgaris

• Kabir Sardana • Neirita Hazarika • Surabhi Sinha

Acne vulgaris (acne) is an inflammatory disease of the pilosebaceous gland. It presents as open and closed comedones that develop into inflammatory red papules or pustules. Atrophic or hypertrophic acne scars may ensue, as can post-inflammatory hyperpigmentation or post-acne erythema. Acne can develop into refractory cysts, nodules, and subcutaneous fistulas. Lesions appear on the sebaceous follicle-rich areas like face, neck, chest, and upper back.

ETIOPATHOGENESIS

The classical etiology of acne vulgaris is believed to involve increased sebum excretion rates, abnormal keratinization of the follicular infundibulum, bacterial proliferation, and subsequent inflammation.

1. Sebaceous Gland in Acne

Sebaceous follicles are located on the face, chest, and upper back. The part of the isthmus where the sebaceous gland attaches to the hair follicle is referred to as the junctional zone. Cells of the junctional zone give rise to the infundibulum and sebaceous gland **(Fig. 1.1)** and play an important role in acne. Comedo-associated sebaceous glands are atrophic suggesting abnormal differentiation of progenitor cells that are responsible for generating the sebaceous gland and infundibulum—this is known as the 'comedo switch' theory (Saurat), whereby growth of the infundibulum is aberrantly promoted in lieu of that of the sebaceous gland. (Clayton et al., 2019). Undifferentiated sebocytes in acne differentiate into sebaceous duct cells and infundibular keratinocytes instead of mature sebocytes, resulting in the abnormal keratinization of follicular channels **(Fig. 1.2)**.

Among signaling pathways, Wingless (Wnt) and Hedgehog signals are important. Low levels of Wnt signaling favor sebaceous differentiation, while high levels promote differentiation of follicular lineages. Androgens promote sebocyte differentiation and inhibit Wnt signaling. Aryl hydrocarbon receptors (AHRs) are linked to chloracne. AHRs also inhibit sebaceous differentiation by promoting the differentiation of junctional zone stem cells into infundibular keratinocytes. Fibroblast growth factor (FGF) 2 stimulates proliferation of the pilosebaceous unit, and epidermal growth factor receptors (EGFRs) can enhance the hyperproliferation of sebaceous glands and increase sebum production.

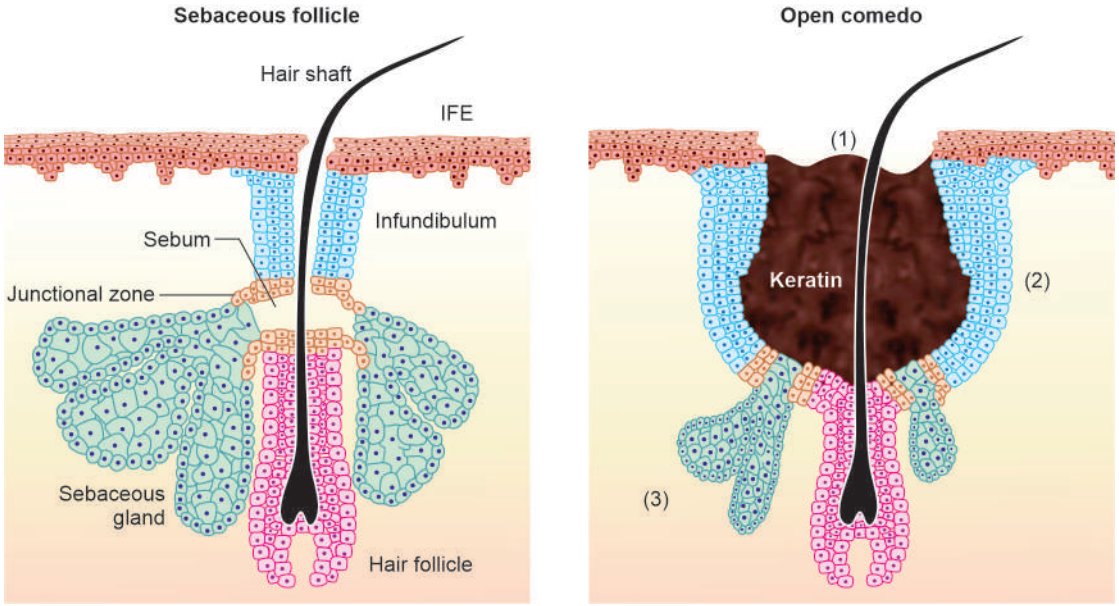

Fig. 1.1: Depiction of normal sebaceous follicle and acne pilosebaceous unit; (Left) Healthy human sebaceous follicle with multilobular sebaceous gland (SG) and normal infundibulum. Cells of the junctional zone give rise to the infundibulum and SG. (Right) Comedo, composed of (1) sebum and infundibular-derived keratin. Other aspects are (2) hyperplasia and abnormal keratinization of the infundibulum, and (3) atrophy of the associated sebaceous glands. [IFE–inter-follicular epidermis].

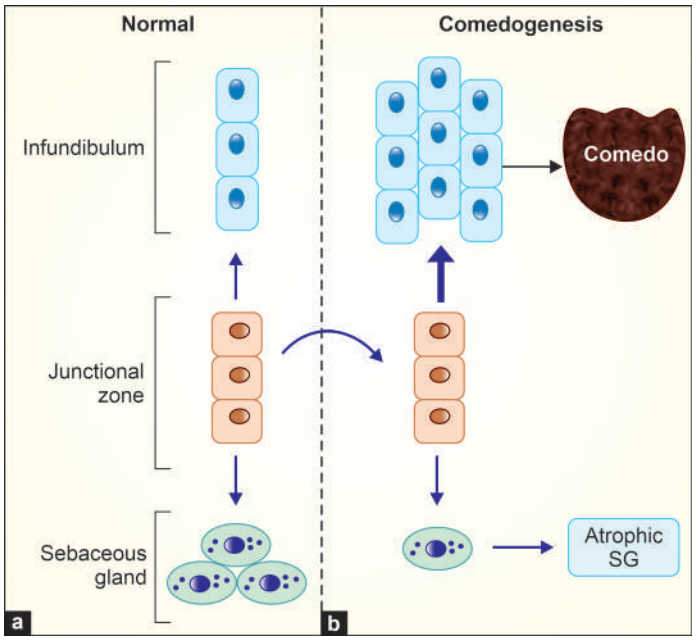

Fig. 1.2: The "comedo switch" hypothesis. (a) Progenitor cells within the junctional zone (JZ) contribute to infundibulum and the sebaceous gland (SG). (b) A comedogenic stimulus acts on cells in the JZ, causing a switch in lineage determination that favors the infundibulum, resulting in the atrophy of SG

An overview of the factors that determine activity of the SG are listed in **Box 1.1**.

Box 1.1 Factors determining the activity of sebaceous glands

- Sex steroids: Androgens, testosterone, 5 alpha-reductase, estrogens, progesterone
- Peroxisome proliferator-activated receptor
- Wnt signaling: Androgens ↓Wnt signaling
- Aryl hydrocarbon receptor
- Fibroblast growth factor receptors
- ErbB family receptor signaling
- Insulin/insulin-like growth factor-1 signaling

Sebum

In acne, sebum production is high and the composition of acne sebum is different. Linoleic acid deficiency, elevated free fatty acids (FFAs), and increased squalene peroxidation in acne sebum promote follicular hyperkeratinization. Sebum FFAs upregulate IL-1α, leukotriene B4, and IL-6 expression through specific signaling pathways. Other inflammatory mediators, like defensins, peptidases also play a role. Increased sebum production provides the perfect lipid-rich anaerobic environment necessary for *Cutibacterium acnes* proliferation, also limiting potential competitors (Okoro OE, et al., 2021).

2. Keratinization in Acne

Abnormal keratinization is an important factor in acne pathogenesis. Expression of the hyperproliferative keratins **(K6, K16, and K17)** is increased in acne lesions. Significant filaggrin expression in the infundibulum is closely associated with the abnormal keratinization involved in acne. **IL-1α** is involved in abnormal keratinization, and inflammation is believed to precede abnormal keratinization.

3. Immunological Aspects and Inflammation

In acne, *Cutibacterium acnes* (*C. acnes*) in the follicular channel stimulates Langerhans cells in the infundibulum via TLR-2, resulting in the production of IL-12 and IL-8 by activating Th1 cells. *C. acnes* also stimulates follicular keratinocytes in the infundibulum via TLR-2, resulting in the production of IL-6 and IL-8, followed by the formation of inflammatory lesions. A Th1 shift occurs in acne lesions with the additional role of Th17. *C. acnes* is a potent inducer of Th17 and Th1. IL-1β and TNF-α are additionally involved in acne inflammation.

An overview of the role of *C. acnes* in acne is given in **Fig. 1.3** and a summary is detailed in **Box 1.2**.

Box 1.2 Role of *C. acnes* in acne

- *C. acnes* activates TLR2 and stimulates release of proinflammatory mediators
- IL-1α, IL-8 (causes neutrophil recruitment), IL-12 (promotes Th1 response), TNF-α, MMP are produced
- *C. acnes* increases keratinocyte expression of TLR2 and TLR4
- *C. acnes* activates NOD-like receptor protein 3 (NLRP3) of inflammasomes in cytoplasm of neutrophils and monocytes → release of proinflammatory IL-1β

4. The Cutaneous Microbiome

Under normal circumstances with a "balanced skin microbiome", *Staphylococcus epidermidis* limits overcolonization and the inflammatory response of the skin by the different *C. acnes* strains

Q List the major factors in the pathogenesis of acne and detail the role of sebaceous glands.

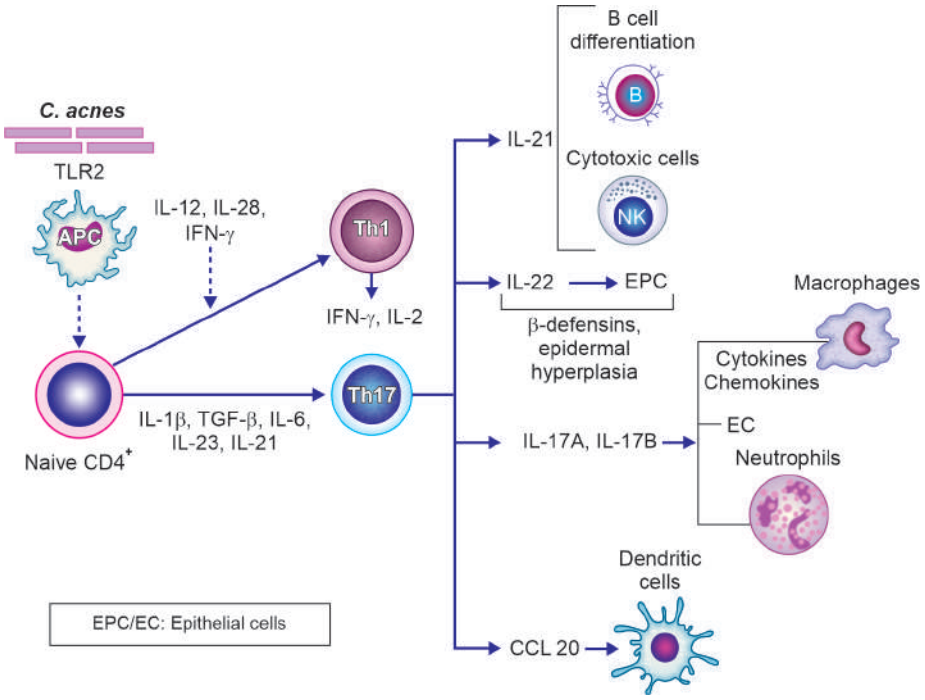

Fig. 1.3: Overview of the immunological mechanisms triggered by *C. acnes*

and suppresses *C. acnes*-induced IL-6 and TNF-α production by keratinocytes. Conversely, *C. acnes* limits the proliferation of *S. aureus* and *S. pyogenes* by maintaining an acidic pH of the pilosebaceous follicle due to hydrolysis of sebum triglycerides and by secreting propionic acid (Ramasamy et al., 2019).

Phylogenetic, biochemical and microscopic analysis of *C. acnes* reveal six distinct phylotypes IA1, IA2, IB, IC, II, and III. Phylotype IA1 is the predominant phylotype isolated from skin of acne patients compared to healthy subjects and exhibit more efficient adhesion, mature biofilm production, and antibiotic tolerance than other phylotypes. Chronic persistence of *C. acnes* and relapse after antibiotic therapy is strongly suggestive of biofilm related colonization, rather than multi-antibiotic-resistant genes (Cavallo I et al., 2022).

Usually, any modification of the natural microbiome composition lead to a disturbed skin barrier, i.e. "dysbiosis" triggering innate immunity and inflammation. The loss of phylotype diversity in acne and dominance of IA1 strains is the "dysbiotic" shift that trigger inflammation in acne.

Genetic Findings

The following genes are postulated to play a role (Hang AHS, et. al, 2021):

- Sebocyte growth and lipid production: EGRF, IL-6, IL-8, VDR
- Androgen metabolism: AR, ADH7, DDB2, PPARG, CYP17A1, CYP19A1, CYP1A1, HSD11B1, HSD3B1, HSD17B3
- Lipid production: IGF1, TGFB2, FST, OVOL1
- Sebaceous gland development: WNT10A, LGR6, SPEC1L, LAMC2
- Sebaceous gland defence: MUC1
- NLRP3 inflammosome pathway: IL-1B, NLRP3

- TGF-beta 2
- TLR signalling: EGFR1, IL-1A, IL1RN, IL-8, IL-10, MAPK11, MMP2, TIMP, TLR2, TLR4, TNF, TNFR2
- Pro-inflammatory factors: ACE, IL-6, IL-17A, IL-17F, IL-23R, RETN, TNF
- Immune and inflammatory response: IL-4, IL-4R, ITLN1, SELL, SEMA4B, TYK
- Hair follicle development: GLI2
- Unclear mechanism: BCL11A, F13A1, FGF2, RORC, PINX1

Diet and Acne

A diet rich in dairy protein and high glycemic index carbohydrates may induce acne by various mechanisms as depicted in **Boxes 1.3 and 1.4**.

Box 1.3 Interplay between FoxO1 and mTORC1 in acne

- The cell's nutritional status is primarily sensed by the forkhead box transcription factor O1 (FoxO1) and the serine/threonine kinase mammalian target of rapamycin complex 1 (mTORC1).
- High glycemic load and dairy protein consumption both increase insulin/insulin-like growth factor-1 (IGF-1) signaling.
- FoxO1 reduces IGF-1 secretion by liver, sebaceous gland lipogenesis, androgen signaling, oxidative stress and enhances antimicrobial peptide (AMP) synthesis.
- Conversely, mTORC1 stimulates gene transcription and translation, protein synthesis, cell growth, cell proliferation and lipid synthesis. An abundance of dairy and meat protein overactivates mTORC1, leading to increased proliferation of acroinfundibular keratinocytes, sebaceous gland hyperplasia and lipogenesis.
- FoxO1 acts as a rheostat regulating mTORC1 under normal conditions. Insulinotropic diets impair gene regulation by FoxO1 and lead to unchecked activity of mTORC1.

Box 1.4 Effects of diet on acne

Dietary agent	*Mechanism*
Milk, whey protein	Fuels FOXO1/mTORC1/SREBP-1c-regulated sebaceous gland hypertrophy and lipogenesis Promotes IGF-1 synthesis Promotes anabolic mTORC1 signalling Inhibits mRNA expression of PTEN, which downregulates nuclear FoxO1
Chocolate	Increases cytokine production, esp. IL-1 beta
High glycemic index carbohydrates	Increase IGF-1 level, decrease IGFBP3 level
Fish, curcumin, silymarin, resveratrol (↓ acne)	Decrease inflammation Suppress sebaceous gland lipogenesis Inhibit SREBP-1
Omega-3 fatty acids (↓ acne)	Suppress production of inflammatory cytokines Decrease IGF-1 level Inhibits TLR-1 and TLR-2 signaling Inhibits mTORC1 signaling Downregulates SREBP-1c pathway
Meat	Promotes anabolic mTORC1 signalling
Alcohol	Disrupts cutaneous microbiome
Smoking	Alter sebum composition, promote follicular hyperkeratinization Increase inflammation via oxidative stress

FoxO1-forkhead box transcription factor O1, mTORC1-serine/threonine kinase mammalian target of rapamycin complex 1.

Q Which food ingredients are associated with acne?

LESIONS OF ACNE

Comedones

The earliest lesion to develop. Can be open ("blackheads") or closed ("whiteheads") **(Fig. 1.4)**. Open comedones allow oxidation of the debris within the follicle leading to the black color. Types of comedones are as follows:

- Sandpaper comedones—multiple, very small whiteheads usually on the forehead. Give a gritty feel to the skin and respond poorly to treatment.
- Macrocomedones—large whiteheads >1 mm in diameter. Respond poorly to treatment.
- Submarine comedones—large comedones >0.5 cm in diameter. Reside deep within the skin and associated with recurrent nodules.

Inflammatory Lesions

Papules, pustules (<5 mm), nodules (>5 mm) which often heal with pigmentation **(Figs 1.5 and 1.6)**.

Sinus tracts may form between deep-seated nodules leading to scarring.

Post-acne macular erythema or post-inflammatory erythema may persist for many weeks.

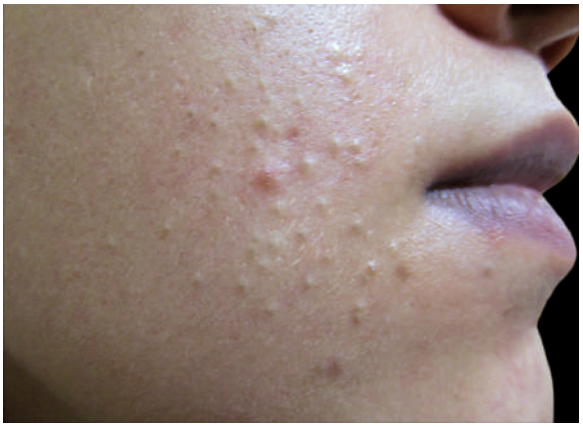

Fig. 1.4: Multiple comedones in a case of mild acne

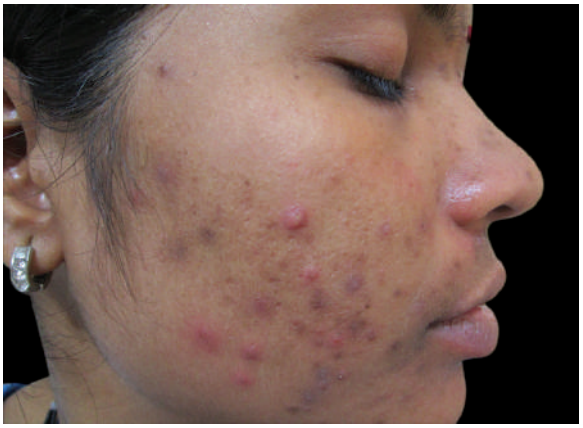

Fig. 1.5: Multiple papules, pustules and associated PIH in a case of acne

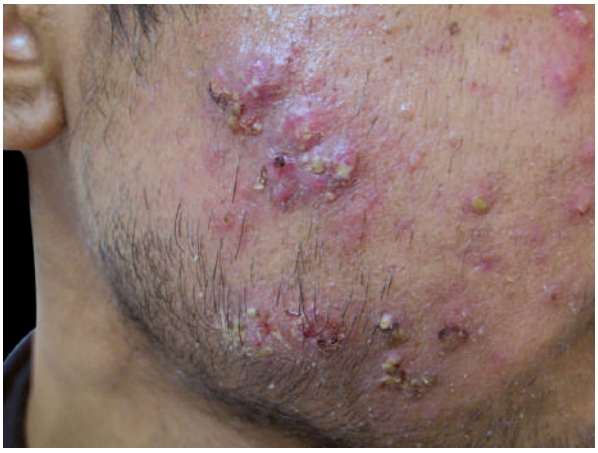

Fig. 1.6: Nodules and pustules in a case of acne

CLINICAL VARIANTS OF ACNE

- **Adult female acne (AFA)/post-adolescent acne (Fig. 1.7)**
  - *Androgen source in females*: Androgen excess disorders manifest by an interaction between circulating androgen levels and the sensitivity of hair follicles to androgen stimulation **(Fig. 1.8)**. In women, the major circulating androgens (in descending order of serum concentration) are dehydroepiandrosterone sulfate (DHEA-S), dehydroepiandrosterone (DHEA), androstenedione, testosterone, and DHT. DHEA-S, DHEA, and androstenedione can be considered prehormones because they have a little or no intrinsic androgenic activity and require conversion to testosterone to exert androgenic effects. DHEA-S is produced almost exclusively by the adrenal glands, DHEA is produced by both the adrenals (50%) and the ovaries (20%) and by peripheral conversion of DHEA-S (30%). Androstenedione production is divided equally between the ovaries and the adrenals

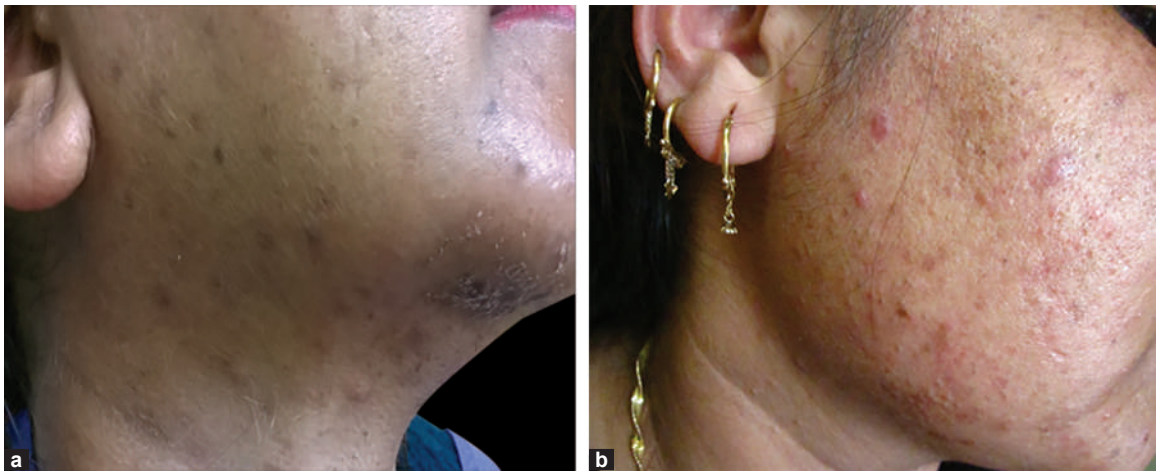

Fig. 1.7: Hormonal or adult female acne has usually jawline acne with hirsutism with signs and symptoms of hyperandrogenism including ovulatory dysfunction (manifesting as irregular menstrual cycles)

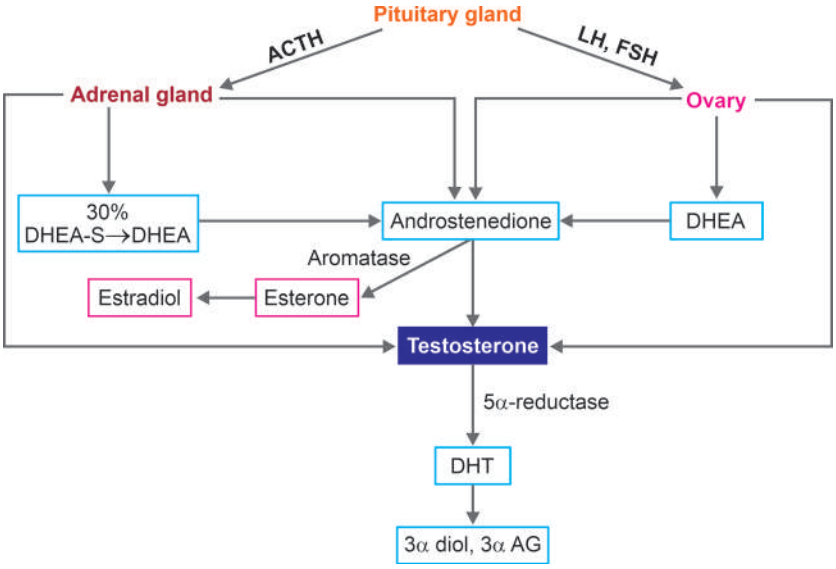

Fig. 1.8: Pathway showing the production and distribution of preandrogens and testosterone and its end organ metabolites which determine hormonal acne

and testosterone production derives from the adrenals (25%), the ovaries (25%), and from peripheral conversion of androstenedione (50%) **(Fig. 1.8)**. In normal women, about 80% of circulating testosterone is bound to a beta globulin known as sex hormone-binding globulin (SHBG), another 19% is loosely bound to albumin, leaving only about 1% unbound or free. 3α-androstanediol is the peripheral tissue metabolite of DHT, and its glucuronide conjugate, 3α-androstanediol glucuronide (3α-AG), can be used as a marker of peripheral androgen metabolism specially in those with normal testosterone levels. The common etiology of androgen excess is listed in **Table 1.1**.

- Clinical manifestations of hyperandrogenism include hirsutism, acne, androgenic alopecia, and virilization. Hirsutism, defined as excessive growth of terminal hair in women in a male-like pattern, is the most commonly used clinical diagnostic criterion of hyperandrogenism. The presence of hirsutism is usually determined by using a standardized scoring system of hair growth and may be seen in up to 80% of patients with hyperandrogenism. Acne and androgenic alopecia are other common androgenic skin changes, and might be observed without hirsutism in some hyperandrogenic women. However, isolated presence of any of these manifestations is not usually considered as a diagnostic criterion for hyperandrogenism. Virilization is a relatively uncommon feature of hyperandrogenism, and its presence often suggests an androgen-producing tumor. A thorough history and a focused clinical examination are extremely helpful in diagnostic evaluation of patients with suspected hyperandrogenism (Yildiz BO, 2006).
- Adult female acne (AFA)/hormonal acne is acne beyond 25 years of age, predominantly distributed in the lower third of the face, and present either as "isolated" acne or with hyperandrogenic signs. AFA can be (a) persistent, (b) late-onset type or recurrent. Two clinical types are seen: (i) Inflammatory (commonest) or (ii) retention type (non-inflammatory). Hormonal workup usually reveals underlying PCOS. End-organ hypersensitivity is the mechanism and anti-androgens benefit (Bansal et. al. 2021).

Q Detail the androgenic pathway and discuss adult female acne.

Table 1.1 Androgen excess disorders among women (Azziz et al., 2004)

Diagnosis	Number	Prevalence (%)
Specific disorders		
Androgen-secreting neoplasm	2	0.23
Classical congenital adrenal hyperplasia	6	0.69
Nonclassical congenital adrenal hyperplasia	18	2.06
Hair-AN syndrome	33	3.78
Disorders of exclusion		
Polycystic ovary syndrome	716	82.02
Idiopathic hirsutism	39	4.47
Hyperandrogenemia, hirsutism, and normal ovulation	59	6.75
Total	873	100.00

  - In a recent study, the late onset type was most common (56.6%) but the persistent acne type (43.33%) had a younger age at onset, past history of adolescent acne (51.92%), truncal predilection (44.23%), polycystic ovary syndrome (PCOS) (44.23%), irregular menses (40.38%), hirsutism (57.69%), increased TT (13.46%), 17-OHP (76.92%), AMH (44.23%), and increased LH/FSH (15.38%) ratio. PCOS was seen more in the persistent acne patients with clinical HA and increased 17-OHP levels (Sardana K et. al., 2012).

- **Acne fulminans:** This is a rare acute severe variant predominantly occurring in adolescent males. Sudden onset of ulcerative, necrotic acne covered with hemorrhagic crusts, fever, arthralgia, and other systemic symptoms occur. Clinical variations include acne fulminans (i) with systemic symptoms, (ii) without systemic symptoms, (iii) isotretinoin-induced with systemic symptoms, isotretinoin-induced without systemic symptoms. Hypotheses proposed include (i) genetic susceptibility, (ii) *C. acnes* behaves as a superantigen, triggering an exaggerated antibody response, (iii) hormonal changes, (iv) viral illness (following measles), (v) iatrogenic (isotretinoin, also doxycycline, erythromycin, lymecycline, oxytetracycline, methylprednisolone, interferon-α-2a). Treatment involves prednisone monotherapy for 2–4 weeks followed by low-dose isotretinoin for 4 weeks, then slowly increase isotretinoin (to avoid paradoxical flare during the acute inflammatory phase). Others: Topical/intralesional corticosteroids, oral antibiotics, TNF-inhibitors, IL-1 antagonists, azathioprine, cyclosporine, dapsone.
- **Acne conglobata:** This is a severe chronic acne variant with multiple grouped (polyporous) comedones, interspersed with papules, and tender inflammatory nodules which may be suppurative and coalesce to form sinus tracts with extensive scarring as usual outcome. Systemic symptoms may be present but not mandatory. Part of **follicular occlusion tetrad:** Dissecting cellulitis of scalp, hidradenitis suppurativa, pilonidal cyst, acne conglobata.

  Treatment is with low dose isotretinoin with concomitant short course of prednisolone for around 2 weeks (to prevent paradoxical flare of acne due to iostretinoin).

  Other **syndromes** associated:
  - PAPA-sterile pyogenic arthritis, pyoderma gangrenosum, acne conglobata (PSTPIP1 mutation)
  - PAPASH-pyogenic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis

- Acne associated with **psychiatric disease:**
  - Acne excoriee
  - Body dysmorphic disorder
  - Eating disorders
- **Granulomatous acne**
- **Neonatal acne and neonatal cephalic pustulosis:** Neonatal acne is seen in >20% healthy newborns around 2 weeks of age, resolves within 3 months. Inflamed papules and pustules appear on nasal bridge and cheek, without comedones. Neonatal cephalic pustulosis presents with similar but widespread papulopustular lesions over face, scalp, upper chest and back, and shoulders.
- **Infantile acne:** Between 3–6 months to 2 years and is due to transient increase in androgen secretion (by the immature adrenals) and luteinizing hormone by the pituitary (stimulating testosterone production). Both inflammatory and non-inflammatory lesions are seen. Topical retinoids or benzoyl peroxide form the mainstay of treatment.
- **Mid-childhood acne:** Seen in children between 1 and 7 years, possibility of underlying hyperandrogenic condition should be considered.
- **Preadolescent acne:** Presents between 7 and 12 years of age with prominent comedo formation, pitted scarring, occasional deep suppurative nodules.
  Resolves within 6–18 months but associated with severe acne during adolescence.

A list of acneiform eruptions is listed in **Table 1.2**.

Table 1.2 Variants of acne/Acneiform eruptions

- **Drug-induced acne:** Anabolic steroids, bromides, corticosteroids, EGFR inhibitors, iodides, isoniazid, lithium, MEK inhibitors (trametinib), phenytoin, progestins
- **Occupational acne:** Comedones with papules, pustules, cystic lesions due to exposure to insoluble, follicle-occluding substances such as cutting oils, petroleum-based products, chlorinated aromatic hydrocarbons, coal tar derivatives
- **Acne cosmetica:** Comedonal acne (mostly closed comedones) due to chronic exposure to follicle-occluding cosmetics
- **Pomade acne:** Comedonal facial acne at the forehead and temples due to follicle-occlusion by hair products
- **Chloracne:** Occurs several weeks after systemic exposure to halogenated aromatic hydrocarbons (percutaneous absorption, inhalation, ingestion)—found in insecticides, insulators, fungicides, herbicides, wood preservatives
- **Acne mechanica:** Comedo formation due to repeated mechanical and frictional obstruction of pilosebaceous unit
- **Tropical acne:** Acneiform eruption after exposure to extreme heat
- **Radiation acne:** Comedo-like papules at sites of previous exposure to therapeutic ionizing radiation
- **Pseudoacne of the nasal crease:** Transverse nasal crease with milia, cysts, and comedones lining up along the fold
- **Idiopathic facial aseptic granuloma:** Affects young children, usually single painless nodule on cheek, resolve spontaneous after 1 year
- **Childhood flexural comedones:** Discrete, double-orifice comedones localized to axillae > groin, usually single lesion, with no association with hidradenitis suppurativa, acne vulgaris, or precocious puberty

INVESTIGATIONS FOR ACNE

Microbiological and Endocrinological Work-up (Table 1.3)

- Routine microbiologic testing is not recommended except when the acne-like lesions are suggestive of gram-negative folliculitis.

- Routine endocrinologic evaluation (e.g. for androgen excess) is not recommended except in AFA and when there are signs of androgen excess. Indications for testing for hormonal acne and the suggested tests are listed in **Table 1.4**.

Table 1.3 List of investigations in acne

Test for organisms	• Pyogenic bacterial folliculitis due to *Staphylococcus aureus* which may mimic acne • Gram negative folliculitis • Malassezia folliculitis • Tinea faciei due to a dermatophyte fungus such as *Trichophyton rubrum* or *Microsporum canis* • In suspected cases of resistance culture and 16-S-RNA verification of *C. acnes*
Hormonal tests	• Possibility of pregnancy, which would influence what treatment is appropriate • Signs suggesting hyperandrogenism including PCOS and NCCAH • Signs suggesting excessive prolactin • Signs suggesting Cushing syndrome
Imaging	• USG, CT, MRI whenever indicated
Tests for monitoring Rx	• LFT, lipids and UPT

Table 1.4 Work up in a suspected case of hormonal acne*

When to evaluate for a hormonal cause?	• Postadolescent acne/acne tarda • A male patient who has cystic acne and has failed therapy • Prepubertal children with acne, early-onset body odor, axillary or pubic hair, accelerated growth, advanced bone age, and genital maturation • A female patient who has failed multiple courses of recommended therapy • Signs of hyperandrogenism • In women, polycystic ovary syndrome (PCOS) • Rapid appearance of acne in conjunction with virilization suggestive of an underlying adrenal or ovarian tumor • Patients with Cushing's disease or syndrome and late-onset congenital adrenal hyperplasia
Which tests to perform	• Total testosterone and free androgen index • DHEA-S • Prolactin • TSH • Anti-Mullerian hormone (AMH) (a sensitive tool to diagnose PCOM: Polycystic ovarian morphology) and PCOS • 17-hydroxyprogesterone (to diagnose nonclassic congenital adrenal hyperplasia [NCCAH]) • USG, CT, MRI whenever indicated

*Performed on the 5th day of the cycle with avoidance of any hormonal treatment in the past 3 months.

Endocrinological Investigations

The aims of investigations are **twofold:**

a. To elicit the source of androgens

b. To eliminate the common causes and differentials including PCOS.

Testosterone levels are usually the best way to start the investigative profile and its levels can predict the possible causes. As free testosterone levels are erratic and inconsistent due to lack of sensitive tools and its miniscule levels in the blood, free androgen index (FAI) is calculated.

Diagnosis of PCOS requires a transvaginal(TV) USG which is the gold standard. Unmarried patients may not consent for a TV USG, Also a transabdominal USG is not sensitive in obese females (Bell et al., 2021). There is no evidence that the presence of PCOM has any implications with regard to the endocrine or metabolic features of PCOS. Although large body of evidence suggests that assessment of PCOM is not needed for the endocrine management of PCOS or hirsutism, an endocrinologist or gynaecologist opinion may be helpful before start of hormonal treatment.

A recent study (Bansal et. al. 2020) found that AFA with PCOS had significant clinical hyperandrogenism, truncal and adolescent acne, and raised hormones (AMH, TT, FAI, LH, and LH/FSH). The **AMH levels** were significantly higher in the PCOS group (6.91 ± 3.85 ng/mL) and positively correlated with TT, FAI, 17OHP, LH, and LH/FSH ratio. AMH at >5.1 ng/mL (sensitivity-70.97% and specificity-82.02%) predicted PCOS and correlated with PCOM. Thus AMH (>5.1 ng/mL) is a sensitive tool to diagnose PCOS (Bansal et al., 2020). This test can have a variation due to the assay used, but as a general rule higher the value "beyond 5", more the chances of PCOS (Rudnicka et al., 2021) and this is a more sensitive tool than USG for diagnosis of PCOM.

It is important to note that values of various tests depend on the reference values which vary between laboratories. A few **cut-off values** that can be used to diagnose hyperandrogenism and include:

- Normal levels of total testosterone should not exceed 1.1 ng/mL (54.5 ng/dL)
- Normal levels of DHEA should not exceed 430 µg/dL
- FAI should not exceed 5
- AMH beyond 5 ng/mL indicates PCOM.

The interpretation of tests depends on the experience of the clinician and an important adage is to minimize unnecessary tests.

TREATMENT OF ACNE

The therapeutic agents can be classified according to the major pathogenic steps they modify in acne **(Fig. 1.9)**, though some would work on more than one of the major factors.

The American Academy of Dermatology (AAD) guidelines on management of acne vulgaris, 2024 (Reynolds RV et. al., 2024) are listed in **Table 1.5**.

An overview of the current treatment guidelines are depicted in **Figs 1.10 and 1.11** and the details are given in the text below.

General measures include use of non-comedogenic products and avoidance of excessive hair oil (common cause of forehead acne).

Table 1.5	Recommendation for the management of acne vulgaris in adults, adolescents, and preadolescents (>9 years) from the American Academy of Dermatology (Reynolds, Rachel V. et al. 2024)
Topical therapy	1. Strong recommendations for topical benzoyl peroxide, topical retinoid as monotherapy 2. Strong recommendation for fixed dose combination of a. topical antibiotic with benzoyl peroxide b. topical retinoid with topical antibiotic c. topical retinoid with benzoyl peroxide 3. Not recommended—topical antibiotic monotherapy 4. Conditional recommendation for a. topical clascoterone, b. topical azelaic acid c. topical salicylic acid
Good practice statement	• Recommendation is for multi-modal topical therapy combining multiple mechanisms of action
Systemic therapy	1. Strong recommendation for doxycycline. 2. Conditional recommendation for minocycline, sarecyclin.
Good practice statement	• Recommendation is to limit the use of systemic antibiotics, to reduce antibiotic resistance and antibiotic associated complications • Recommended that systemic antibiotics are used concomitantly with benzoyl peroxide and other topical therapy.
Hormonal therapy	1. Conditional recommendation for a. oral contraceptive pills b. spironolactone
Good practice statement	• Recommendation for intralesional corticosteroid injections into larger papules or nodules
Isotretinoin	1. Conditional recommendation for a. either standard isotretinoin or lidose isotretinoin b. daily dose over intermittent dose
Good practice statement	• Recommendation for isotretinoin a. severe acne b. who have failed standard treatment with oral or topical therapy c. with psychosocial burden or scarring

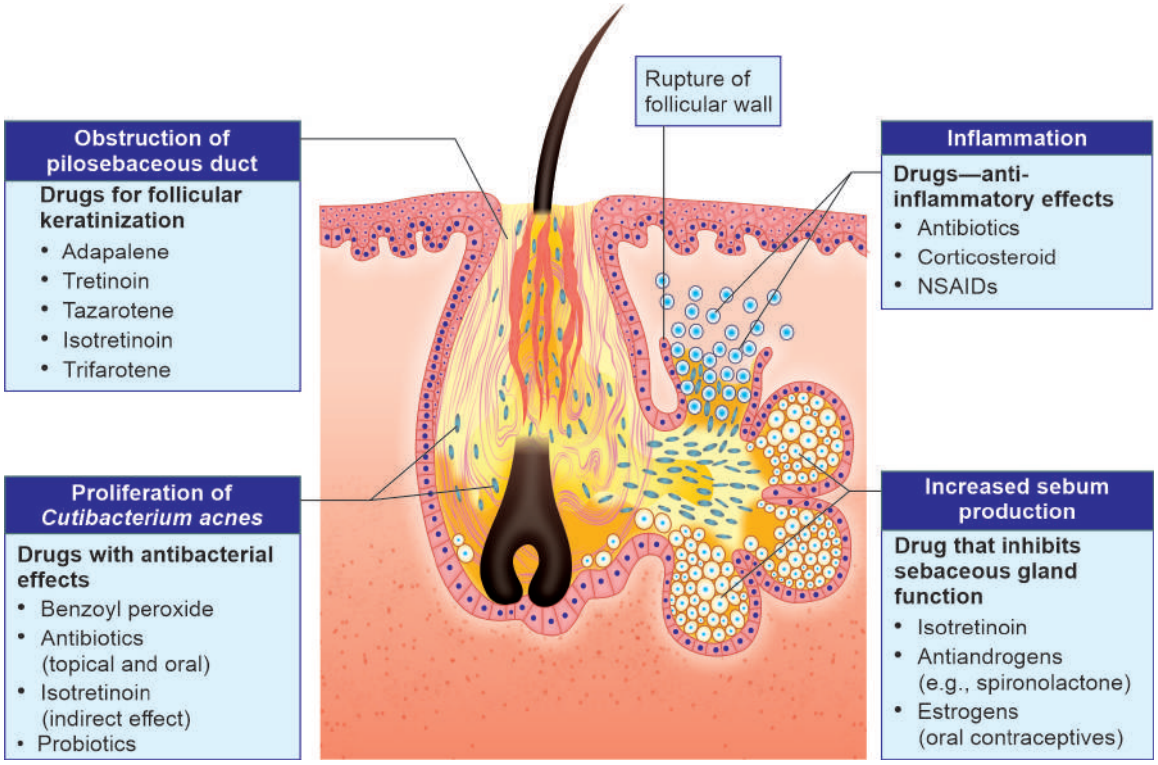

Fig. 1.9: Overview of the major targets of therapeutic agents in acne vulgaris

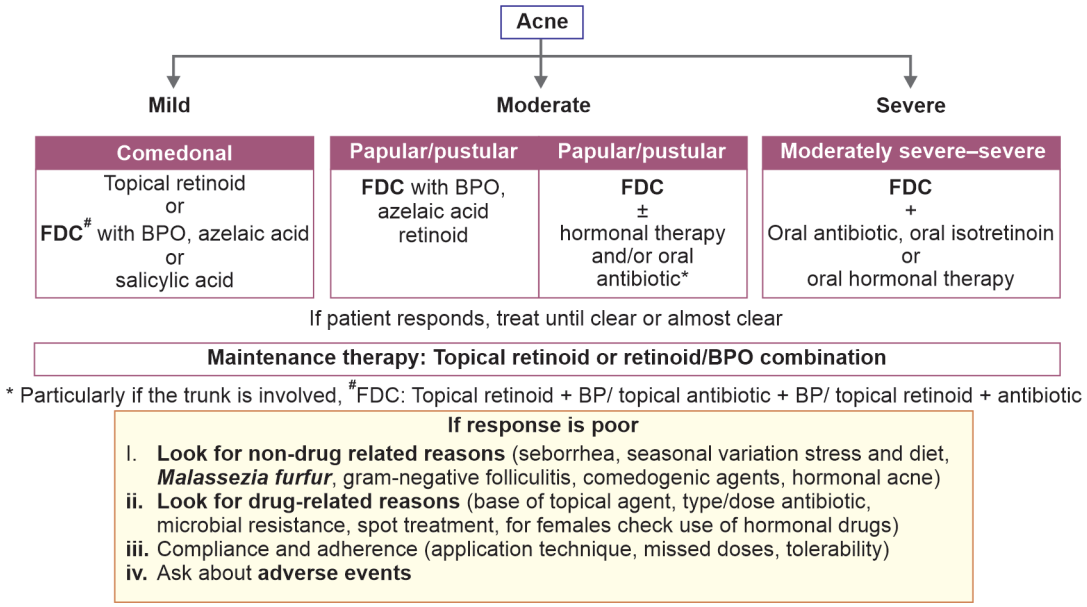

Fig. 1.10: Overview of standard treatment for various grades of acne

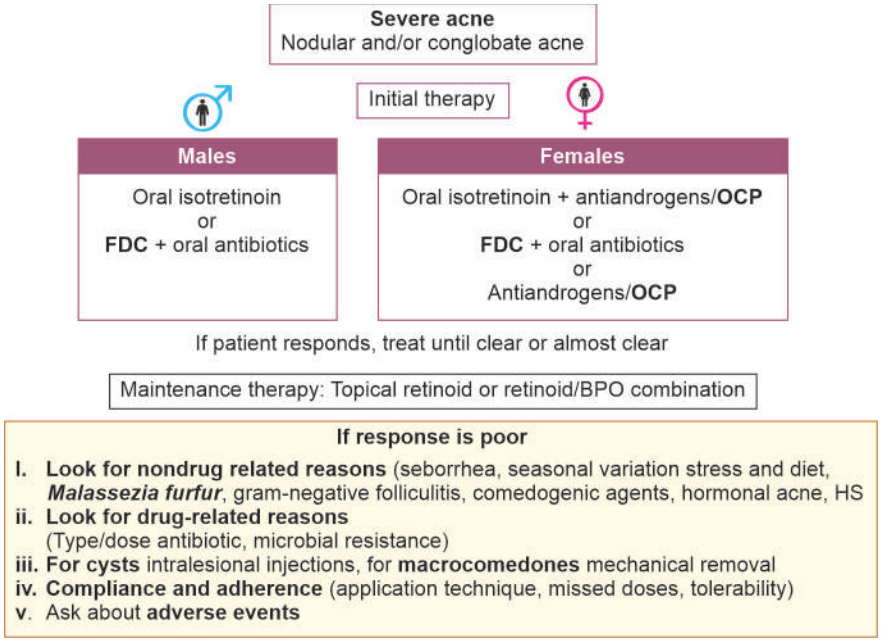

Fig. 1.11: Management of severe acne

1. Topical Agents

Common topical agents are listed in **Table 1.6A**. A recent systematic review and network meta-analysis on topical treatment of mild-to-moderate acne concluded that adapalene plus benzoyl peroxide may be the most effective therapy but with a slightly higher incidence of withdrawal (Stuart et. al., 2021).

Table 1.6A Overview of topical agents*

Benzoyl peroxide (BPO)	If irritation is not a factor, BP alone or in combination with clindamycin is an effective treatment and recommended as monotherapy for mild acne, or in conjunction with a topical retinoid, or systemic antibiotic therapy for moderate to severe acne.
Topical antibiotics	Avoid as monotherapy
Retinoids	Ideal initial agents and can be used alone for comedonal acne, or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions.
Azelaic acid	Aside from retinoids, azelaic acid is a useful adjunctive acne treatment and is recommended in the treatment of postinflammatory dyspigmentation
Topical dapsone 5% gel	In adult female acne
Combination agents	Stable, fixed-combination agents are available with erythromycin 3%/BPO 5%, clindamycin 1%/BPO 5%, and clindamycin 1%/BPO 3.75%., adapalene 0.3%/benzoyl peroxide 2.5%.

*Sardana K, Narang I; IADVL *Textbook of Dermatology*, 5th edn, 2022.

Novel Topical Agents (Table 1.6B)

Table 1.6B Novel topical agents

Name	Mechanism of action
Available in market	
Trifarotene 0.005%	Novel 4th-generation retinoid, selective for γ-RAR
Clascoterone 1%	Androgen receptor inhibitor, block DTH action on sebocytes
Minocyclin 4%	Antibiotic; only gel formulation in India; foam not available
Under clinical trial	
JNJ 10229570	Melanocortin receptor antagonist, ↓α-MSH induced sebogenesis;
Cortexolone 17a-propionate 1%	Inhibit androgen-dependent sebum production
Olumacostat Glasaretil 5%	Acetyl coenzyme A carboxylase (ACC) inhibitor
NVN1000 gel or SB204	Inhibit androgen-dependent sebum production
Lupeol 2%	↓ lipogenesis via (Pl3K)/SREBP signaling pathway
Epigallocatechin-3-gallate (EGCG) 1%, 5%	Inhibits 5α-reductase-1 activity
N-Acetyl-GED-0507-34-LEVO 5%	Selective (PPAR-γ) modulator
NAI-Acne gel 3%	Antibacterial against *C. acnes* via inhibition of protein synthesis
MBI 226 2.5%, 5%	Antimicrobial peptide
Tyrothricin 0.1%	Antimicrobial peptide
Cetomacrogol	*C. acnes* bacteriophage
Vit C 5%	Antioxidant
NO-np	Nitric oxide-releasing nanoparticle, antimicrobial, anti-inflammatory
Next Science Acne Gel (NAG)	Causes *C. acnes* biofilm degradation

2. Systemic Agents

Recommendations for Antibiotics

Systemic antibiotics have been the mainstay of acne treatment for years and are probably the most misused drugs even though elaborate guidelines have been made to restrict their misuse. Evidence supports the efficacy of erythromycin, azithromycin, amoxicillin, tetracycline, doxycycline, minocycline, trimethoprim, trimethoprim/sulfamethoxazole (TMP/SMX), and cephalexin. An overview of the general principles that dictate use of systemic agents is given in **Table 1.7**. A pilot study confirmed high antibiotic resistance of *P. acnes* (identified by 16S RNA PCR) and the antibiotic sensitivity pattern in India is depicted in **Fig. 1.12**. The study concluded that minocycline works better in India, **not** azithromycin (Sardana K, et al.,2021).

Sarecycline is a once-daily, oral, narrow-spectrum, tetracycline-derived antibiotic with anti-inflammatory properties. At 1.5 and 3.0 mg/kg, it significantly reduced inflammatory lesion counts (no difference in non-inflammatory lesions) from baseline compared with placebo (by 52.7%, 51.8%, and 38.3%, respectively), in a phase 2 trial of patients with moderate or severe acne. Sarecycline, being a narrow-spectrum tetracycline, is notable for being very effective against *Cutibacterium acnes* without affecting other bacteria and thus seems to preserve the natural microbiome. It is available in India as SEYSARA® (sarecycline) tablet.

Q Discuss the role of antibiotics in acne in view of resistance data in India.