23.11 Sebaceous and sweat gland disorders 5699 Ali

23.11 Sebaceous and sweat gland disorders 5699 Alison M. Layton

ESSENTIALS Cutaneous glands in humans include holocrine or sebaceous glands and merocrine or sweat glands. Merocrine glands are subdivided into apocrine, eccrine, and apoeccrine glands. Disorders of each of these cutaneous glands have been associated with disease. Apocrine glands in adults are found predominantly in the axillae and anogenital regions, with a few located in the ear canal (ceru- minous glands) and eyelids (Moll's glands). Disorders associated with apocrine glands include hidradenitis suppurativa, Fox–Fordyce dis- ease, bromhidrosis, trimethylaminuria, and chromhidrosis. Eccrine glands are the sweat-producing glands of the skin. Many drugs and systemic diseases can influence the degree of sweating, such as thyroid disease, infection, carcinoid, and cholinergic drugs. In cystic fibrosis, the concentration of sodium chloride in sweat is increased. Sebaceous glands form part of the pilosebaceous unit and are found over the entire body surface, with the exception of palms and soles. They are under the influence of androgenic hormones. Acne is a common inflammatory skin disease often associated with significant psychosocial morbidity. Early effective intervention reduces emotional and physical scarring. An understanding of pathophysiology allows top- ical and systemic therapies to be combined logically to target therapy. Disorders of apocrine glands Apocrine glands are compound sweat glands with a secretory coil that extends deep through the dermis into subcutaneous tissue and drains via a long, straight secretory duct, into a hair follicle. Their function in man is not altogether clear, but in other mammals they are responsible for sexual attraction and scent production. This is re- sponsible for axillary and inguinal odour. The glands become larger and functionally active at puberty. The secretion is opalescent and malodorous. The glands are innervated by adrenergic fibres of the sympathetic nervous system. Hidradenitis suppurativa (HS) synonymous
with acne inversa Introduction This is a chronic, inflammatory, suppurative disease affecting apocrine-gland bearing skin sites, including the axillae, groins, perineum, and/or submammary area (in women). Hidradenitis suppurativa has a predilection for intertriginous regions, the ax- illae

and inguinoperineal regions being the most commonly affected (see Figs. 23.11.1 and 23.11.2). The extent and severity of disease varies, most patients have more than one major site involved but some patients have relatively mild forms of the disease. It is a chronic disabling disease that generally progresses with time and frequently causes scarring, contractures, and significant morbidity for patients. Aetiology and epidemiology The aetiology of hidradenitis suppurativa is unclear; there is a female predominance with a ratio of 3:1 and it is associated with obesity and smoking. There is a significant risk of increased cardiovascular associated death in patients with hidradenitis suppurativa compared with controls, in keeping with high rates of smoking, type II dia- betes, hypertension and hyperlipidaemia. Hidradenitis suppurativa is associated with acne and pilonidal sinuses as well as Crohn's dis- ease. The incidence in England is said to be around 1:600. Patients of African descent have been reported to have a higher prevalence than Europeans which might reflect the higher density of apocrine glands in black versus white skin. The age of onset ranges from 11 to 50 years, but it is very rare to see hidradenitis suppurativa before pu- berty or after the menopause. A familial form of the condition with autosomal dominance has been described. Specific bacteria (e.g. an- aerobic streptococci like Streptococcus milleri) have been reported in hidradenitis suppurativa and although cultures are frequently sterile, microbiological assessment allows treatment to be based on documented sensitivities. Pathogenesis Hidradenitis suppurativa was first described as a clinical entity in 1839 by Velpeau who described a patient with superficial abscesses in the axillary, perianal, and mammary regions. In 1854 Verneuil associated the suppurative condition with sweat glands. In 1922 the sweat glands were classified as apocrine and eccrine and it was suggested that hidradenitis was localized to the apocrine glands. Occlusion of the follicular infundibula is the initial event in patho- genesis and a defect of the terminal follicular epithelium is recog- nized. This is followed by inflammation of the apocrine glands and rupture of the follicles. The disease is sometimes referred to as acne inversa, reflecting the similarities to acne in terms of the follicular occlusion but the locations are inverse to acne and no increase in 23.11 Sebaceous and sweat gland disorders Alison M. Layton

section 23 Disorders of the skin 5700 sebum secretion is seen in hidradenitis suppurativa. A family his- tory of hidradenitis suppurativa is reported in up to 42% of cases and the condition can represent an autosomal dominant inheritance in some kindreds. Recent familial studies have reported heterozygous mutations in the γ-secretase genes PSEN1, PSENEN and NCTSN. In animal models alteration in the γ-secretase gene expression can re- sult in follicular occlusion. Clinical features A consensus approach suggests that three key elements are required to diagnose hidradenitis suppurativa. These include typical lesions, characteristic distribution, and recurrence. Typical primary lesions embrace painful and/or tender erythematous papules, painful or tender abscesses, and inflamed discharging papules or nodules, dermal contractures, and rope-like elevation of the skin and double- ended comedones. The groins and axillae are the most frequently affected sites. As a result of associated pain, purulent discharge, malodour and the involvement of sensitive and intimate areas, hidradenitis suppurativa can result in significant morbidity and impact on many aspects of quality of life. Diagnosis and differential diagnosis Some authors have based the diagnosis on several questions, including: Is there more than one inflamed lesion? Is the course chronic, are le- sions bilateral, and are lesions located to the primary milk line? Distinction from septic furunculosis can be difficult in the early stages. Clinical investigations The diagnosis is primarily a clinical one and diagnostic biopsy is rarely required. Microbiological culture might be helpful as might histological examination. Treatment Treatment is notoriously difficult. Many patients are smokers but smoking cessation does not universally result in improvement of

hidradenitis suppurativa. Reducing friction and moist hot envir- onments, together with weight reduction and cotton clothing will help some patients. Laser hair removal can be beneficial in some patients. Localized inflammatory lesions benefit from intralesional injections using triamcinolone (5 mg/ml). Small studies have shown a combination of oral clindamycin (300 mg twice daily) and rimfampicin (600 mg daily) is beneficial. Systemic antibiotics, including erythromycin 500 mg twice each day or minocycline 100 mg daily, are frequently used but topical clindamycin lotion is the only antibiotic that has been shown to be beneficial in a double-blind, placebo-controlled trial. Systemic steroids frequently produce improvement but recurrence is usual on withdrawal. Antiandrogen therapy alone as cyproterone acetate or in com- bination with ethinylestradiol has been used successfully in some women as has spironolactone; Finasteride, the 5-α reductase in- hibitor, has also been tried. Isotretinoin produces minimal benefit and the longer acting retinoid acitretin 25 mg daily has shown more promise. Ciclosporin A and tumour necrosis factor-α (TNFα) in- hibitors have demonstrated improvement in refractory disease. Clinical trials using adalimumab, an IgG monoclonal antibody spe- cific for TNFα, and infliximab have produced good results in some patients. Good results have also been reported following radical surgical excision of involved areas with laying open of sinus tracts. More limited surgical intervention, consisting of unroofing abscesses and sinus tracts and leaving to heal with secondary-intention have also proved effective in some patients. Nonablative radiofrequency has also been used for certain stages of disease. Prognosis/outcome Hidradenitis suppurativa is a chronic disabling disorder and has a tendency to progression with recurrent episodes of painful inflam- mation and resultant scarring. Patients frequently have to have time off work and negative impact on quality of life is significant.

Fox–Fordyce disease Introduction Fox–Fordyce disease represents a papular eruption localized to apo- crine glands. Aetiology and epidemiology This is seen most frequently in females in a ratio of 9:1. It is most commonly seen around 13–35 years and is rare outside this age range. There is no geographical influence or racial predilection al- though heat, humidity, and excessive sweating are often noted as exacerbating factors. Pathogenesis The histology reflects a keratin pug in the hair follicle infun- dibulum which obstructs the acrosyringium, resulting in apocrine anhidrosis. Rupture of the excretory duct then occurs, resulting in inflammation. Clinical features Light brown flesh-coloured papules appear in areas of apocrine glands around the breasts, vulva, and axillae in females and may occur around the glans in males. The lesions are frequently itchy and inflamed. Treatment If symptomatic, electrodessication or hyfrecation of the irrit- able lesions will help. Other treatments advocated include topical clindamycin lotion, ultraviolet radiation, topical retinoids, oral contraceptives, and systemic retinoids.

Bromhidrosis (synonymous with Bromihidrosis and body odour) Introduction Apocrine bromhidrosis is the most common form and should be discriminated from the less common eccrine bromhidrosis. Bacterial decomposition which liberates fatty acids will influence apocrine odour; this is most commonly from corynebacteria. Increased axillary pH might facilitate overgrowth of bacteria. In rare cases, bromhidrosis can become a significant chronic condi- tion which impacts negatively on the lives of certain individuals. Eccrine secretion is odourless when it is first excreted onto the surface of the skin but certain food substances (e.g. garlic,

 onion, curry, alcohol, and some drugs can cause eccrine bromhidrosis). Hyperhidrosis might contribute to apocrine bromhidrosis by encouraging a moist environment for overgrowth of bacteria. Aetiology and epidemiology This is considered a rare condition. Apocrine bromhidrosis is thought to be more common in black skin and, in Asian patients, might be associated with a family history. Males are more commonly affected which

might reflect greater apocrine activity in males. Axillary bromhidrosis presents exclusively in puberty and is rare in older people; conversely, eccrine bromhidrosis is more common in childhood but can occur at any age. Clinical features A family history is common and an autosomal dominant pattern of inheritance has been described. Pathogenesis Human apocrine glands appears to be under sympathetic ner- vous control alongside peripheral mechanisms regulated by catecholamines. Treatment Deodorants that lower the skin's pH will reduce the bacterial growth. Treatment of axillary bromhidrosis includes avoidance of relevant food substances, frequent washing, and local anti- bacterial substances. Surgical ablation of eccrine and apocrine glands can be beneficial in patients not helped by conservative approaches. Trimethylaminuria (TMAU) synonymous
with fish odour syndrome (FOS) Introduction Trimethylaminuria, also known as fish odor syndrome, is a psychologically disabling condition in which a patient emits a foul odour resembling that of rotting fish. Primary TMAU is most commonly caused by an inherited deficiency in flavin monooxygenase 3 (FMO3), the enzyme required for the metab- olism of trimethylamine (TMA), which is responsible for the odour found in sweat, urine, and breath. The disorder can cause profound psychosocial problems. While there is no cure, some simple treatment options can improve the quality of life of these patients. Aetiology Primary TMAU is caused by a deficiency in FMO3 resulting from an autosomal recessive inheritance. Under normal circumstances, dietary TMA precursors, such as choline, are ingested and then re- duced to TMA by colonic bacteria. The TMA passively diffuses and enters the enterohepatic circulation where it is removed and is oxi- dized by FMO3 into odourless compounds. Patients with primary TMAU lack adequate functional FMO3 and therefore experience an excess of foul-smelling TMA. Primary trimethylaminuria accounts for most cases, but there also exists secondary or acquired trimethylaminuria where FMO3 might still retain varying degrees of functionality. Secondary cases can occur in the setting of excess dietary burden as occurred after therapeutic administration of choline for the treatment of Huntington's chorea and Alzheimer's disease. Hepatic disease might serve as another cause, as in viral hepatitis, and this has also been reported in chronic kidney disease. Fish odour syndrome has been described transiently in early child- hood when FMO3 levels are minimal and in the perimenstrual period when steroid hormones might have caused a reduction in FMO3 expression. Clinical investigations The diagnosis is made on the basis of the clinical presentation and urinalysis. Urine can be analysed for the concentration of both TMA and TMAO, and the results may be given as an oxidizing ratio based on the formula TMAO/(TMAO + TMA) × 100%. A ratio of less than 84% should be observed in an affected in- dividual with two FMO3 inactivating mutations. Conversely, in- dividuals not affected with fish odour syndrome should have a ratio of greater than 92%. Many patients, in an attempt to reduce their odour, may have empirically tailored their diet to exclude TMA precursors, which could cause a false-negative test result. Therefore, it is critical to ensure that adequate substrate has been ingested in order to allow for maximum sensitivity; this can be achieved by loading the patient with a 300 g marine fish meal. Genetic testing is available. Treatment considerations Once the diagnosis has been established, there are several poten- tially helpful treatment options; however, no single regimen seems universally efficacious and no systematic study has been performed to test the various recommendations. A first step for the patient might be to wash frequently with an acidic soap (pH 5.5–6.5). The patient should be informed that the malodour will intensify with hyperhidrosis, fever, stress, and exercise. Reduction or exclusion of TMAO from the diet might help; this is found in high concentration in marine fish. Foods with high con- centrations of choline include eggs, mustard seeds, chicken and beef, and raw soybeans. Oral activated charcoal has been shown to elevate oxidizing ratios to greater than 90%.

Short courses of oral neomycin, metronidazole, and amoxicillin have been reported to be useful in some cases. The mechanism involves the destruction of gut bacteria, which are re- sponsible for the reduction of TMAO into TMA. Lactulose, which also acts in the alimentary canal, is another therapy that has dem- onstrated an ability to decrease urinary TMA. Patients should be offered psychological support. Complications Fish odour syndrome is often associated with significant psycho- social disturbances. Anxiety, social withdrawal, and depression can be an issue for these patients. Chromhidrosis Introduction Chromhidrosis represents a rare condition in which the apocrine sweat can be blue/black, yellow, or green resulting from the secretion

section 23 Disorders of the skin 5702 of lipofuscins. The more oxidized lipofuscins appear deeper in colour and the lighter coloured lipofuscins might fluoresce. The onset of coloured sweat starts in puberty and resolves in old age as apocrine function regresses. The axillae are most frequently affected, although areolar and facial chromhidrosis have been re- ported. Topical capsaicin may be beneficial. Aetiology and epidemiology Apocrine chromhidrosis is more common in black than white popu- lations but facial chromhidrosis is described only in white skinned individuals. There is no sex predilection. Pathophysiology Lipofuscin is a yellow-brown pigment normally found in the cyto- plasm of some cells. In chromhidrosis lipofuscins are found in a higher oxidative state or in higher numbers. It is unclear what causes the higher oxidative state. Pseudochromhidrosis represents a chem- ical on the surface of the skin that reacts with eccrine secretions, resulting in the colour transformation. Clinical presentation The sweat as just described, if coloured, and the yellow, green, or blue secretions fluoresce yellow under a Woods lamp in contrast to the dark brown and black secretions which do not. Disorders of eccrine glands Eccrine glands represent small tubular structures draining dir- ectly onto the skin surface. Up to four million sweat glands are present in all sites of the skin excluding mucous membranes, palms, soles, axillae, and forehead, the latter having the highest density. Sweat is formed by active secretion involving the so- dium pump. After tubular resorption of electrolytes and water the sweat becomes isotonic. Sweat contains sodium, potassium chloride, lactate, urea, and ammonia. The concentration of so- dium chloride in sweat is increased in cystic fibrosis. Sweat glands exhibit thermoregulatory control, the skin surface being cooled by evaporation. Eccrine glands are innervated by cholin- ergic fibres of the sympathetic nervous system and sweating can, therefore, be induced by cholinergic drugs and blocked by anti- cholinergic therapies. The preoptic hypothalamic sweat centre controls sweating centrally. Hyperhidrosis or excessive sweating Introduction Hyperhidrosis is an acutely embarrassing condition involving excess production of sweat and can manifest itself as generalized or local- ized disease. Aetiology and epidemiology The incidence rate is reported as 0.6–1% in adolescents. Localized palmoplantar hyperhidrosis can occur in all races, but is 20 times more frequent in the Japanese than any other ethnic group. Both sexes can be affected. Hyperhidrosis might relate to underlying organic conditions and these should be considered as outlined in Box 23.11.1. Pathophysiology Generalized hyperhidrosis can develop as a consequence of auto- nomic dysregulation or might develop as a result of an underlying metabolic, malignant, or febrile disease. Palmoplantar hyperhidrosis can be inherited as an autosomal dominant disease. Clinical features Localized hyperhidrosis most commonly affects the palms, soles, and/or axillae and usually begins in childhood or adolescence. Clinical investigations Potential underlying systemic disease should be considered as out- lined in Box 23.11.1 and appropriate investigations conducted for more generalized disease. Treatment Treatment of hyperhidrosis is not always successful. Practical ad- vice on appropriate cotton clothing, heat avoidance, and weight re- duction along with relaxation techniques and anxiolytics in selected cases might all prove helpful. Topical

anticholinergic drugs can produce local benefits without causing systemic adverse effects. Topical 0.5% glycopyrrolate cream has been used with some success in gustatory hyperhidrosis associated with diabetes. Box 23.11.1 Causes of generalized hyperhidrosis • Thermoregulatory triggers — Hot weather/environment — Exercise • Infection — Fever/nausea — Tuberculosis/malaria/brucellosis/endocarditis, and so on • Metabolic/hormonal — Thyrotoxicosis, acromegaly, diabetes, Cushing's syndrome — Hypoglycaemia, alcohol intoxication, hyperpituitarism — Phaeochromocytoma — Menopause • Neoplastic — Lymphoma — Carcinoid — Carcinoma • Gustatory — Spicy/hot foods or drinks • Neurological — Lesions of the sympathetic nervous system, cortex, basal ganglia, or spinal cord — Peripheral neuropathies — Familial dysautonomia (Riley–Day) — Congenital autonomic dysfunction with universal pain loss — Cold-induced profuse sweating • Drugs — Cholinergic drugs — Fluoxetine — Opiate withdrawal • Psychological — Anxiety — Fear

23.11 Sebaceous and sweat gland disorders 5703 Eccrine blocking agents work by impeding the delivery of sweat to the skin surface. Soaks using 3% formalin and 10% glutaraldehyde solution help pedal hyperhidrosis but they are irritant to other sites. Aluminium chloride is the most frequently used preparation for ax- illae and hands but is also irritant and damages clothes. Botulinum toxin A injections produce blockade of neuronal acetylcholine release at the neuromuscular junction and in cho- linergic autonomic neurons. Intradermal injections can reduce sweating within 48 h and have lasting effects (eight months in the axillae and six months in palms). Injections can be safely repeated with good effect. Iontophoresis using tap water or anticholinergic drugs, such as glycopyrronium bromide, is very helpful for palmoplantar hyperhidrosis. A small, battery operated unit can be purchased for home maintenance. While atropine-like drugs are effective for hyperhidrosis, ad- verse effects including dryness of the mouth, constipation, visual disturbances, and rarely glaucoma, hyperthermia, and convulsions may outweigh their benefits. Propantheline is the most frequently used preparation at 15 mg three times daily, increasing as tolerated to 150 mg daily. Calcium channel blockers such as diltiazem have helped some cases. Anxiolytic agents might be beneficial where there is psychological overlay. Clonazepam and amitriptyline have both been reported to help unusual localized hyperhidrosis. Surgical sympathectomy will result in anhidrosis. This is gen- erally performed endoscopically and is very successful in treating palmar, axillary, and craniofacial hyperhidrosis. Postoperative compensatory hyperhidrosis frequently ensues, particularly in warmer climates and, although usually mild, it can prove disabling. Axillary hyperhidrosis can be greatly helped by surgical excision of axillary glands. Hypohidrosis/anhidrosis These rare problems may occur under the following conditions: • Abnormalities of the sweat glands: • Prematurity—in neonates/premature babies the sweat glands function poorly. • Ectodermal dysplasia—this is a rare, inherited, X-linked reces- sive disorder in which sweat glands are either absent or decreased. Boys have characteristic facies with abnormal teeth and hair and experience heat intolerance. See Chapter 23.3. • Heat stroke—this is due to sweat gland exhaustion and repre- sents a medical emergency. It is seen most often in older people exposed to a hot climate. It may occur in the young during or after prolonged exercise. Patients present with headache, cramps, fa- tigue, confusion, and hyperthermia. This progresses to vomiting, hypotension, oliguria, metabolic acidosis, and hyperkalaemia. Morbidity is high if they are not cooled down immediately and given fluid and electrolyte replacement. • Abnormalities of the nervous system—any abnormality in the sympathetic tract from the hypothalamus to peripheral nerves can result in anhidrosis. The symptoms of anhidrosis include heat in- tolerance, nausea, dizziness, tachycardia, and hyperthermia in hot environments. • Skin disease—anhidrosis has been

reported in several skin dis- eases including ichthyosis, psoriasis, lupus erythematosus, and morphoea and may be associated with Sjögren's syndrome. A localized loss of sweating ability might be due to tuberculoid leprosy, syringomyelia, or diabetes mellitus. Miliaria This results from occlusion of the eccrine ducts leading to sweat retention. Typically, it occurs in hot, humid climates, and in all ages, particularly when excessive clothing is worn and excessive sweating occurs. It might also be seen in association with high fever. Depending on the level of ductal occlusion, the clinical picture can vary. • Miliaria crystallina results from ductal plugs in the stratum cor- neum and presents with vesicles of 1–2 mm. The lesions are usu- ally nonsymptomatic, and as they rupture desquamation of the skin occurs. • Miliaria rubra (prickly heat) reflects intraepidermal ductal ob- struction and occurs in 1:3 people exposed to hot climates. Itchy red papules typically occur at points of friction and flexures. Relief is usually gained quickly by cooling the skin. • Miliaria profunda relates to dermal ductal occlusion and presents with pale firm papules 1–3 mm diameter. It is rare outside the tropics. Disorders of sebaceous glands and the pilosebaceous unit Sebaceous glands are an integral part of the pilosebaceous unit and are found over the entire body surface with the exception of palms and soles. The glands are multilobed and contain lipid filled cells. The lobules empty sebum into the upper hair follicle via a short duct. The sebum lubricates and waterproofs the skin and has some bactericidal and fungistatic activity. Free sebaceous glands are found in the eyelid (meibomian glands), mucous mem- branes (Fordyce's spots), areolar, perianal, and genital skin. The hair follicle, the hair, the sebaceous gland, arrectores pilorum muscle, and (in certain regions) the apocrine glands make up the pilosebaceous unit. Sebaceous glands are under the influence of androgenic hor- mones especially dehydrotestosterone (DHT). Human sebaceous glands contain 5α-reductase, 3β-, and 17β-hydroxysteroid dehydro- genase, which convert androgens to DHT. A surge of androgens at puberty is associated with the onset of acne in adolescence. Acne Introduction Acne is a polymorphic inflammatory disease of the pilosebaceous follicles, predominantly affecting the skin of the face and trunk. It is one of the most common skin diseases encountered by commu- nity physicians and dermatologists. Acne can present at any age, from neonates to mature adults, but is most prevalent and most se- vere during adolescence with 30% of teenagers requiring medical treatment. Aetiology/epidemiology Acne is considered a disease of puberty but it is now starting earlier and lasting longer; earlier onset of puberty has been proposed as a cause

section 23 Disorders of the skin 5704 but earlier recognition might also lead to earlier age of presentation. Comedonal acne can be detected before any overt signs of puberty are detected and established acne starts at a younger age in girls than boys Post-adolescent acne, both persistent and late-onset, is more common in women than men. Peak prevalence occurs between the ages of 15 and 20 in all ethnic groups. Acne severity increases with age in both sexes. Pathogenesis The pathogenesis of acne relates to an increase in androgen- mediated sebum production, follicular hyperkeratosis, prolifer- ation of Propionibacterium acnes, and inflammation. There appear to be three phases in the development of acne: an innate immune response mediated by IL-1α, followed by microcomedo formation, and then visible inflammation associated with a specific delayed- type hypersensitivity response. Hyperkeratinization of the sebaceous duct is mediated by IL-1α and tumour necrosis factor-α (TNFα) from keratinocytes and T lymphocytes. The result is hyperproliferation of keratinocytes, re- duced apoptosis, and consequent hypergranulosis. The sebaceous follicle becomes blocked with dense keratin and so evolves the microcomedo, considered to be the precursor to both the non- inflammatory (blackheads/whiteheads; Fig. 23.11.1) and inflam- matory lesions seen in acne. P. acnes colonize the skin surface and

pilosebaceous ducts and bind to the Toll-like receptor 2 (TLR-2) on monocytes and neutrophils, leading to the induction of macrophage or keratinocyte secretion of IL-12. This results in the differentiation of T cells, leading to the activation of Th 1 cells when they encounter their antigen in the dermis. Clinical features Acne lesions embrace inflammatory papules and pustules in most cases, but deeper inflamed lesions can present as acne nodules (Fig. 23.11.2). Noninflammatory lesions present clinically as open and closed comedones (blackheads and whiteheads respectively). Scars which might represent an increase in collagen (hypertrophic and keloid scars) or a loss of collagen (atrophic scars) frequently occur in acne and are not necessarily related to the severity of the inflamed acne lesions. The patient might also develop persistent post-inflammatory hyperpigmentation, although this is more common in patients with darker skin phototypes. Differential diagnosis Acne is generally easy to diagnose based on history and clinical pres- entation but several conditions should be considered in the differen- tial (Table 23.11.1) Comedones or comedonal-like lesions can arise from drugs or cosmetics, as seen in pomade acne. Comedonal acne is also a characteristic feature of chloracne. Clinical investigations Clinical investigations are not usually required to make a diagnosis of acne but some cases might relate to underlying endocrinopathies. Table 23.11.2 summarizes conditions that may be implicated in acne and suggested investigations. Treatment Assessment of acne should include a thorough history, including details of family history, duration of acne, previous therapies, and response to treatments, along with careful physical examination. Most patients do not have an endocrine problem relating to their acne; however, polycystic ovary syndrome should be considered in women who have persistent/late-onset disease, particularly if this coexists with other signs of hyperandrogenism, such as hirsutism, irregular menses, or infertility. Cushingoid features, androgenic alopecia, acanthosis nigricans, and deepening of the voice might also reflect hyperandrogenism. These patients frequently have insulin resistance and are at increased risk of developing type 2 diabetes and possibly cardiovascular disease. Late-onset adrenal hyperplasia can also trigger late-onset acne in both sexes. Table 23.11.2 summarizes the investigations used to confirm or refute these diagnoses. Response to treatment can be slow and patients must be encour- aged to adhere to the chosen treatment regimen. Acne and scar- ring can result in significant psychological and social disability in Fig. 23.11.1 Inflammatory papular acne interspersed with closed, non- inflammatory lesions of the forehead. Fig. 23.11.2 Inflammatory nodular acne of the back with associated scarring.

 predisposed individuals (e.g. anxiety, depression, social isolation, and interpersonal difficulties). Topical therapies form the mainstay of treatment for mild to mod- erate acne. The choice of preparation will depend on the type of acne present (Table 23.11.3). Topical retinoids treat noninflammatory and inflammatory acne. They reverse hypercornification and induce proliferation of the follicular epithelium, thus helping to ‘unplug’ the follicle. The less anaerobic conditions that result lead to a reduction in P. acnes. Given the central role of the microcomedo in the early development of both noninflammatory and inflammatory lesions, most patients require a topical retinoid as part of their treatment regime. Retinoids are also now being considered for maintenance therapy. Skin irritation is a common side effect but is less problem- atic with the newer retinoids (topical isotretinoin and adapalene). Irritation is minimized by using lower concentrations for shorter durations. Topical retinoids are contraindicated in pregnancy. Benzoyl peroxide (BPO) is a powerful antimicrobial agent. It de- composes to release free oxygen radicals in the sebaceous follicles, which have bactericidal and anti-inflammatory effects. BPO is ac- tive against fully sensitive and resistant strains of P. acnes.

One high quality, randomized controlled trial demonstrated that BPO was as effective as oral oxytetracline and minocycline in mild/mild to moderate acne. BPO is available alone in concentrations of 2.5– 10% and in combination with agents including hydroxyquinoline, erythromycin, and clindamycin. Lower concentrations are as ef- fective as 10% and less irritant. Infrequently an allergic contact dermatitis occurs. Benzoyl peroxide can bleach clothes and hair, so patients should be informed. Topical antibiotics both reduce P. acnes and are anti-inflammatory through suppressing leucocyte chemotaxis and decreasing a propor- tion of proinflammatory free fatty acids and surface lipids. Topical erythromycin and clindamycin have been shown to be as effective as benzoyl peroxide in mild acne and are seemingly equally effective in treating moderate facial acne. As topical antibiotics drive bacterial resistance, they should be avoided as monotherapy over prolonged periods. Evidence supports a direct correlation between P. acnes resistance and failure to respond to oral antibiotic treatment. Resistance to erythromycin can be reduced by using a combination of erythro- mycin and zinc or erythromycin and benzoyl peroxide. Azelaic acid has some effect on inflamed acne lesions as it can re- duce the number of P. acnes. It can be irritant and, rarely, photosensi- tivity can occur. Nicotinamide gel represents an alternative topical anti-inflammatory therapy; it has been shown to be as effective as 1% clindamycin gel and has the advantage of not promoting bac- terial resistance. Topical treatments can work synergistically when used in com- bination. Topical antibiotics and benzoyl peroxide are more ef- fective than benzoyl peroxide as a single therapy. When combined with zinc, topical erythromycin has increased therapeutic efficacy. When retinoids are used in combination with antimicrobial agents, the combination produces faster results and significantly greater re- ductions in acne lesions. Compliance might be enhanced by using combinations products. Current European Dermatology Forum evidence-based guidelines advocate the use of novel fixed dose com- bination topical therapies for mild to moderate disease. Systemic therapy is used for moderate to severe acne, or mild to moderate acne associated with scarring or significant psychosocial disability and/or failure to respond to topical treatment when it may be given in combination with topical therapy. Systemic anti- biotic therapy (Table 23.11.4) reduces the numbers of P. acnes and Table 23.11.1 Outlines conditions which could be considered in the differential of acne vulgaris Milia Plane warts Syringomas Adenoma sebaceum (angiofibromas) Ectopic sebaceous glands (Fordyce spots) Pilosebaceous naevoid disorders Favre-Racouchot syndrome Birt-Hogg-Dube syndrome Sebaceous gland hyperplasia, adenoma, and carcinoma Sebaceous cysts and steatocystoma multiplex Lupus miliaris disemminatus facei Chloracne Aneiform eruptions related to drugs and cosmetics Acne keloidalis nuchae Keratosis pilaris Rosacea Pyoderma faciale Perioral dermatitis Folliculitis Gram negative Demodex Candida/Malassezia folliculitis Folliculitis of the scalp Hidradenitis suppuritiva Miscellaneous causes of a papular facial rash Mimics of acne scarring Table 23.11.2 Investigating the underlying endocrine abnormalities implicated in acne Cause Investigations Polycystic ovary syndrome Day 1–5 of menstrual cycle: Total and free testosterone LH/FSH SHBG Ultrasonography of ovaries (not mandatory but may help to support the clinical impression) Congenital adrenal hyperplasia 17-Hydroxyprogesterone DHEAS Cortisol levels Cushing’s syndrome Dexamethasone suppression test Gonadal or adrenal tumours Total and free testosterone DHEAS DHEAS, dehydroepiandrosterone sulphate; LH/FSH, luteinizing/follicle-stimulating hormone ratio; SHBG, sex-hormone binding globulin.

 S. epidermidis and proinflammatory mediators in the microcomedo. It also modulates the host response to these stimuli. Patients with marked seborrhoea and truncal acne respond less well to anti- biotics. If oral antibiotics are to be

incorporated into a regimen con- taining oral contraceptives, patients should still be warned about the possible decreased efficacy of the oral contraceptive, although, with the exception of rifampicin, there is currently no evidence to support the fact that commonly prescribed antibiotics either reduce blood levels and/or the effectiveness of oral contraceptives. Based on efficacy, safety, and bacterial resistance, tetracyclines should be used in preference to other classes of antibiotics. Oxytetracycline needs to be taken 30 min pre-food and not with milk to ensure adequate absorption. Second-generation tetracyclines such as lymecycline (300–600 mg/day) and doxycycline (100–200 mg/day) may ensure better compliance and both have a better side effect profile than minocycline. Tetracyclines are contraindicated in children below 12 years of age and in pregnancy as they can affect dentition and re- sult in inhibition of skeletal growth in the fetus. The increasing incidence of P. acnes resistance to erythromycin and the link between erythromycin resistant P. acnes and reduced therapeutic response has resulted in the recommendation that erythromycin should be restricted. Erythromycin 1 g daily is the antibiotic of choice in pregnancy. Trimethoprim 200–300 mg daily is a third-line option for patients who have failed to respond to al- ternative antibiotics. Combining topical and systemic treatment aids more rapid effi- cacy and potentially reduces the length of exposure to antibiotics, so reducing the likelihood of emerging antibiotic resistance. Antibiotic resistant P. acnes were first detected in the United States of America in the late 1970s. The worldwide incidence of antibiotic resistant P. acnes has increased significantly over the last decade. Carriage of resistant P. acnes can result in reduced therapeutic response to anti- biotics. This is true for both erythromycin and tetracycline. To reduce emerging resistance, oral antibiotics should only be used for 6–12 weeks in the first instance and only for as long as there is further clinical improvement. If the patient relapses after discontinuing the antibiotics, the same antibiotic should be restarted where possible. The addition of topical benzoyl peroxide can be used to try and eliminate resistant organisms. Hormonal therapies can help females with acne, whether or not their serum androgen levels are normal. They aim to reduce circu- lating androgen levels and/or block androgen receptors. Possible options are oestrogens, androgen receptor blockers, or agents de- signed to decrease the endogenous production of androgens by the ovary or adrenal gland. The oestrogen component of oral contra- ceptives increases sex-hormone binding globulin, thus decreasing free testosterone in healthy women. Oestrogens also decrease pro- duction of ovarian androgens by suppressing secretion of pituitary gonadotropins. The progestin component of oral contraceptives minimizes the risk of endometrial cancer. However, progestins like norethisterone have intrinsic androgenic activity so might aggravate acne. Drospirenone 3 mg combined with ethinylestradiol 30 μg has been shown to have a superior effect to a third generation-combined pill. However, it is not licensed in the United Kingdom as a treatment for acne. Cyproterone acetate (CPA) has been shown to reduce sebum pro- duction and comedogenesis. CPA (2 mg) in combination with 35 mg ethinylestradiol has a licence for the treatment of severe acne in the United Kingdom and achieves significant improvement in 75–90% of female patients. Treatment is frequently required for six months before a response is seen. The relative thromboembolic risk with co- cyprindiol is slightly higher than that linked to non-antiandrogenic combined oral contraceptives but no higher than those containing third generation progestins. Spironolactone acts as an androgen receptor blocker and inhibits 5α-reductase. In doses of 50–100 mg twice daily, it reduces sebum Table 23.11.3 Topical therapies for acne: impact on aetiology Medication Inflammation Comedogenesis Reduction in
P. acnes Antimicrobials and antibiotics
BPO Erythromycin Clindamycin Dapsone ++ +++ +++ +++ + – +/– – +++ +++ +++ ++ Retinoids Tretinoin Isotretinoin Adapalene + + ++ +++ + ++ – – – Combination therapies Zinc and

erythromycin BPO and erythromycin BPO and clindamycin BPO and adapalene Tretinoin and clindamycin +++ +++ +++ ++ ++ – + + ++ +++ +++ +++ +++ +++ ++ Others Azelaic acid ++ + ++ BPO, benzoyl peroxide. Table 23.11.4 Systemic antibiotics for acne—dosage and adverse effects Drug Dosage Adverse effects Oxytetracycline 500 mg twice a day Rare onycholysis, photosensitivity, benign intracranial hypertension Erythromycin 500 mg twice a day Gastrointestinal upset, nausea, diarrhoea all fairly common Minocycline 100–200 mg daily Headaches (dose dependent), pigmentary changes, autoimmune hepatitis/lupus erythematosus-like syndromea Doxycycline 100–200 mg daily Photosensitivity (dose dependent) Lymecycline 300–600 mg daily Fewer than minocycline Trimethoprim 200–300 mg twice a day Rare hepatic/renal toxicity agranulocytosis ANA, antinuclear antibody; LFT, liver function test; p-ANCA, perinuclear antineutrophilic cytoplasmic antibody.a Advise, monitor LFTs, ANA, and p-ANCA in ‘at risk’ patients or when treatment is prolonged (>6 months). Cyclines are contraindicated in pregnancy and in children below 12 years.

23.11 Sebaceous and sweat gland disorders 5707 production and improves acne. Side effects are dose-related and in- clude potential hyperkalaemia, irregular menstrual periods, breast tenderness, headache, and fatigue. Although tumours have been re- ported in rodent models treated with spironolactone, this drug has not been directly linked with cancer in humans. There is a risk of feminization of a male fetus and thus pregnancy should be avoided. Isotretinoin is a synthetic form of vitamin A and is effective in severe inflammatory acne that has failed to respond to other treat- ments. Oral isotretinoin is the only agent that impacts on the four main aetiological factors driving acne. It is a lipid soluble drug, hence its absorption is enhanced when administered with food. Oral isotretinoin should not be combined with tetracyclines as both can lead to benign intracranial hypertension. Mucocutaneous prob- lems are the most common side effect of oral isotretinoin, including cheilitis, irritant dermatitis, and blepharoconjunctivitis. These side effects are dose dependent. Oral isotretinoin is a potent teratogen and women of childbearing age should not start therapy until a negative pregnancy test has been obtained, ideally two to three days prior to menstruation. Adequate contraception is essential for fertile, sexu- ally active females before, during, and up to five weeks post-therapy. A recent European directive recommends mandatory pregnancy testing prior to the start of treatment and five weeks post-therapy and advocates monthly pregnancy testing throughout the treatment period. Baseline blood tests, including fasting lipids and liver func- tion, should be done before starting therapy and are recommended at one month, then three-monthly throughout the treatment course. Adverse psychiatric events such as mood swings, depression, and suicidal ideation have been reported as possible idiosyncratic re- actions to isotretinoin and must be highlighted. Epidemiological studies have not demonstrated a definite causal relationship between psychological effects and isotretinoin, but the association of depres- sion with isotretinoin has not been satisfactorily investigated. Several small studies have trialled lasers, photodynamic therapy, and phototherapy with either clear blue or mixed blue-red light/ra- diation in inflammatory acne. Whereas some success has been re- ported, optimum regimes are still being assessed. Prognosis/outcome Acne is a chronic inflammatory skin disease which can result in physical and emotional scarring. Treatment regimens should be adopted to address as many aetiological factors as possible to opti- mize treatment results. Special circumstances: Unusual acne variants Acne excoriée This occurs frequently in adolescent girls and young women. Patients pick their skin leading to inflammatory lesions. Treatment can be difficult, psychological problems should be investigated, and underlying acne lesions managed with standard acne treatment. Successful treatment with habit reversal has been reported.

Dysmorphophobia This occurs in a small number of acne patients. The patient's percep- tion of their acne is disproportionate to their physical signs. There is often associated depression and/or obsessional neurosis. The acne should be treated in the standard fashion and psychiatric collaboration is important. Drug-induced acne This is well recognized. Corticosteroids are the most common of- fenders. Steroid acne has a monomorphic appearance and consists of noninflammatory and inflammatory lesions. Other drugs im- plicated include anticonvulsants, lithium, and the novel epidermal growth factor receptor (EGFR) inhibitors currently used for solid tumours. Cosmetic acne Various cosmetic ingredients induce comedones, in particular lanolins, petrolatum, and certain vegetable oils. Hair pomades can produce a monomorphic, low-grade acne. Infantile acne This is rare but can result in scarring if left untreated. Patients de- velop inflammatory lesions, particularly on the cheeks, usually after three months of age. These can evolve into deep-seated nodules and sinus tracts. Treatment is similar to adult acne, but tetracyclines should be avoided due to the risk of discoloured teeth. Topical ther- apies and/or oral erythromycin (125 mg twice daily) or trimetho- prim (100 mg twice daily) can be used safely. Gram-negative folliculitis This occurs as a complication of any long-term topical or oral antibiotic therapy. It is characterized by sudden onset of multiple pustules, often localized periorally and perinasally. This results from overgrowth of Gram-negative organisms including Escherichia coli, proteus, pseudo- monas, and klebsiella. The offending antibiotic should be stopped and changed to oral trimethoprim or ampicillin. Oral isotretinoin gener- ally produces a more rapid and permanent response. Acne conglobata This is an uncommon severe form of acne characterized by acne nodules, interconnecting sinuses, grouped comedones, and ex- tensive scarring. Treatment is difficult and the problem usually runs a chronic course. Isotretinoin is usually the preferred therapy. Concomitant short courses of antibiotics and oral steroids might be required to control acute exacerbations. Acne fulminans This is rare, most frequently affecting adolescent boys. Acute erosive inflammatory lesions occur predominantly on the trunk. Associated systemic symptoms including fever, weight loss, arthralgia, and my- algia are evident. The aetiology is uncertain, but the presence of microscopic haematuria, erythema nodosum, increased response to P. acnes antigen on skin tests, and depressed response to intradermal purified protein derivatives are in favour of an abnormal immuno- logical response. Oral prednisolone is the treatment of choice followed by the cautious introduction of systemic isotretinoin. Several cases of acne fulminans have been triggered by anabolic steroids and testosterone. Pyoderma faciale This disorder is more common in adult women and often occurs in the context of emotional stress. These patients are not systemically unwell but the appearance of the disorder often adds considerably

 to the stress. Treatment with prednisolone reducing over four to six weeks and the daily application of moderate to potent topical steroid for one week will help. Isotretinoin should be introduced after one week, and, if tolerated, can be gradually increased. SAPHO This is the acronym for synovitis, acne, pustulosis, hyperostosis, and osteitis in which a group of overlapping joint diseases occur in conjunction with palmoplantar pustulosis and, less frequently, with psoriasis, acne, and inflammatory bowel disease. Complications and comorbidities The main complications that arise from acne relate to subsequent physical and emotional scarring. Post-inflammatory erythema or pigment changes may also result in visible abnormalities that are cosmetically unacceptable to patients. Acne scarring is a common consequence of acne and can occur, albeit mildly, in up to 90% of patients. A delay in appropriate acne management is more likely to result in significant scarring. Scarring commonly follows deep-seated inflammatory lesions, but can also occur as a result of more superficial inflamed lesions in scar-prone patients. Scars might show increased collagen (hypertrophic scars and keloids) or be associated with loss of

collagen (i.e. atrophic scars). Psychosocial effects of acne Studies have shown that many acne patients experience shame (70%), embarrassment and anxiety (63%), lack of confidence (67%), impaired social contact (57%) and significant problems with un- employment. When compared to other serious organic diseases, acne patients describe levels of social, psychological, and emotional problems as great as those reported with chronic disabling diseases such as asthma, epilepsy, back pain, arthritis, and diabetes. Clinical depression has been demonstrated in acne patients and the preva- lence of active suicidal ideation is higher in acne patients than re- ported in the general population. The psychological impairment does not necessarily correlate with the clinical severity of disease. It has been suggested that the depressed acne patient should be as- sessed for suicide risk. Conclusions and the future Acne is a common inflammatory skin disease often associated with significant psychosocial morbidity. Early effective intervention pre- vents emotional and physical scarring. Understanding of patho- physiology allows topical and systemic therapies to be combined logically to target the individual aetiological factors. Research into the pathogenesis has defined acne as a T-cell mediated dermatosis. The possibilities for using immunomodulatory therapies and spe- cific anti-inflammatory treatments are open to further develop- mental research studies and controlled trials. In theory, a TLR-2 antagonist, IL-1α antagonist, and cytokine therapy could be possible candidates for future acne treatment. Other possibilities include in- sulin sensitizing agents, 5α-reductase type 1 inhibitors, and possibly new anti-inflammatory agents such as lipoxygenase inhibitors. FURTHER READING Burns T, et al. (eds) (2016). Rook’s textbook of dermatology, 9th edition. Blackwell Science, Oxford. Lee RA, et al. (2015). Treatment of hidradenitis suppuritiva with bio- logic medications. JAAD, 73 (5 Suppl 1), S82–8. Nast B, et al. (2016). European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol, 30(8), 1261–8. National Institute for Health and Care Excellence (NICE) (2014). Acne Vulgaris: Clinical Knowledge Summary. http://cks.nice.org.uk/ acne-vulgaris Thiboutot D, et al. (2018). Practical Management of acne for clinicians. An international consensus from the Global Alliance to Improve Outcomes in Acne. JAAD, 78(2), S1–S23. e1. Zouboulis C, Katsambas A, Kligman A (2014). Pathogenesis and treat- ment of acne and rosacea. Springer, Berlin.

Revision #1
Created 2026-01-22 16:42:55 UTC by Omar Ayman
Updated 2026-01-22 16:42:55 UTC by Omar Ayman