# Hair in Infectious Disease

Recognition, Treatment, and Prevention

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*Editors*

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# Preface

*The characteristic microbe of a disease might be a symptom instead of a cause.*
From: "The Doctor's Dilemma" by George Bernard Shaw (1856–1950)

The discovery of *Trichophyton schoenleinii* as the causative agent of favus by Johann Lukas Schönlein (1793–1864) in 1839 heralded the introduction of a microbial, in fact fungal, cause of cutaneous disease. Up until the advent of modern therapies, favus was widespread worldwide, and prior to Schönlein's recognition of it as of fungal origin, it was either considered a hereditary condition (hence the older German term "Erbgrind," with "Erb" meaning inheritance, and "Grind" scurf, scab, or crust) or confused with leprosy, and sufferers sometimes were confined to leprosaria. Today, due to the species' high susceptibility to the antifungal agent griseofulvin, it has been eliminated from most parts of the world, except scattered rural areas of Africa. It is mainly a disease connected to demographic poverty and isolation, but is so readily treatable that it is among the diseases most likely to be completely eliminated by modern medicine.

With reference to George Bernard Shaw, we must recognize that infectious diseases have wider preconditions besides the infectious agents, to include environmental and societal factors. Unless we also take account of the ecological, immunological, and behavioral circumstances that affect the emergence and spread of infectious diseases, including those of the hair and scalp, our knowledge of the pathogens and their connection to clinical disease presentation remain only partial and incomplete.

Probably one of the oldest and most authoritative texts on the importance of making a distinction between common baldness and inflammatory scarring alopecia is found in the Old Testament:

*40"If a man's hair is gone this does not make him a leper even though he is bald!*
*41If the hair is gone from the front part of his head, he simply has a bald forehead, but this is not leprosy.*
*42However, if in the baldness there is a reddish white spot, it may be leprosy breaking out.*
*43In that case the priest shall examine him (Leviticus 13:40–43).*

The original Hebrew noun tzaraath, צרעת, describes any disfigurative conditions of the skin and body hair mainly referred to in chapters 13–14 of Leviticus. It is

only in the Septuagint, a translation of the Hebrew Bible, that the term tzaraath was translated with Greek lepra, λεπρα, from which the cognate leprosy was traditionally used in English Bibles. The New Jewish Publication Society of America Tanakh translates it as a scaly affection in Leviticus 13:2. The affected individual had to consult the Priest or kohen, who was trained in examining the lesions and determining whether or not they meet the specifications of tzaraath. If characteristics of the lesions met the criteria for tzaraath, including spreading of the disease, the kohen declared the individual ritually impure. The individual who is declared impure with tzaraath was shunned and had to live alone outside the confines of the community (Leviticus 13:46), had to tear his garments in mourning like those who are in mourning for a close family member, not cut his hair, cover his face until the upper lip in the fashion of mourners, and call out "impure, impure" to warn others to keep their distance. Irrespective of the contagiosity of the underlying skin condition or not, the concept of tzaraath underscores the social stigmatization that results from affections of the skin and hair while setting them into a moral context. It is clear today that Biblical leprosy does not refer to Hansen's disease, but may represent any skin disease fulfilling the criteria for diagnosis of tzaraath, including vitiligo, pseudopelade, cutaneous lupus erythematosus, folliculitis decalvans, and tinea capitis. These days, the affected individual would consult the dermatologist skilled in infectious diseases of the hair and scalp for the respective clinical, microbiological, and histological examination as indicated, and an eventually successful treatment based on circumstantial understanding and free of moral bias.

Most recently, the novel viral pandemic coronavirus disease 2019 (COVID-19) has originally sparked uncertainties and controversies as to its origin, epidemiology, and natural course. In this situation, the medical disciplines have strived to contribute to a better understanding of the disease with the best available evidence gained from the scientific method of observation and statistics. The study of the cutaneous manifestations of COVID-19 including the hair has evolved with the hope that they may be useful as markers for the disease, for prognostication, and further insights into the pathomechanisms of the disease manifestations.

In the wake of COVID-19, we have decided to take a more general look at the hair and scalp in infectious diseases including their geographical peculiarities. This book aims at illustrating in detail the environmental and individual preconditions, the pathogens, the clinical presentations, and the management of the infectious diseases that affect the hair and scalp, to include superficial and deep bacterial, fungal, and viral infections, infestations, systemic infectious diseases causing hair loss, their effective treatment, and their prevention.

Wallisellen, Switzerland — Ralph M. Trüeb
São Paulo, Brazil — Hudson Dutra Rezende
Rio de Janeiro, Brazil — Maria Fernanda Reis Gavazzoni Dias

# Acknowledgments

We would like to acknowledge the support of our distinguished peers who have retained common sense and remained analytical in their thought in the wake of the COVID-19 pandemic and studied from the history and nature of the infectious diseases of the past, irrespective of mainstream common opinion, prejudice, sensationalism, conspiracist ideation, and propaganda.

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# Editors and Contributors

## About the Editors

**Ralph M. Trüeb, MD** is Professor of Dermatology. He received his MD and Swiss Board Certification for Dermatology and Venerology as well as for Allergology and Clinical Immunology from the University of Zurich, Switzerland. In 1994–1995 he spent a year at the University of Texas Southwestern Medical Center at Dallas with Rick Sontheimer and at the Howard Hughes Medical Institute in Dallas with Bruce Beutler to complete his Fellowship in Immunodermatology. After 20 years tenure at the Department of Dermatology, University Hospital of Zurich, where he founded and was head of the Hair Consultation Clinic, he established in 2010 his private Center for Dermatology and Hair Diseases in Zurich, where he offers since 2013 doctors-in-training and dermatologists international traineeships in Trichiatry. He is founding President of the Swiss Trichology Study group (founding year: 1999), and past-President of the European Hair Research Society (2008–2011). His clinical research interests focus on hair loss, inflammatory phenomena, hair aging and anti-aging, hair and nutrition, hair care and cosmetics, patient expectation management, and medical ethics. He is currently the author of 261 peer-reviewed scientific publications and 8 textbooks on hair.

**Hudson Dutra Rezende, MD** is a board-certified Dermatologist especially dedicated to the management of hair and scalp conditions. In 2018, Dr. Dutra completed a fellowship in Trichiatry with Prof. Trüeb at the Center for Dermatology and Hair Diseases in Switzerland. From 2019 to 2020, he was invited to join a board of Dermatologists of the Brazilian Society of Dermatology, Regional Fluminense, Rio de Janeiro, when he was in charge of several medical events. In addition to his private practice in Sao Paulo, Dr. Dutra also teaches Trichology at Lusíada Foundation, Santos, working with physicians enrolled in the Postgraduate Dermatology Course. In 2020, as the pandemic spread, he focused his clinical research on the better understanding of COVID-19-related hair loss and its impact on the quality of life in patients from Sao Paulo University (USP). He is one of the Editors of the Brazilian book *Dermatologia das Alopecias e Estudos dos Cabelos,* and he has also published numerous peer-reviewed papers and book chapters on hair and scalp diseases.

**Maria Fernanda Reis Gavazzoni Dias, MD, MsC, PhD** is Professor of Dermatology; Chair of the Postgraduate Dermatology Course; and Co-Chair of the Residency Training Program in Dermatology, at Fluminense Federal University (UFF), Brazil. She is thesis advisor at the Department of Dermatopathology-UFF. Dr. Maria Fernanda Gavazzoni is the founder of the First Alopecia Clinic at Antonio Pedro Federal Hospital-UFF, with special interest in cicatricial alopecia in patients of color and tropical infections. She did her PhD thesis on her research into paracoccidioidomycosis. She is a board member of the American Hair Research Society (AHRS) since 2018, former Treasurer and Secretary of the Brazilian Society of Dermatology (SBD) 2009–2010, and former president of Fluminense Society of Brazilian Dermatologists 2019–2020. She is the editor and author of the first textbook on hair in Portuguese, several book chapters, and peer-reviewed scientific publications.

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# Brief History of Microbiology

# 1

Ralph M. Trüeb

*The Microbe is so very small*
*You cannot make him out at all,*
*But many sanguine people hope*
*To see him through a microscope.*
*His jointed tongue that lies beneath*
*A hundred curious rows of teeth;*
*His seven tufted tails with lots*
*Of lovely pink and purple spots,*
*On each of which a pattern stands,*
*Composed of forty separate bands;*
*His eyebrows of a tender green;*
*All these have never yet been seen—*
*But Scientists, who ought to know,*
*Assure us that they must be so ...*
*Oh! let us never, never doubt*
*What nobody is sure about!*

***The microbe****—by Hilaire Belloc (1870–1953)*

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Infectious diseases emerging through the history of mankind have included some of the most dreaded of the past. New infections continue to emerge. Depending on the virulence and contagiousness of the infectious agent, environmental and societal factors, and ecological and behavioral circumstances that affect the emergence and spread of infectious diseases, these may represent either as regional or as global problems. As demonstrated by the influenza epidemics and the novel viral pandemic, coronavirus disease 2019 (COVID-19), a new infection first appearing anywhere in the world can traverse entire continents irrespective of geographic or political boundaries within day or weeks. From the plagues of biblical times to the HIV pandemic of the modern age, infectious diseases have played an indisputably major role in human history and civilization, both in terms of disfigurement and fatality. Particularly, the ailments affecting the skin and hair have been notorious for their social stigmatization.

Since biblical times, leprosy has been the object of horror and many misunderstandings, later popularized in literature and more recently in the film industry. Most importantly, leprosy has been the prototype and most prominent example of stigmatization through dermatologic disease.

In nineteenth-century France, French symbolist writer Auguste Villiers de l'Isle-Adam (1838–1889) portrayed in his *Contes Cruels* (1883) the Duke of Portland as the "last leper of our times": upon his visit to the Levante, Richard, Duke of Portland contracted the disease from a beggar, whom the people avoided with horror. Despite the warnings of his guides, he advanced into the cave-like hole amidst abandoned ruins in the vicinity of Antiochia, where the wretched individual in question resided in seclusion. Driven by a momentary mood of ostentatiousness rather than of compassion, the Duke, fearless to the extent of madness, reached his hand to the leprous beggar while donating pieces of gold. The Duke of Portland, who had been famous in all of England for his glittering feasts, victorious thoroughbred horses, boxing artistry, fox hunting, castles, wealth, political activities in parliament, adventurous journeys, and romances, thereafter disappeared completely from all former activities into the somber solitude of a recluse and eventually succumbed to the tragic fate of having contracted the disease.

Among the films in which leprosy is particularly dramatized are "Ben-Hur" (1959), set in ancient Rome at the time of Christ's crucifixion, and "Kingdom of Heaven" (2005), set in Jerusalem in the days of the Crusades, in the portrait of King Baldwin IV of Jerusalem (1161–1185, reign: 1174–1185), the "Leper King."

The plague or "Black Death," fancifully reiterated in Edgar Alan Poe's (1809–1849) short story, "The Mask of the Red Death" (1842), is the next among the great scourges of humanity. The first epidemic to be reliably reported in history by the historian Procopius and others occurred in sixth century CE during the reign

of the Byzantine emperor Justinian I (482–565). The next great plague pandemic was the dreaded Black Death of Europe in the fourteenth century. The number of casualties was enormous, reaching 30–60% of the European population. It has been dramatized in literature in Hermann Hesse's novel *Narziss und Goldmund* (1930) and cinematographically in Ingmar Bergman's film "Det sjunde inseglet" (1957). Outbreaks recurred at various locations around the world until the early twentieth century, to include the French Algerian city Oran, the setting for Albert Camus' existentialist classic *La Peste* (1947). The novel stresses the powerlessness of the individual characters to affect their destinies, the very pith of absurdism.

And yet, seventeenth-century discovery of living forms invisible to the naked eye was a significant milestone in the history of medicine, since from the thirteenth century on, it was believed that invisible entities were responsible for disease. Finally, the term microbe was coined in the late nineteenth century to describe these microscopic organisms, and microbiology eventually emerged as a specialized science dealing with the microbes, their characterization, and taxonomy.

The history of infectious diseases is also a history of human population. Crowding, low hygienic standards, and globalization all have their implications for the spread of disease. For instance, up until Schönlein's recognition of the fungal origin of favus in 1839, the condition was considered to be hereditary, hence the older German term *Erbgrind*, with *Erb* meaning inheritance and *Grind* scurf, scab, or crust. Despite a relatively low transmissibility, through the crowding of families under poor hygienic conditions, favus tended to occur within families. On the other hand, economic and social changes in the emerging markets, initially driven by colonialism and later by globalization, with better road, rail, and plane connections have accounted for the international spread of originally regional infectious diseases, more recently the viral pandemics AIDS, SARS, Ebola, and COVID-19.

Finally, man's relationship to animals may be determinant to the contagion and spread of infectious diseases. The direct contact with both farm animals (cattle, horses) and pets (cats, dogs, guinea pigs, rodents) may lead to mycotic infections of the skin, and there is ample evidence that ecological changes in the natural habitat of wild animals and the consumption of exotic species have been responsible for the emergence and eventual spread of viral infectious diseases such as Ebola (bats), AIDS (monkeys), and COVID-19 (civet cats).

## 1.1 Mahavira's Nigodas

The existence of microorganisms was postulated many centuries before their actual discovery. In fact, unseen microbiological life was believed in as early as sixth century BCE in Jainism. Jainism is an ancient Indian religion that traces its spiritual ideas and history through a succession of twenty-four leaders (Tirthankaras), with the first in current time cycle being Lord Rishabhanatha, whom the tradition holds to have lived millions of years ago, and the 24th Tirthankara, Lord Mahavira (599–527 BCE). Based on Mahavira's teachings, in Jainism cosmology, Nigodas

are unseen microbiological creatures living in large clusters and having a very short life. Nigodas represent a realm existing in which the lowest forms of life reside in endless numbers and without any hope of release by self-effort [1].

The seventh to fifth century BCE was a period of intellectual, philosophical, religious, and social ferment in India, a time of emerging opposition toward the cultural domination of the Brahmans, who claimed authority by virtue of their supposed innate purity. In particular, there was growing opposition to the large-scale Vedic sacrifices that involved the killing of animals. Because of the popularity of the doctrine of continual rebirth, which linked animals and humans in the same cycle of birth, death, and rebirth, unnecessary killing had become objectionable to many people, encouraging the growth of the doctrine of non-violence. This advocacy of non-violence strongly encouraged vegetarianism. Mahavira and his contemporary, Siddhartha Gautama, the Buddha, were two of the greatest leaders in this movement.

The eternal mystery of the world is its intelligibility (Albert Einstein). Jainism teaches that the universe is filled with a profusion of life and that every living organism is of importance and that any harm to any organism affects the order of the universe. While this reflects a profound respect for the order of nature and for all living beings, the question arises to what extent the Nigodas, the microscopic beings having momentary life spans, living in colonies, and being omnipresent, which modern microbiology would associate with the microbiomes, may cause disease according to Jainism teaching. According to the legend, Lord Mahavira would spare even insects smiting him, irrespective of the discomfort they may inflict or the diseases they may transmit.

## 1.2 Marcus Terentius Varro and the Roman Marshlands

The Roman scholar Marcus Terentius Varro (116–27 BC), who stood in the favor of Emperor Augustus and whose protection secured him the quiet to devote himself to study, made reference to microbes in his writings on agriculture (Rerum rusticarum libri tres), warning against locating a homestead in the vicinity of swamps and marshland, since in such areas "...there are bred certain minute creatures which cannot be seen by the eyes, but which float in the air and enter the body through the mouth and nose and cause serious diseases" [2].

References to the unique periodic fevers of malaria are found throughout history. In ancient Greece, Hippocrates (460–370 BC) (Fig. 1.1) described periodic fevers in his "Epidemics." The prominent writer on agriculture in the Roman empire (De re rustica), Lucius Junius Moderatus Columella (4–c. 70 AD), associated the disease with insects from swamps. Malaria was so pervasive in Rome that it was known as the "Roman fever." Several regions in ancient Rome, in particular southern Italy, the island of Sardinia, the Pontine Marshes, the lower regions of coastal Etruria, and the

**Fig. 1.1** Hippocrates. (From the desk of the author)

city of Rome along the Tiber, were at risk for the disease because of the favorable conditions present for malaria vectors. Specifically, the presence of stagnant water in these places was preferred by mosquitoes for breeding grounds. Irrigated gardens, swamp-like grounds, runoff from agriculture, and drainage problems from road construction led to the increase of standing water.

Although the parasite responsible for malaria has been in existence for 50,000–100,000 years, as evidenced by ancient malaria oocysts preserved in amber, the population size of the parasite did not increase until about 10,000 years ago, concurrently with the development of human settlements and the advances in agriculture.

Scientific studies on malaria made their first significant advance only in 1880, when French Nobel Prize laureate in Medicine (1907) Charles Louis Alphonse Laveran (1845–1922), then an army doctor working in the military hospital of Constantine in Algeria, observed the parasites inside the red blood cells of infected people for the first time. He proposed that malaria is caused by this organism, the first time a protist was identified as the causing agent [3].

## 1.3 The Golden Age of Islamic Civilization

During the Islamic Golden Age, in which the translations of Greco-Roman, Persian, and Indian texts were studied extensively, Islamic scientists further hypothesized the existence of microorganisms, such as Avicenna (Ibn Sina, ابن سينا) in his book *The Canon of Medicine*, Avenzoar (Ibn Zuhr, زهر بن الملك عبد مروان أبو, born in Sevilla, 1094–1162) who discovered scabies mites that contributed to the scientific advancement of microbiology, and Al-Razi (ابوبکر محمّد زکریای رازی, 854–925 CE) who gave the earliest known description of smallpox in his book *The Virtuous Life* (al-Hawi). Razi wrote:

> Smallpox appears when blood "boils" and is infected, resulting in vapors being expelled. Thus juvenile blood (which looks like wet extracts appearing on the skin) is being transformed into richer blood, having the color of mature wine. At this stage, smallpox shows up essentially as "*bubbles found in wine*" (as blisters).. *this disease can also occur at other times* (meaning: not only during childhood). *The best thing to do during this first stage is to keep away from it, otherwise this disease might turn into an epidemic.*

## 1.4 Girolamo Fracastoro's Seeds of Disease

In 1546, Italian scholar and physician Girolamo Fracastoro (c. 1476/8–1553) proposed that epidemic diseases were caused by transferable seed-like entities that could transmit infection by direct or indirect contact or vehicle transmission. Fracastoro rejected appeals to hidden causes in scientific investigation. His studies of the mode of syphilis transmission are an early example of epidemiology. Nineteenth-century bacteriologists studied Fracastoro's works and his "seeds of disease" theory as a predecessor to the germ theory of disease.

Fracastoro appears to have first used the Latin word *fomes*, meaning "tinder," in the sense of infectious agent, in his essay on contagion *De Contagione et Contagiosis Morbis*, published in 1546: "I call fomites (from the Latin fomes, meaning "tinder") such things as clothes, linen, etc., which although not themselves corrupt, can nevertheless foster the essential seeds of the contagion and thus cause infection" [4]. However, such views were held in disdain in Europe, where Galen's miasma theory (the theory held that epidemics were caused by miasma, emanating from rotting organic matter) remained dominant among scientists and doctors.

The name for syphilis is derived from Fracastoro's 1530 epic poem in three books, *Syphilis sive morbus gallicus* (*Syphilis, or The French Disease*), about a shepherd boy named Syphilus who insulted the Greek god Apollo and was punished by that god with a horrible infliction.

Finally, in 1546, Fracastoro described an epidemic in cattle that devastated farmers near Verona, Italy. The disease is now recognized as foot-and-mouth disease (FMD). Humans can be infected with FMD through contact with infected animals (zoonosis), but this is extremely rare. Because the virus that causes FMD is sensitive to stomach acid, it cannot spread to humans via consumption of infected meat, except in the mouth before the meat is swallowed. In the UK, the last confirmed human case occurred in 1966, and only a few other cases have been recorded in

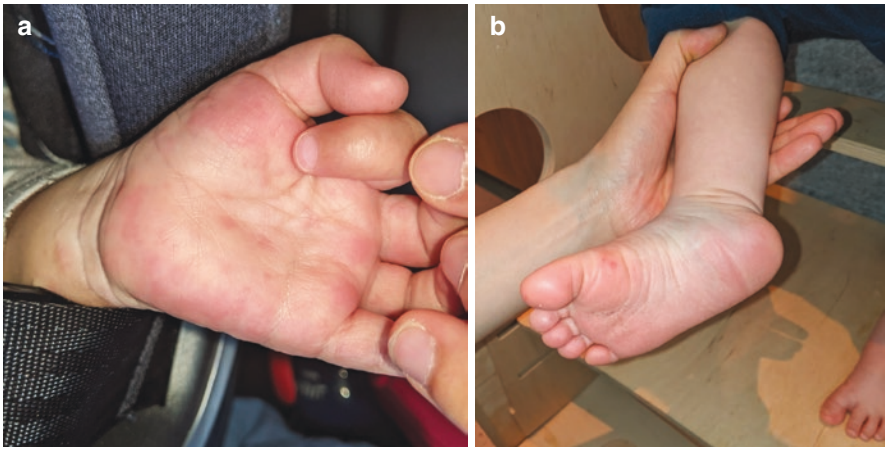


**Fig. 1.2** (**a**, **b**) Hand-foot-mouth disease. (Courtesy of Dr. med. Ngoc-Nhi C. Luu)

countries of continental Europe, Africa, and South America. According to a newspaper report, FMD killed two children in England in 1884, supposedly due to infected milk.

Another viral disease with similar symptoms, hand-foot-and-mouth disease, occurs more frequently in humans (Fig. 1.2a, b). The cause, Coxsackie A virus, is different from the FMD virus. Hand-foot-mouth disease is recognized a typical exanthematous disease of children less than 10 years of age. However, in the last years, reports concerning atypical dermatological presentations have been published, including adults, and with scalp involvement in the form of itchy papules, vesicles, and crusts on the scalp [5].

## 1.5 Antonie van Leuwenhoek and the Invention of the Microscope

Arguably, the first to have observed microorganisms was the German Jesuit scholar and polymath Athanasius Kircher (1602–1680). In fact, Kircher was ahead of his time in proposing that the plague was caused by an infectious microorganism and in suggesting effective measures to prevent the spread of the disease. He took a notably modern approach to the study of diseases, as early as 1646, using a microscope to investigate the blood of plague victims. In his *Scrutinium Pestis* of 1658, he noted the presence of "little worms" or "animalcules" in the blood and concluded that the disease was caused by microorganisms [6]. The conclusion was correct, although it is likely that what he saw were rather red or white blood cells and not the plague agent, *Yersinia pestis*. He proposed hygienic measures to prevent the spread of disease, such as isolation, quarantine, burning clothes worn by the infected, and wearing face masks to prevent the inhalation of germs. He wrote "Concerning the wonderful structure of things in nature, investigated by Microscope" in 1646, stating "who would believe that vinegar and milk abound with an innumerable

multitude of worms." He also noted that putrid material is full of innumerable creeping animalcules.

And yet, the Dutch microscopist Antonie van Leeuwenhoek (1673–1723) is universally acknowledged as the father of microbiology. He discovered both protists and bacteria. More than being the first to see this unimagined world of "animalcules," he is claimed to be the first even to think of looking and, certainly, the first with the power to see. Using his own deceptively simple, single-lensed microscopes, he did not merely observe but conducted ingenious experiments, exploring and manipulating his microscopic universe with a curiosity that belied his lack of a map or bearings. Leeuwenhoek was a pioneer, a scientist of the highest level, yet his reputation suffered at the hands of those who envied his fame or scorned his unschooled origins, as well as through his own mistrustful secrecy of his methods, which opened a world that others could not comprehend. A largely self-taught man in science, he is without doubt one of the first league of microscopists and microbiologists, best known for his pioneering work in microscopy and contributions toward the establishment of microbiology as a scientific discipline. While running his draper shop, van Leeuwenhoek originally pursued to see the quality of the thread better than what was possible using the magnifying lenses of the time. He developed an interest in lens-making. van Leeuwenhoek's familiarity with glass processing led to one of the most significant, and simultaneously well-hidden, technical insights in the history of science: by placing the middle of a small rod of soda lime glass in a hot flame, van Leeuwenhoek could pull the hot section apart to create two long whiskers of glass. Then, by reinserting the end of one whisker into the flame, he could create a very small, high-quality glass sphere. These spheres became the lenses of his microscopes, with the smallest spheres providing the highest magnifications [7]. Ultimately, van Leeuwenhoek's work fully captured the attention of the Royal Society of London, with which he began corresponding regularly regarding his observations. Despite the initial success of van Leeuwenhoek's relationship with the Royal Society, soon relations became severely strained. His credibility was questioned when he sent the Royal Society a copy of his first observations of microscopic single-celled organisms dated 1676. Previously, the existence of single-celled organisms was entirely unknown. Thus, even with his established reputation with the Royal Society as a reliable observer, his observations of microscopic life were initially met with some skepticism. Eventually, in the face of van Leeuwenhoek's insistence, the Royal Society arranged for Alexander Petrie, minister to the English Reformed Church in Delft, Benedict Haan, at that time Lutheran minister at Delft, and Henrik Cordes, then Lutheran minister at the Hague, accompanied by Sir Robert Gordon and four others, to determine whether it was in fact van Leeuwenhoek's ability to observe and reason clearly or, perhaps, the Royal Society's theories of life that might require reform. Finally, in 1677, van Leeuwenhoek's observations were fully acknowledged by the Royal Society. Although van Leeuwenhoek did not write any books, his discoveries came to light through correspondence with the Royal Society, which published his letters. By the end of the seventeenth century, van Leeuwenhoek had a virtual monopoly on microscopic study and discovery and was visited over the years by many notable individuals, such as the Russian Tsar Peter

**Fig. 1.3** Late 1800s antique brass microscope with original glass slides in wooden box. (From the personal collection of the author)

the Great, German philosopher Leibniz, William III, Prince of Orange, Queen Mary II of England, and the mayor (burgemeester) of Amsterdam Johan Huydecoper, and all gazed with awe at the tiny creatures. To the disappointment of his guests though, van Leeuwenhoek refused to reveal the cutting-edge microscopes he relied on for his discoveries, instead showing visitors a collection of average-quality lenses.

Meanwhile, his contemporary Robert Hooke (1635–1703), yet another early microscope pioneer, bemoaned that the field had come to rest entirely on one man's shoulders. Robert Hooke was an English scientist, architect, and polymath, who, using a microscope, was among the first to visualize a microorganism. Hooke's 1665 book *Micrographia*, describing observations with microscopes and telescopes, as well as original work in biology, contains the earliest of an observed microorganism, the microfungus *Mucor*. Finally, Hooke coined the term cell, suggesting plant structure's resemblance to honeycomb cells.

Ultimately, the performance of a light microscope depends on the quality and correct use of the condenser lens system to focus light on the specimen and the objective lens to capture the light from the specimen and form an image. Early instruments were limited until this principle was fully appreciated and developed from the late nineteenth to very early twentieth century (Fig. 1.3) and until electric

lamps were available as light sources. In 1893, August Köhler (1866–1948) developed a key principle of sample illumination, Köhler illumination, which is central to achieving the theoretical limits of resolution for the light microscope. This method of sample illumination produces even lighting and overcomes the limited contrast and resolution imposed by early techniques of sample illumination.

## 1.6 History of Medical Mycology: Johann Lukas Schönlein and David Gruby

Mycology is the branch of biology concerned with the study of the fungi, including their genetic and biochemical properties, their taxonomy, their use in nutrition and in medicine, as well as their hazards, such as toxicity or infection. Mycology branches into the field of plant pathology, with the two disciplines being closely related since the majority of plant pathogens are of fungal origin. Some fungi can cause disease in animals and humans. Pathogenic fungi are fungi that cause disease in humans or other organisms. Approximately 300 fungi are known to be pathogenic to humans. The study of pathogenic fungi that infect humans is referred to as medical mycology.

Mycology is a relatively new science that became systematic only after the development of the microscope in the seventeenth century.

Although fungal spores were first observed by Italian polymath and "professor of secrets" Giambattista della Porta (1535–1615) in 1588, the seminal work in the development of mycology is considered to be the publication of Italian botanist Pier Antonio Micheli's (1679–1737) work *Nova plantarum genera* in Florence in 1737, which laid the foundations for the systematic classification of grasses, mosses, and fungi. In this seminal work, he gave descriptions of 1900 plants, of which about 1400 were described for the first time. Among these were 900 fungi and lichens, accompanied by 73 plates. He included information on "the planting, origin and growth of fungi, mucors, and allied plants" and was the first to point out that fungi have reproductive bodies or spores, disputing the theory of spontaneous regeneration, i.e., the body of thought on the ordinary formation of living organisms without descent from similar organisms. The theory held that living creatures could arise from nonliving matter. It was hypothesized that certain forms such as fleas could arise from inanimate matter such as dust or that maggots could arise from dead flesh.

The doctrine of spontaneous generation was originally amalgamated by Aristotle (384–322 BC), who compiled and expanded the work of earlier natural philosophers and the various ancient explanations for the appearance of organisms, and was taken as scientific fact for two millennia, until challenged in the seventeenth and eighteenth centuries by the experiments of Francesco Redi (1626–1697), who demonstrated that maggots come from eggs of flies, and of Lazzaro Spallanzani (1729–1799), an Italian Catholic priest, whose research on biogenesis paved the way for the downfall of the theory of spontaneous generation.

The founding nomenclaturist Carl Linnaeus (1707–1778) included fungi in his binomial naming system of 1753, where each type of organism has a two-word

name consisting of the genus and the species, whereas up to then, organisms were often designated with Latin phrases containing many words. He originated the scientific names, still used today, of numerous well-known mushroom taxa. At that period, fungi were considered to belong to the plant kingdom, and so they find their place in his magnum opus *Species Plantarum*, though fungi are evolutionarily more closely related to animals than to plants, which has been recognized only a few decades ago.

A characteristic that places fungi in a different kingdom from plants, bacteria, and some protists is chitin in their cell walls. Fungi, like animals, are heterotrophs, i.e., they acquire their food by absorbing dissolved molecules, typically by secreting digestive enzymes into their environment. Fungi do not photosynthesize. Growth is their means of mobility, except for spores, which may travel through the air.

Extending the use of the binomial system of nomenclature of Carl Linnaeus, Dutch Christiaan Hendrik Persoon (1761–1836) established the first classification of mushrooms with such skill as to be considered a founder of modern mycology. Later, Elias Magnus Fries (1794–1878) further elaborated the classification of fungi, using spore color and microscopic characteristics, methods still used by taxonomists today. Other notable early contributors to mycology in the seventeenth to nineteenth and early twentieth centuries include Miles Joseph Berkeley (1803–1889), August Carl Joseph Corda (1809–1849), Anton de Bary (1831–1888), the brothers Louis René (1815–1885) and Charles Tulasne (1816–1884), Arthur H. R. Buller (1874–1944), Curtis G. Lloyd (1859–1926), and Pier Andrea Saccardo (1845–1920).

Inspired by Italian entomologist Agostino Bassi's (1773–1856) 1835 discovery that the muscardine disease of silkworms was caused by a living, very small, parasitic organism, a fungus that would be named eventually *Beauveria bassiana* in his honor, German Professor of Medicine Johann Lukas Schönlein (1793–1864) identified the fungal origin of favus in 1839. The fungus was initially named after a microscopic structure termed *Achorion* (a term no longer used), seen in scrapings of infected skin, which consists of slender, mycelial threads matted together, bearing oval, nucleated fungal spores (conidia), either free or jointed (arthroconidia). This structure corresponds with the characteristic lesion of favus, the scutula, a yellow, saucer-shaped crust, consisting of a mass of hyphae, pus, and scales. The fungus itself is now called *Trichophyton schoenleinii* [8].

While Bassi originally maintained that not only insect but also human diseases may be caused by other living microorganisms, Schönlein ultimately provided the proof of concept. It was the first disease in which a fungus was discovered. The discovery was published in a brief note of twenty lines in *Miller's Archive* for that year (p. 82).

Independently of Schönlein's discovery 2 years earlier, Hungarian physician David Gruby (1810–1898) described in 1841 the fungus associated with favus in his *Mémoire sur une vegétation qui constitue la vraie teigne*; in 1842, he described *Trichophyton mentagrophytes* that is associated with tinea barbae (*Sur une espèce de mentagre contagieuse résultant du dévelopement d'un nouveau cryptogame dans la racine des poils de la barbe de l'homme*). Gruby discovered *Candida (Monilia) albicans* as the cause of pediatric thrush (*Recherches anatomiques sun une plante*

*cryptogame qui constitue le vrai muguet des enfants*), and in 1843 he described *Microsporum audouinii* as the cause of a type of scalp ringworm (*Recherches sur la nature, le siège et le développement du Porrigo decalvans ou phytoalopécie*). Finally, he is commemorated with the eponym Gruby disease for tinea capitis in children due to an infection with *Trichophyton tonsurans* (*Recherches sur les cryptogames qui constituent la maladie contagieuse du cuir chevelu sous le nom de Teigne*) [9].

In 1892, two additional "species" of the fungus-causing favus were described by a German physician specialized in dermatology, Paul Gerson Unna (1850–1929), the *Favus griseus*, giving rise to grayish-yellow scutula, and the *Favus sulphureus celerior*, causing sulfur-yellow scutula of a rapid growth. This was in the days before scientists learned to rigorously distinguish microorganism identities from disease identities, and these antique, ambiguous disease-based names no longer have status either in mycology or in dermatology.

In 1927, Unna described for the first time what was to be called Unna disease, a long-term skin disorder associated with seborrhea and greasy scales on the scalp, the eyebrows, or other parts of the skin that are rich in sebaceous follicles, basically considered as seborrheic dermatitis today. Currently, the condition is understood to be due to an inflammatory (eczematous) response to over-colonization by *Malassezia* fungi species in sebum-producing skin areas.

In the twentieth and twenty-first centuries, advances in biochemistry, genetics, molecular biology, biotechnology, DNA sequencing, and phylogenetic analysis have provided new insights into fungal relationships and biodiversity and have challenged traditional morphology-based groupings in fungal taxonomy.

Medical mycology represents a fundamental part of dermatology, since a significant number of diseases of the skin, hair, nails, and mucous membranes are of fungal origin and may range from embarrassing to life-threatening. They have been classified as superficial and cutaneous mycoses by anatomical location and by organism (dermatophytes and others), subcutaneous, systemic, and opportunistic.

## 1.7 Birth of Modern Bacteriology: Robert Koch and Louis Pasteur

Bacteriology is the branch and specialty of biology that studies the morphology, ecology, genetics, and biochemistry of bacteria as well as other aspects related to them. This subdivision of microbiology involves the identification, classification, and characterization of the bacterial species. Lastly, bacteriology is the study of bacteria in their relation to medicine. While bacteriology evolved from physicians needing to apply the germ theory to test the concerns relating to the spoilage of foods and wines in the nineteenth century, the eventual identification and characterizing of bacteria being associated with disease led to advances in pathogenic bacteriology. Ultimately, Koch's postulates played a role into identifying the relationships between bacteria and specific diseases. Since then, bacteriology has had many successful advances like effective vaccines and provided the discovery of antibiotics.

Pathogenic bacteria are bacteria that can cause disease. Although most bacteria are harmless or often beneficial, some are pathogenic, with the number of species estimated as fewer than a hundred that are seen to cause infectious diseases in humans. Each species has specific effect and causes symptoms in people who are infected. Bacterial pathogens often cause infection in specific areas of the body. Others are generalists. The symptoms of disease appear as pathogenic bacteria that damage host tissues or interfere with their function. Koch's postulates are the standard to establish a causative relationship between a microbe and a disease.

Robert Koch (1843–1910) was a German physician and microbiologist and one of the main founders of modern bacteriology. He identified the specific causative agents of tuberculosis, cholera, and anthrax and also gave experimental support for the concept of infectious disease, which included experiments on animals and humans. His research led to the creation of Koch's postulates, a series of four generalized principles linking specific microorganisms to specific diseases.

In an attempt to isolate and grow bacteria, Koch began to use solid nutrients such as potato slices, though these proved not suitable for all organisms. Therefore, he began to use nutrient solutions with gelatin; however, gelatin, like potato slices, was not the optimal medium for bacterial growth, as it did not remain solid at 37 °C, the ideal temperature for growth of most human pathogens. Eventually, he began to utilize agar to grow and isolate pure cultures, because this polysaccharide remains solid at 37 °C, is not degraded by most bacteria, and results in a transparent medium.

Eventually, Koch developed a generic set of postulates for the determination of the cause of most infectious diseases. These postulates not only outlined a method for linking cause and effect of an infectious disease but also established the significance of laboratory culture of infectious agents [10]:

1. The organism must always be present, in every case of the disease.
2. The organism must be isolated from a host containing the disease and grown in pure culture.
3. Samples of the organism taken from pure culture must cause the same disease when inoculated into a healthy, susceptible animal in the laboratory.
4. The organism must be isolated from the inoculated animal and must be identified as the same original organism first isolated from the originally diseased host.

During his time as government advisor with the Imperial Department of Health in Berlin in the 1880s, Koch became interested in tuberculosis research. At the time, it was widely believed that tuberculosis was an inherited disease. However, Koch was convinced that the disease was caused by a bacterium and was infectious and tested his four postulates using guinea pigs. Through these experiments, he found that his experiments with tuberculosis fulfilled all four of his postulates, and in 1882, he published his findings, in which he reported the causative agent of tuberculosis to be the slow-growing *Mycobacterium tuberculosis.*

Louis Pasteur (1822–1895) (Fig. 1.4) was a French biologist, microbiologist, and chemist renowned for his discoveries of the principles of vaccination, microbial fermentation, and pasteurization. Most importantly, he provided the final disproval of the doctrine of spontaneous generation, which was still ardently supported by his opponent Félix Archimède Pouchet (1800–1872), and direct support for the germ theory of disease and its application in clinical medicine.

In a series of experiments to disapprove the doctrine of spontaneous generation, Pasteur placed boiled liquid in a flask and let hot air enter the flask. Then he closed the flask, and no organisms grew in it. In another experiment, when he opened flasks containing boiled liquid, dust entered the flasks, causing organisms to grow in some. Pasteur also used swan neck flasks containing a fermentable liquid. Air was allowed to enter the flask via a long curving tube that made dust particles stick to it. Nothing grew in the broths unless the flasks were tilted, making the liquid touch the contaminated walls of the neck. This showed that living organisms that grew in such broths came from outside, on dust, rather than spontaneously generating within the liquid or from the action of pure air. The French Academy of Sciences viewed Pasteur's experiments and observations as sophisticated and convincing. Along with this and due to the religious climate of this time, Pasteur had an advantage because his view that only life produces life was aligned with the views of the church [11].

**Fig. 1.4** Louis Pasteur. (From the desk of the author)

Pasteur is best known though for his courageous experiments on rabies and the first production of a respective vaccine, dramatically commemorated in Axel Munthe's *The Story of San Michele* [12]. The vaccine's success finally laid the foundations for the manufacture of further vaccines, and the first of the Pasteur Institutes was built on the foundation of this accomplishment.

Shortly after finishing his undergraduate studies at the University of Aberdeen in Scotland and embarking on his career as a surgeon, Alexander Ogston (1844–1929) presented in 1880 at the Ninth Surgical Congress in Berlin his work establishing the causative role of bacteria in wound infection and septicemia. Building on the teachings of his senior contemporary Louis Pasteur, Ogston had observed pus from 88 human abscesses under his microscope and noted Gram-positive spherical micrococci. Taking from the Greek word σταφυλή for "bunches of grapes," he named the organism *Staphylococcus*. After injecting the isolated bacteria into healthy guinea pigs and mice and recreating the abscesses from which the isolates were derived, he had conclusively proven the pathogenicity of the infectious agent, now known as *Staphylococcus aureus* due to its golden color in culture [13]. Mostly, staphylococci are responsible for skin infections such as boil, carbuncle, and furuncle, superficial bacterial folliculitis of the scalp, and folliculitis decalvans.

The identification of bacteria in the laboratory has been particularly relevant in medicine, where the correct treatment is determined by the bacterial species causing an infection. Consequently, the need to identify human pathogens was a major impetus for the development of techniques to identify bacteria.

The Gram stain, developed in 1884 by Danish bacteriologist Hans Christian Gram (1853–1938), characterizes bacteria based on the structural characteristics of their cell walls. The thick layers of peptidoglycan in the Gram-positive cell wall stain purple, while the thin Gram-negative cell wall appears pink. By combining morphology and Gram staining, most bacteria can be classified as belonging to one of four groups (Gram-positive cocci, Gram-positive bacilli, Gram-negative cocci, and Gram-negative bacilli) [14]. Some organisms are best identified by stains other than the Gram stain, particularly mycobacteria, which show acid fastness on Ziehl-Neelsen. Other organisms may need to be identified by their growth in special media or by other techniques. As with bacterial classification, identification of bacteria is increasingly using molecular methods. Diagnostics using DNA-based tools, such as polymerase chain reaction (PCR), are increasingly popular due to their specificity and speed, compared to culture-based methods. These methods also allow the detection and identification of viable but nonculturable cells that are metabolically active but non-dividing.

## 1.8 Birth of Virology: Dmitri Ivanovsky and Martinus Beijerinck

Virology is a subspecialty of microbiology that deals with the study of viruses. A virus is a submicroscopic infectious agent that replicates only inside the living cells of an organism. When infected, a host cell is forced to rapidly produce thousands of

identical copies of the original virus. Most virus species have virions too small to be seen with an optical microscope, as they are one-hundredth the size of most bacteria.

The Russian botanist Dmitri Iosifovich Ivanovsky (1864–1920) is credited with the discovery of viruses. He studied at the University of Saint Petersburg in 1887, when he was sent to Ukraine and Bessarabia to investigate a tobacco disease causing great damage to plantations located there at the time. Three years later, he was assigned to look into a similar disease occurrence of tobacco plants, this time raging in the Crimea region. He discovered that both incidents of disease were caused by an extremely minuscule infectious agent, capable of permeating porcelain Chamberland filters, something which bacteria could never do, and described his findings in an article in 1892 and a dissertation in 1902. In 1898, the Dutch microbiologist Martinus Beijerinck (1851–1931) independently reproduced Ivanovsky's experiments and became convinced that the filtered solution contained a new form of infectious agent, which he named *Contagium vivum fluidum* (Latin: "contagious living fluid"), underlining its ability to slip through the finest mesh filters then available, giving it almost liquid properties. Ivanovsky, irked that Beijerinck had not cited him, recreated Beijerinck's experimental setup and demonstrated that particles of ink were small enough to pass through the filter, thus leaving the particulate or fluid nature of the pathogen unresolved. Nevertheless, Beijerinck subsequently acknowledged Ivanovsky's priority of discovery.

It was only the invention of the electron microscope in 1931 that enabled the first imaging of viruses in 1935 by the American virologist Wendell Meredith Stanley (1904–1971). The second half of the 1900s resulted in the discovery of more than 2000 virus species infecting animals, plants, and bacteria [15].

One main motivation for the study of viruses is the fact that they cause many important infectious diseases, including in the skin (herpes, varicella zoster, human papilloma virus, and others), and have given rise to important pandemics, such as the Spanish flu (1918), the great parrot fever pandemic (1930), AIDS (1981), SARS (2002), Ebola (2014), Zika (2016), and recently COVID-19 [16].

Urbanization and globalization, by concentrating large numbers of people in cramped and often unsanitary spaces, and greater global interconnectivity driven by international travel and commerce are undoubtedly key factors for the emergence and rapid spread of infectious diseases, as well as the growing demand for animal protein in rapidly industrializing countries, putting pressure on remote animal habitats where pathogens reside.

As most viruses are too small to be seen by a light microscope, sequencing is one of the main tools in virology to identify and study the virus. Traditional Sanger sequencing and next-generation sequencing (NGS) are used to sequence viruses in basic and clinical research, as well as for the diagnosis of emerging viral infections, molecular epidemiology of viral pathogens, and drug resistance testing. There are more than 2.3 million unique viral sequences in GenBank.

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# General Considerations on Infectious Diseases

2

Ralph M. Trüeb

## Contents



As opposed to noncommunicable diseases, i.e., cardiovascular diseases (heart attack and stroke), cancers, respiratory diseases (chronic obstructive pulmonary disease and asthma), and diabetes, which represent the leading cause of death globally today, infectious diseases, also known as communicable diseases or transmissible diseases, are an illness resulting from the invasion of an organism's body tissues by disease-causing agents, their multiplication, and the reaction of host tissues to the infectious agents and the toxins they produce. They can be spread from one person to another and under certain conditions may cause a large number of people to get sick.

Infections are caused by a wide range of pathogens, including bacteria, viruses, fungi, parasites, and arthropods.

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The infectious agents are spread in a number of ways including:

- Physical contact with an infected person, through contact with skin, sexual contact, fecal/oral contact, or respiratory droplets
- Mother to unborn child
- Contact with a contaminated surface or object, food, blood, or water
- Bites from insects or animals capable of passing the specific disease
- Through the air

Epidemiology is the study and analysis of who, why, and where disease occurs and what determines whether various populations have a disease. Epidemiologists may determine differences among groups within a population, such as whether certain age groups have a greater or lesser rate of infection, whether groups living in different environs are more likely to be infected, and by other factors, such as gender and ethnicity. Researchers also may assess whether a disease outbreak is sporadic or just an occasional occurrence; endemic, with a steady level of regular cases occurring in a region; epidemic, with a fast arising and unusually high number of cases in a region; or pandemic, which is a global epidemic.

Contagious skin diseases present with a wide range of symptoms. Some have similarities such as rashes, but most are very different.

If the cause of the infectious disease is unknown, epidemiology can be used to assist with tracking down the sources of infection.

The control of certain communicable diseases is required by law. The respective public health office prevents and controls these diseases through prevention programs, including immunization, and by monitoring and following up on cases when they are reported. Doctors, nurses, the laboratories, and eventually others report the respective communicable diseases when they occur.

## 2.1 Definition

An infectious disease is a disease that spreads from one person or animal to another. Some people also refer to infectious diseases as “communicable” or “transmissible” diseases.

Once a pathogen has entered a person’s body, it will begin replicating. The individual may then begin to experience symptoms. Some symptoms are a direct result of the pathogen damaging the body’s cells; others are due to the body’s immune response to the infection. The host reacts to infections with an innate response, often involving inflammation, followed by an adaptive response.

Communicable diseases are often mild, and symptoms pass after a few days. However, some can be serious and potentially life-threatening.

The skin is our body’s defense, protecting it from harmful environmental forces. And yet, viruses, bacteria, or fungi may sometimes penetrate the skin barriers and

cause infectious diseases. These infections are called contagious skin diseases. They present with a wide range of symptoms. Some have similarities, such as rashes, while others present in a quite specific manner for the causative infectious agent.

Infections of the scalp include bacterial infection of hair follicles (folliculitis), infestation with head lice (pediculosis capitis), and fungal infection or scalp ringworm (tinea capitis). Itching and excessive flaking of the scalp are seen with dandruff and seborrheic dermatitis, of which both are associated with perturbations of the normal scalp microbiome [1]. But also systemic infectious disease may manifest with hair shedding, such as syphilis [2], and systemic febrile infections, like dengue hemorrhagic fever [3] or COVID-19 [4].

## 2.2 Classification

Infections are caused by a wide range of pathogens, including bacteria, fungi, viruses, and parasites. The invasion of a human or animal body with an arthropod is usually termed infestation.

The symptoms of an infection depend on the type of disease. Some signs of infection affect the whole body generally, while others are specific to individual body parts, such as the skin and hair. An infection is not synonymous with an infectious disease, as some infections do not cause illness in a host. In certain cases, infectious diseases may be asymptomatic for much or even all of their course in a given host. The condition may only be defined as a disease, which by definition means an illness, in hosts who secondarily become ill after contact with an asymptomatic carrier. Persistent infections occur when the body is unable to clear the organism after the initial infection. Persistent infections are characterized by the continual presence of the infectious agent, often as latent infection with occasional recurrent relapses of active infection.

Since the introduction of specific therapeutic agents, the focus of attention has been on the determination of the specific infectious agents so that the proper choice of therapy can be made. This has rendered pointless, and in fact out-of-date, descriptions of some of the dermatologic entities whose status depended on ill-defined morphologic criteria rather than on etiologic considerations. From the pragmatic perspective, the approach has been to classify the infectious diseases by their microbial causation.

The normal skin of healthy individuals is highly resistant to invasion by bacteria to which it is constantly exposed. Bacteria are unable to penetrate the keratinized layers of normal skin and, when applied to the surface, rapidly decrease in number. The susceptibility to infection with pathogenic bacteria is determined by specific and unspecific factors, such as immunocompetence, nutritional state, and integrity of the cutaneous barrier. Meanwhile, certain bacterial species colonize the skin surface successfully. The microorganisms that characteristically survive and multiply in various ecologic niches of the skin constitute the normal cutaneous flora or microbiome. An appreciation of the composition of this flora and the attributes of its

major elements has gained the focus of attention for understanding and treating dermatologic diseases including the scalp.

Bacterial skin infections have been classified into (1) primary infections, (2) secondary infections, and (3) the cutaneous manifestations of systemic bacterial disease.

Primary bacterial infections are produced by the invasion of seemingly normal skin by a single species of pathogenic bacteria. Treatment aimed at the pathogen almost invariably results in the cure of the lesion, since there is usually no doubt as to the primary etiologic role of the specific agent in the pathogenesis of the lesion. Examples are follicular impetigo, folliculitis decalvans, sycosis barbae, furuncles, and carbuncles.

Secondary bacterial infections develop in areas of already damaged skin, and the appearance of these lesions is largely determined by the underlying skin condition. Although the bacteria did not produce the underlying skin condition, their proliferation and invasion of the skin may aggravate and prolong the disease. Secondary infections often show a mixture of organisms on culture, and not infrequently, it is difficult to determine which plays the major role. Examples are bacterial infections complicating traumatic lesions, eczematous dermatitis or dermatophytosis, dissecting cellulitis of the scalp, and pilonidal sinus.

The dermatophytes are a group of taxonomically related fungi capable of colonizing keratinized tissues such as the stratum corneum of the epidermis, the hair, and the nails, since dermatophytes can use keratin as a source of nutrients. The classification of the dermatophytes emphasizes ecologic features of the pathogens, as well as the pattern of infection of the hair.

Those species found only in soil are called *geophilic*, those in association with domestic or wild animals *zoophilic*, and those found only in association with human beings *anthropophilic*.

A number of different species of fungi are involved in dermatophytosis. Dermatophytes of the genera *Microsporum* and *Trichophyton* are the most causative agents.

Tinea capitis is a dermatophytosis of the scalp and associated hair. When suspected hairs are placed on microscope slides with clearing solution to be examined by low-power microscopy, one out of three patterns of infection may be seen: *ectothrix* with fungal arthrospores outside the hair shaft, *endothrix* with arthrospores contained within the hair shaft, or *favic* with a linear arrangement of hyphal fragments in chains along the longitudinal axis of the hair shaft. Finally, the different organisms causing tinea capitis may present with different clinical patterns: (1) noninflammatory, human, or epidemic type, (2) inflammatory type, (3) “black dot” tinea capitis, and (4) tinea favosa, with their respective causative agents, (1) *M. audouinii* and *M. ferrugineum*, (2) *M. canis* and *M. gypseum*, (3) *T. tonsurans* and *T. violaceum*, and (4) *T. schoenleinii*, respectively. Kerion celsi is the most pronounced type of inflammatory tinea capitis which is a result of the host’s response on the fungal infection of the hair follicles. It can be accompanied by secondary bacterial infection. It usually appears as raised, spongy lesions and typically occurs

in children. This honeycomb is a painful inflammatory reaction with deep suppurative lesions on the scalp and follicles discharging pus.

Tinea barbae is a fungal infection limited to coarse hair-bearing areas such as the beard and moustache.

Piedra is a condition in which the fungus causes formation of nodules on the hair shaft. Depending on the fungal agent, the clinical presentation, and climatic preferences, a classification is made into white and black piedra.

Yeast infections of the scalp can be classified into candidiasis and pityrosporum infections.

*Candida albicans* is the most important fungal opportunistic pathogen that can cause infection when the host becomes debilitated or immunocompromised. Systemic candidiasis usually follows dissemination of *Candida* spp. from the gastrointestinal tract or via the bloodstream. Skin lesions may occur particularly in two situations: (1) in neutropenic patients with severe disseminated disease and widespread muscle pain and (2) in intravenous drug abusers, where candidiasis may present with a follicular pustular rash in the beard area and scalp. *Candida* infection of the scalp in immunocompetent patients is rare [5].

Meanwhile, *Pityrosporum* spp. are part of the normal flora, particularly in sebum-rich areas of the skin, including the scalp. Under appropriate conditions, it may convert from the saprophytic yeast to the predominantly parasitic mycelial morphology associated with clinical disease, such as tinea versicolor. Dandruff, seborrheic dermatitis, the head-and-neck type atopic dermatitis, and folliculitis are typical scalp conditions related to *Pityrosporum*.

Molds growing in mycological cultures (Petri dishes) taken from the scalp and hair usually represent external contaminations. Molds are a large and taxonomically diverse number of fungal species in which the growth of hyphae results in discoloration and a fuzzy appearance. They reproduce by producing large numbers of small spores. Some molds produce small, hydrophobic spores that are adapted for wind dispersal and may remain airborne for long periods. Although molds can grow on dead organic matter everywhere in nature, their presence is visible to the unaided eye only when they form large colonies. A mold colony does not consist of discrete organisms but is an interconnected network of hyphae called a mycelium. In artificial environments, humidity and temperature are often stable enough to foster the growth of mold colonies, commonly seen as a downy or furry coating growing on surfaces.

Viruses represent a diverse group of infectious agents that share a distinctive composition and a unique mode of replication. They are not cellular organisms. A virus is a submicroscopic infectious agent that replicates only inside the living cells of an organism. Viruses infect all life forms, from animals and plants to microorganisms, including bacteria. The most important element of a virus is its genetic information, which it transfers to a susceptible host. When infected, a host cell is forced to rapidly produce thousands of copies of the original virus. Viruses are by far the most abundant biological entities on Earth, and they outnumber all the others put together. They display a wide diversity of shapes and sizes. Accordingly, the animal

viruses have been divided into several large families according to their morphologies, the structure of the virion, and the type of viral nucleic acid (DNA or RNA). Finally, the range of structural and biochemical effects that viruses have on the host cell is also extensive. These are called cytopathic effects. Most virus infections eventually result in the death of the host cell. The causes of death include cell lysis, alterations to the cell's surface membrane, and apoptosis. Some viruses cause no apparent changes to the infected cell. Cells in which the virus is latent and inactive show few signs of infection and often function normally. This causes persistent infections, and the virus is often dormant for many months or years. This is often the case with herpesviruses.

By definition, parasitism is a symbiotic relationship between species, where one organism, the parasite, lives on (ectoparasites) or inside (endoparasites) another organism, the host, causing it some harm, and is adapted structurally to this way of life. Parasites reduce host fitness by general or specialized pathology while increasing their own fitness by exploiting hosts for resources necessary for their survival, in particular by feeding on them and by using intermediate (secondary) hosts to assist in their transmission from one definitive (primary) host to another. Parasitism has an extremely wide taxonomic range, including animals, plants, fungi, protozoans, bacteria, and viruses. Parasites use a variety of methods to infect animal hosts, including physical contact, the fecal-oral route, free-living infectious stages, and vectors, suiting their differing hosts, life cycles, and ecological contexts.

Infestation is the state of being invaded by parasites. In general, the term refers to parasitic diseases caused by animals such as arthropods, such as mites, ticks, and lice, and worms, but excluding conditions caused by protozoa, fungi, bacteria, and viruses, which are called infections. Medically, the term infestation is also reserved for external ectoparasitic infestations, while the term infection refers to internal endoparasitic conditions.

Bacteriology is the study of bacteria and their relation to medicine, virology that of the viruses, mycology that of the fungi, parasitology that of the parasites, and entomology that of the arthropods. Tropical medicine is the study of the world's major diseases endemic to the tropics and related conditions. Because of the similarity of thinking and working with microorganisms other than bacteria, fungi, viruses, and protozoa, there has been a tendency for the field of bacteriology to extend as microbiology. The dermatologist should be knowledgeable of the respective specialties as they relate to the skin, hair, and nails. Infectiology is the medical specialty dealing with the diagnosis and treatment of complex infections. An infectious disease specialist's practice consists of managing nosocomial (healthcare-acquired) infections or community-acquired infections and is historically associated with travel medicine and tropical medicine.

## 2.3 Pathophysiology

There is a general chain of events that leads to infections. The chain of events involves several steps, which include the infectious agent, reservoir, entering a susceptible host, exit, and transmission to new hosts. Each of the links must be present in a chronological order for an infection to develop and spread.

Infection begins when the pathogen successfully enters the body, grows, and multiplies. This is referred to as colonization. The variables involved in the outcome of a host becoming inoculated by a pathogen and the ultimate outcome include:

- The route of entry of the pathogen and the access to host regions that it gains
- The intrinsic virulence of the particular organism
- The quantity or load of the initial inoculant
- The immune status of the host being colonized

Hosts can fight infections using their immune system. Mammalian hosts react to infections with an innate response, often involving inflammation, followed by an adaptive response. Disease arises if the host's protective immune mechanisms are compromised and the organism inflicts damage on the host.

The disease-producing capacity of bacteria is determined by (1) the invasion potential of the microorganism and (2) its toxigenic properties. Though it is useful to distinguish between these two major pathogenic mechanisms, most bacterial infections result from a combination of the invasive and toxigenic properties of the organism.

For many disease-producing bacteria, including the suppurative lesions of *S. aureus*, a clear understanding of the basis for pathogenicity has been lacking. And yet, it is recognized that exotoxins constitute essential components of the virulence mechanisms of *S. aureus*. Nearly all strains secrete lethal factors that convert host tissues into nutrients required for bacterial growth. Panton-Valentine leukocidin (PVL) is one of many toxins associated with *S. aureus* infection. It was initially discovered by Van deVelde in 1894 due to its ability to lyse leukocytes. It was named after Sir Philip Noel Panton and Francis Valentine when they associated it with soft tissue infections in 1932 [6]. The presence of PVL is associated with increased virulence of certain strains of *S. aureus*. It is present in the majority of community-associated methicillin-resistant *S. aureus* isolates studied [7] and is the cause of necrotic lesions of the skin.

What's more, the role of bacterial biofilms as pathogenetic factors in chronic recurrent bacterial disease of the skin and hair has only recently gained attention. A biofilm comprises any syntrophic consortium of microorganisms in which cells stick to each other and to a surface. These adherent cells become embedded within a slimy extracellular matrix that is composed of extracellular polymeric substances, such as polysaccharides, proteins, lipids, and DNA. Biofilms may form on living or

nonliving surfaces in response to a number of different factors, which may include cellular recognition of specific or nonspecific attachment sites on a surface and nutritional cues. A cell that switches to the biofilm mode of growth undergoes a phenotypic shift in behavior in which large suites of genes are differentially regulated. Biofilms are not just bacterial slime layers but biological systems; the bacteria organize themselves into a coordinated functional community. The biofilm bacteria can share nutrients and are sheltered from harmful factors in the environment, such as desiccation, antibiotics, and a host body's immune system.

It is suggested that around two-thirds of bacterial infections in humans involve biofilms [8, 9]. Infections associated with biofilm growth usually are challenging to eradicate due to the fact that mature biofilms display antimicrobial tolerance and immune response evasions [10, 11]. Biofilms often form on the inert surfaces of implanted devices such as catheters, prosthetic cardiac valves, and intrauterine devices. Some of the most difficult infections to treat are those associated with the use of medical devices [8]. Biofilms can form on the teeth as dental plaque, where they may cause tooth decay and gum disease. Biofilm formation in the skin has been identified in soft tissue fillers [12] and more recently in folliculitis decalvans [13].

In the case of clinical fungal infection of the skin and hair, a suitable environment on the host skin is of critical importance: trauma, hydration, and occlusion all interfere with the barrier function of the stratum corneum. Once the host skin is inoculated under the suitable conditions, there follow several stages through which the dermatophyte infection progresses. During an initial incubation period, the dermatophyte grows in the stratum corneum, sometimes with minimal clinical symptoms of infection. A *carrier status* has been postulated when the presence of a dermatophyte is detected on seemingly normal skin. Once the infection is established in the stratum corneum of the skin, (1) the rate of growth of the organism, in its relation to (2) the epidermal turnover rate, is determinant, since the fungal growth rate must equal or exceed the epidermal turnover rate or the organism will be shed quickly. Proteolytic enzymes, including keratinases, and toxins produced by the organism and the host immunologic response finally account for the clinical presentation of disease.

Resistance to fungal infection may involve non-immunologic as well as immunologic mechanisms.

Noteworthy is the increase in saturated fatty acids on the skin that occurs after puberty, explaining for the higher incidence of tinea capitis during childhood.

The major immunologic defense mechanism is the type IV delayed hypersensitivity response. Infections by dermatophytes naturally stimulate the immune system as in those by other microorganisms. However, differing from other infections, the infecting organisms cannot become a direct target of antibody response or phagocytosis because they reside only in the barrier membrane of the body surface, specifically, in the stratum corneum. In dermatophytosis, a unique behavior of the epidermis as noted in contact dermatitis plays an important role in the defense against infection. Dermatitic changes induced by fungal products, particularly those due to contact sensitivity to a fungal antigen, trichophytin, enhance epidermopoiesis, which leads to increased turnover of the epidermis with their resultant elimination from the

skin surface. Furthermore, the dermatophytes in the stratum corneum provoke transepidermal leukocyte chemotaxis by generating chemotactic C5a anaphylatoxin in exudating serum via alternative complement pathway activation in addition to a release of low-molecular-weight chemotactic factors. Such neutrophilic migration with the formation of subcorneal pustules also enhances epidermal proliferation [14].

In the past, skin testing has been used both to determine the causative organisms of infection or to discover a respective immunologic deficiency state. Characteristic skin lesions usually develop after intradermal injection of the microbial antigen. However, false-positive and false-negative reactions, which antigens to use in an antigen battery, their lack of standardization, and the method of administration have been important issues dealing with the skin tests [15].

Patients with chronic dermatophytosis appear to have a relatively specific defect in delayed hypersensitivity to trichophytin, and their cell-mediated responses to other antigens may also be somewhat decreased. However, the subjects do not appear to suffer excessive morbidity from infectious diseases other than dermatophytosis [16].

Chronic mucocutaneous candidiasis (CMC) refers to a heterogeneous group of disorders characterized by recurrent or persistent superficial infections of the skin, mucous membranes, and nails with *Candida* organisms, usually *Candida albicans*, with little propensity for systemic dissemination. CMC does not represent a specific condition but rather a phenotypic presentation with a spectrum of immunologic, endocrinologic, and autoimmune disorders. The unifying feature of these heterogeneous disorders is impaired cell-mediated immunity against *Candida* species.

CMC is inherited either as an autosomal dominant or recessive trait, with nine types depending on the gene and chromosomal locus, including the interleukin 17 (IL-17) family and receptor genes.

The autoimmune polyendocrinopathy syndrome with chronic mucocutaneous candidiasis (APECED) is an autosomal recessive disease caused by mutations in the autoimmune regulator (AIRE) gene and characterized by the clinical triad of CMC, hypoparathyroidism, and adrenal insufficiency. Additional features may be insulin-dependent diabetes mellitus, chronic atrophic gastritis with pernicious anemia, hypogonadism, alopecia areata, and vitiligo. Onset is in childhood, candidiasis is usually the first symptom, and manifestations continue to appear until the fifth decade, including alopecia. AIRE is the first gene identified underlying autoimmune disease. This gene plays a critical role in the body's ability to distinguish between its own proteins and cells and those of bacteria and viruses. The marked susceptibility to mucocutaneous candidiasis without systemic candidiasis in this condition is less understood. Böni and Trüeb reported unsuccessful sensitization to diphenylcyclopropenone (DPCP) and treatment of alopecia universalis in a patient with APECED [17].

The deep fungal infections involve two distinct groups of conditions: (1) the subcutaneous and (2) the systemic mycoses. Neither are common, are largely confined to the tropics and subtropics, or are encountered as opportunistic infections in the immunocompromised, including those with AIDS or with neutropenia

associated with malignancy and solid organ transplants. Subcutaneous fungal infections usually present with signs of skin involvement, while systemic mycoses only occasionally have skin lesions, either as portal of entry or following dissemination from a deep focus of infection.

Mycetoma is a chronic localized infection caused by different species of fungi or actinomycetes, which is characterized by the formation of aggregates of the causative organisms (grains) within abscesses. These communicate via sinuses onto the skin surface or may involve adjacent bone causing a form of osteomyelitis. The organisms are usually soil or plant saprophytes that are only incidental human pathogens implanted subcutaneously, usually after a penetrating injury. Dermatophytic mycetoma of the scalp is a rarity, especially when not associated with tinea capitis [18]. Actinomyctoma of the scalp has been reported after a car accident [19]. Because of this topography and potential spread to the brain, this condition may be a particular diagnostic and therapeutic challenge.

Dermatophytic pseudomycetoma represents a chronic infection characterized by a tumor-like growth containing dermatophytes arranged as clustered aggregates (grains) within the dermis. In contrast to mycetomas, they lack sinus tracts and are more common in the scalp [20]. Both are similar to eumycetoma clinically and histopathology, being distinguished through the isolation of the fungus, which in the case of pseudomycetoma can be *Microsporum* spp. or *Trichophyton* spp. [21].

Skin lesions are a prominent feature of a number of viral diseases. In some instances, the cutaneous lesions may suggest a specific viral disease, of which diagnosis can be quickly established. At other times, the differential diagnosis is broader, particularly in the case of unspecific rashes and diffuse effluvium. In general, virus infections may affect the skin and hair by three different routes: (1) direct inoculation, (2) systemic infection, or (3) local spread from an internal focus. The skin lesions may be produced by the direct effect of virus replication on infected cells, the host response to the virus, or the interaction of replication and host response. Typically, infected cells develop gross cytopathic changes and eventually die. Viral cytopathic effects usually account for the appearance of early lesions, while the host immune response presumably contributes to the evolution of those lesions that subsequently develop an inflammatory response. The severity of illness produced by a particular virus varies significantly from individual to individual, with host factors believed to be determinant for most of this variation. Specific cell-mediated immunity is elicited during viral infections and influences the course of many viral infections. Antibody responses to viral infection represent the major host defense against reinfection by the same virus. Inflammatory cells may produce some of their antiviral effects through the production of interferons (IFNs). IFN, which can be induced by foreign RNA or DNA, is secreted into the extracellular fluid, where it confers resistance to virus infections to those cells that come in contact with the IFN. Finally, genetic factors may play a role in determining the outcome of viral infections. For instance, loss-of-function variants of X-chromosomal TLR7 have been identified in association with impaired IFN responses in young men with severe COVID-19 [22].

## 2.4 Transmission

For infecting organisms to survive and repeat the infection cycle in other hosts, they or their progeny must leave an existing reservoir and cause infection elsewhere. Infection transmission can take place via many potential routes:

- Droplet contact—also known as the respiratory route or airborne disease. If an infected person coughs or sneezes on another person, the microorganisms, suspended in warm, moist droplets, may enter the body through the nose, mouth, or eye surfaces.
- Oral transmission—diseases that are transmitted primarily by oral means may be caught through direct oral contact such as kissing or by indirect contact such as by sharing a drinking glass.
- Transmission by direct contact.
- Sexual transmission—with the resulting disease being called sexually transmitted disease.
- Vertical transmission—directly from the mother to an embryo, fetus, or baby during pregnancy or childbirth. It can occur as a result of a preexisting infection or one acquired during pregnancy.
- Fecal-oral transmission—foodstuffs or water becomes contaminated by people not washing their hands before preparing food or untreated sewage being released into a drinking water supply, and the people who eat and drink them become infected.
- Vehicle transmission—transmission by an inanimate reservoir such as food, water, or soil.
- Iatrogenic transmission—due to medical procedures such as injection or transplantation of infected material.
- Vector-borne transmission—transmitted by a vector, which is an organism that does not cause disease itself but that transmits infection by conveying pathogens from one host to another.

Once transmission occurs, the pathogen must establish an infection to continue. The more competent the host immune system, the less chance there is for the pathogen to survive. It may require multiple transmission events to find a suitably vulnerable host. During this time, the invader is dependent upon the survival of its current host. Multiple infections can also result in gene swapping among pathogens, increasing the pathogen's ability to cause damage to a host (virulence). A potential for virulence exists whenever a pathogen invades a new environment, host, or tissue. The new host is likely to be poorly adapted to the intruder.

## 2.5 Epidemiology

As opposed to the noncommunicable disease, i.e. cardiovascular diseases, cancers, respiratory diseases, and diabetes, infectious diseases, also known as communicable diseases or transmissible diseases, are an illness resulting from the invasion of an organism's body tissues by disease-causing agents, their multiplication, and the reaction of host tissues to the infectious agents and the toxins they produce.

Infections can be caused by a wide range of pathogens, including bacteria, viruses, fungi, parasites, and arthropods.

Epidemiology centers around the idea that disease and illness do not exist randomly or in a bubble. It is the study and analysis of who, why, and where disease occurs and what determines whether various populations have a disease. Epidemiologists conduct research to establish the factors that lead to public health issues, the appropriate responses, interventions, and solutions. By using research, from the field and in the lab, and statistical analysis, epidemiologists can track disease and predict its future outcomes. This type of epidemiology is at the forefront of today's world as epidemiologists work on the front lines to track and trace the spread of COVID-19.

Epidemiology is at the foundation of public health. Epidemiological research helps us understand not only who has a disease but why and how it was brought to this individual or region. Another task of epidemiology is monitoring or surveillance of time trends to show which diseases are increasing or decreasing in incidence and which are changing in their distribution. This information is needed to identify emerging problems and also to assess the effectiveness of measures to control old problems.

Epidemiologists may determine differences among groups within a population, such as whether certain age groups have a greater or lesser rate of infection, whether groups living in different environs are more likely to be infected, and by other factors, such as gender and ethnicity.

Researchers also may assess whether a disease outbreak is sporadic, or just an occasional occurrence; endemic, with a steady level of regular cases occurring in a region; epidemic, with a fast arising and unusually high number of cases in a region; or pandemic, which is a global epidemic. If the cause of the infectious disease is unknown, epidemiology can be used to assist with tracking down the sources of infection.

Like the clinical findings and pathology, the epidemiology of a disease is an integral part of its basic description. Ultimately, epidemiology has developed into a vibrant scientific discipline that brings together the social and biological sciences, incorporating everything from statistics to the philosophy of science in its aim to study and track the distribution and determinants of health events.

With their potential for unpredictable and explosive impacts, infectious diseases have been major actors in human history [23]. In 2010, about ten million people died of infectious diseases.

Nevertheless, microorganisms ordinarily live in harmony with their hosts via mutual or commensal interactions. Diseases emerge when existing microorganisms

become pathogenic or when new pathogenic microorganisms enter a new host. For instance, the introduction of smallpox, measles, and typhus to Central and South America by European explorers during the fifteenth and sixteenth centuries caused pandemics among the native inhabitants. Between 1518 and 1568, disease pandemics purportedly caused the population of Mexico to fall from 20 million to 3 million [24].

Human activity is involved with many emerging infectious diseases, such as environmental change enabling a microorganism to occupy new niches. When that happens, a pathogen that had been confined to a remote habitat has a wider distribution and possibly a new host organism. Pathogens jumping from nonhuman to human hosts are known as zoonoses [25].

Several human activities have led to the emergence of zoonotic human pathogens [26, 27] and spread of vector-borne diseases:

- Encroachment on wildlife habitats, hunting, and bushmeat
- Changes in agriculture
- Deforestation, biodiversity loss, and environmental degradation
- Climate change
- Uncontrolled urbanization with crowding
- Greater global interconnectivity driven by international travel and commerce

These understandings underline the way in which infectious diseases are a part of an ecological web that itself is influenced by shifting economic, social, and environmental factors. Ultimately, René Dubos (French-American microbiologist, experimental pathologist, environmentalist, 1901–1982) remarked in 1958 that "microbial disease is one of the inevitable consequences of life in a world where nothing is stable" [28].

## 2.6 Prevention

Disease prevention is a procedure through which individuals, particularly those with risk factors for a disease, are treated in order to prevent a disease from occurring.

Disease prevention, understood as specific, population-based, and individual-based interventions, aims at minimizing the burden of diseases and associated risk factors, whereby there are three levels of prevention:

- Primary prevention—intervening before health effects occur
- Secondary prevention—screening to identify diseases in the earliest
- Tertiary prevention—managing disease post diagnosis to slow or stop

Primary prevention refers to actions aimed at avoiding the manifestation of a disease. This may include actions to improve health through changing the impact of social and economic determinants on health; the provision of information on behavioral and medical health risks, alongside consultation and measures to decrease them at the personal and community level; nutritional and food supplementation; hygiene education; and clinical preventive services such as immunization and vaccination.

Secondary prevention deals with early detection when this improves the chances for positive health outcomes. This comprises activities such as evidence-based screening programs for early detection of diseases and preventive drug therapies of proven effectiveness when administered at an early stage of the disease.

One of the ways to prevent or slow down the transmission of infectious diseases is to recognize the different characteristics of various diseases. Some critical disease characteristics that should be evaluated include virulence, distance traveled by victims, and level of contagiousness.

Infectious diseases are caused by microorganism harbored in other people, animals, or the environment. Avoiding contact is a means to prevent many infections and diseases. While specific diseases are passed in specific ways, there are basic steps to take to stay healthy and lower the risk of catching and spreading any infectious disease:

**Vaccinate and Use Medicines Properly**

- Keep immunizations up to date. Follow recommended immunizations for children, adults, and pets.
- Use antibiotics exactly as prescribed. Take them for the full course prescribed by your doctor, but not for colds or other nonbacterial illnesses. Never self-medicate with antibiotics or share them with family or friends.
- Report to your doctor any quickly worsening infection or any infection that does not get better after you take a prescribed antibiotic.
- If you travel internationally, get all recommended immunizations, and use protective medications for travel, especially to areas with malaria.

**Keep Clean**

- Wash your hands often, especially during cold and flu season.
- Be aware of what you eat, and prepare foods carefully.
- Protect yourself from disease carriers.
- Be cautious around all wild and domestic animals that are not familiar to you.
- After any animal bite, clean the skin with soap and water, and seek medical care immediately.
- Avoid areas where there are ticks.
- Protect yourself from mosquitoes.
- Stay alert to disease threats when you travel or visit undeveloped areas.

- Don't drink untreated water while hiking or camping. If you become ill when you return home, tell your doctor where you've been.

**Don't Spread Disease**

- If you are sick with a cold or flu, stay at home, and don't spread germs.
- Practice safer sex.
- Do not use intravenous drugs or share syringes.

Key risk factors for communicable diseases identified in the academic literature can be broadly grouped into categories such as water, sanitation, and hygiene (WASH), health and public health system, environment, infrastructure, living conditions, nutrition, and overcrowding [29]. Within those broader categories, individual risk factors are defined more specifically, although the categories themselves serve as general risk factors as well, particularly for communicable disease outbreaks in humanitarian emergencies and disasters.

Knowing key risk factors and their thresholds and weight in different types of infections can help guide risk reduction efforts and emergency response.

Besides the illustration of the pertinent pathogens, the clinical presentations of disease, and the treatment, the following book chapters attempt also to address the epidemiology of risk factors for the infectious diseases with manifestation on the hair and scalp for the respective measures of prevention.

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# Bacterial Diseases

# 3

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The patient with inflammatory cutaneous lesions of either the scalp or beard area presents both a challenging and frequently gratifying problem in dermatology. The question of a treatable aetiology of infectious origin should always be raised initially, either bacterial, fungal, or viral.

This chapter deals with the bacterial infections as a primary cutaneous process. The physician must actively and effectively consider these possibilities and seek confirmation by appropriate diagnostic techniques to ensure optimal antimicrobial therapy. Often the clinical presentation is so typical that treatment can be initiated before the study results are available; at other times, it is ambiguous so that the physician must remain thoughtful with regard to a differential diagnosis.

In view of the limited cell types of the skin, the variety of distinctive clinical presentations of bacterial infection is remarkable. In most instances, it is the anatomic site of the infection and the respective inflammatory response pattern, rather than the specific pathogen, that provide the characteristic clinical presentation as impetigo, folliculitis (superficial and deep), furuncle (boil), carbuncle, or cellulitis. Moreover, the cutaneous lesions associated with bacterial infection are not always suppurative but may present with granulomas, depending on the pathogen, host immunity, and chronicity.

## 3.1 Pyodermas

By definition, pyoderma means any skin disease that is pyogenic, i.e., involving the production of pus, and therefore neutrophilic on histopathologic examination. These include superficial bacterial infections, such as impetigo, follicular impetigo, or Bockhart's impetigo (ostiofolliculitis), and deep bacterial infections, such as sycosis barbae, pyoderma faciale and folliculitis decalvans, furuncles, carbuncles, erysipelas, and cellulitis. Secondary bacterial infections may complicate pre-existing skin lesions, such as traumatic lesions (burns, abrasions, infestations), eczematous dermatitis, and dermatophytosis. Distinctive dermatologic entities are perifolliculitis capitis abscedens et suffodiens (dissecting cellulitis of the scalp), infectious eczematous dermatitis, and pilonidal sinus, which are not primary infectious diseases. Primary immune-mediated disorders with a neutrophilic inflammation include pyoderma gangrenosum and erosive pustular dermatosis of the scalp. They

are diagnosed by their characteristic clinical presentations, histopathology, and exclusion of infection.

Pyodermas affect more than 111 million children worldwide, making it one of the three most common skin disorders in children along with tinea and scabies.

The majority of the pyodermas are due to either *Staphylococcus aureus* or group A *Streptococcus*. *Staphylococcus aureus* pyodermas frequently occur in individuals with nasal carriage of the pathogen, which, when translocated onto the skin, is able to gain access via small breaks in the cutaneous integrity and cause superficial infections. Group A streptococcal pyodermas rather occur following transfer to the skin from the skin of another individual colonized with the organism. Both may cause a broad clinical spectrum of infection, depending on the organism, the anatomical location of infection, and host immunity.

Gram-negative folliculitis, occurs in its acute form from exposure to strains of *Pseudomonas aeruginosa* in whirlpools or hot tubs, which cannot be adequately chlorinated due to the warm temperature, or from *Klebsiella*, *Escherichia coli*, *Enterobacter*, or *Proteus* in patients who suffer from acne or folliculitis decalvans and have been treated on a long-term basis with antibiotics, particularly tetracyclines.

### 3.1.1 Superficial Folliculitis

The most common superficial form of infectious folliculitis is known as impetigo of Bockhart and is caused by *S. aureus*. It is a frequent condition on the scalp of young adults with seborrhoea and occurring in all races with no gender predilection. The lesions can be tender, painful, or simply pruritic.

Clinically, the condition is characterized by 1–6 mm erythematous follicular-based papules (Fig. 3.1) or fragile pustules (Fig. 3.2), which may rupture and leave a yellow crust. The pustule is often pierced by a hair that is easily extracted from the follicle. Because of the superficial nature of the process, scarring is uncommon.

Bacterial folliculitis is characterized histologically by the presence of neutrophilic inflammatory cells within the wall and ostia of the hair follicle (Fig. 3.3), associated with bacterial colonization, most commonly gram-negative cocci visualized with Gram stains for bacteria. The inflammation is typically limited to the superficial aspect of the follicle, primarily involving the infundibulum.

There are several risk factors that increase an individual's susceptibility to bacterial folliculitis. These include seborrhoea, pre-existing dermatoses, particularly seborrhoeic dermatitis, long-term steroid use, occlusive dressings, exposure to certain oils, exposure to hot temperatures and high humidity, and chronic nasal carriage of *S. aureus*.

Up to 20% of patients experience recurrent disease, which may be the result of community-type methicillin-resistant *S. aureus* (MRSA).

For uncomplicated superficial folliculitis, use of antibacterial soaps and shampoos, such as povidone-iodine liquid soap or 0.2% chlorhexidine gluconate shampoo, good handwashing and frequent shampooing of the hair may be all that is

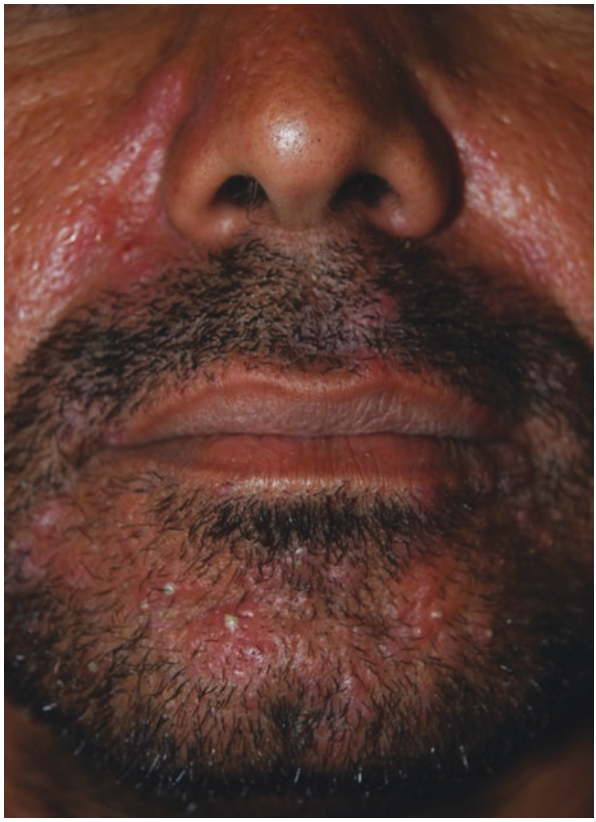

**Fig. 3.1** Superficial bacterial folliculitis of the beard area (sycosis barbae). Follicular-based papules

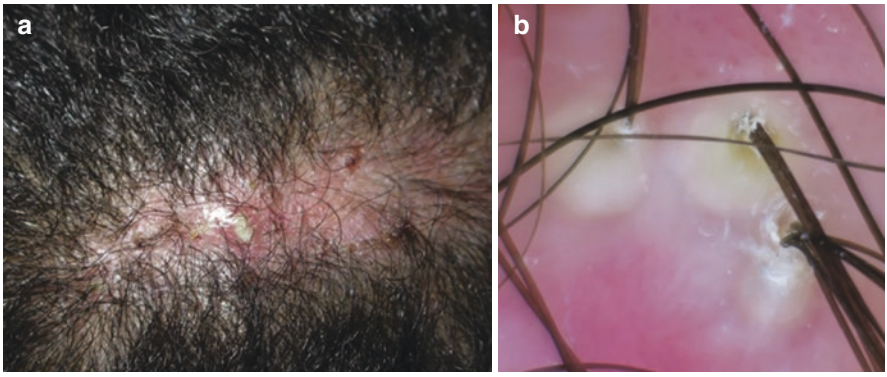


**Fig. 3.2** (**a**, **b**) Superficial bacterial folliculitis of the scalp: (**a**) follicular-based pustules. (Courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil). (**b**) Detail

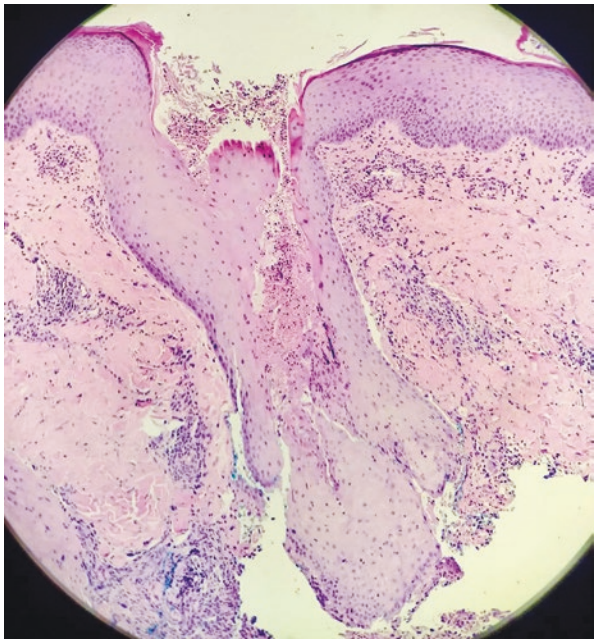

**Fig. 3.3** Superficial bacterial folliculitis. Histopathology: neutrophilic inflammatory cells within the wall and ostia of the hair follicle

needed. For refractory lesions due to gram-positive organisms, empiric treatment with topical antibiotics, such as 2% fusidic acid cream or 1% clindamycin phosphate lotion b.i.d., and/or oral antibiotics may be beneficial. Since *S. aureus* is the most common pathogen, systemic therapy must cover this organism, as well as other gram-positive bacteria. Since *S. aureus* is penicillin resistant, flucloxacillin or cephalosporin is the first line of treatment. Also, fusidic acid 3 × 500 mg for 5–10 days is a good choice. Methicillin-resistant organisms are becoming more common, and treatment may require clindamycin 3 × 300 mg. For recurrent recalcitrant folliculitis, 2% mupirocin ointment in the nasal vestibule twice a day for 5 days may eliminate the *S. aureus* carrier state. Family members also may be nasal carriers of *S. aureus*; the use of mupirocin ointment in the nasal vestibule twice a day and a body wash with 2% chlorhexidine gluconate including the axillary pits for 5 days and/or rifampicin 2 × 450 mg in combination with flucloxacillin 4 × 500 mg or clindamycin 2 × 300 mg orally for 14 days is recommended.

Most cases of superficial folliculitis resolve without complications.

If a patient does not improve with a standard treatment regimen, other causes of folliculitis must be investigated. The differential diagnosis includes other forms of folliculitis that arise from gram-negative bacteria, fungal infections (*Pityrosporum* folliculitis, tinea capitis, tinea barbae), herpes folliculitis (sycosis herpetica), or *Demodex* folliculitis. In addition, eosinophilic folliculitis; acne necrotica; drug-induced folliculitis, specifically from epidermal growth factor receptor (EGF-R) inhibitors for cancer treatment; and in the beard area, pseudofolliculitis barbae (razor bumps) from ingrowing hairs (pili recurvati/incarnati) are to be considered in the differential.

### 3.1.2 Acne Necrotica

Acne necrotica is a peculiar dermatosis of the scalp that preferentially affects adult males, with chronic symptoms that wax and wane over time [1]. Traditionally, the condition has been nosologically classified among the primary scarring alopecias. There is circumstantial evidence to also classify it among the psychophysiological disorders.

Psychophysiological disorder is the term used for psychocutaneous cases in which a specific dermatologic skin disorder is exacerbated by emotional stress in a significant proportion of patients. This category also includes the psychosomatic disorders—the physical symptomatic representation of unsolved emotional conflicts. For classification, we may consider the different levels of psychosomatic disorder: the first level is physiological and includes bodily sensations in response to emotional shifts, great or small. In health, these bodily sensations make little or no impact on consciousness. At the second level, the person becomes more or less constantly aware of the somatic sensations, which are of purely functional nature at this time point, attempts to analyse them, and becomes anxious that they might signify some serious organic disease. The third level is the important one, at which internal somatic medicine and psychiatry meet. The organs and parts of the body have enormous elasticity and rebound, but if the underlying emotional distress is too prolonged, they supposedly lose their elasticity, no longer being able to cope, and finally protest in terms of the psychosomatic organ lesion or organ pathology.

It has long been recognized that psychosomatic factors play a role in dermatologic disease. It has been hypothesized that an organ system is vulnerable to psychosomatic ailments when several etiologic factors are operable. These factors include emotional factors mediated by the central nervous system; intrapsychic processes such as self-concept, identity, or eroticism; specific correlations between the emotional drive and the target organ, i.e., social values and standards linked with the organ system; and a constitutional vulnerability of the target organ [2].

Acne necrotica is characterized by minute and usually intensely pruritic follicular erythematous papules and pustules of the scalp that may become sore and crusted due to repeated scratching. The lesions may concentrate along the frontal hairline but can appear anywhere on the scalp, varying in number from just a few to numerous lesions covering the scalp (Fig. 3.4a, b). The disease has been classified into acne necrotica miliaris and acne necrotica varioliformis. The former affects the superficial portion of the hair follicle, allowing for hair regrowth after successful treatment. Miliaris refers to a millet, a term for a small seed. The latter represents deeper lesions that progress to scabs that leave smallpox-like (varioliform) scars in their wake (Fig. 3.4c). Focal permanent alopecia may occur where the scalp has been scarred.

Patients with acne necrotica tend to be middle-aged executives, with lesions often triggered by stress. Many have jobs that place a lot of responsibility on them.

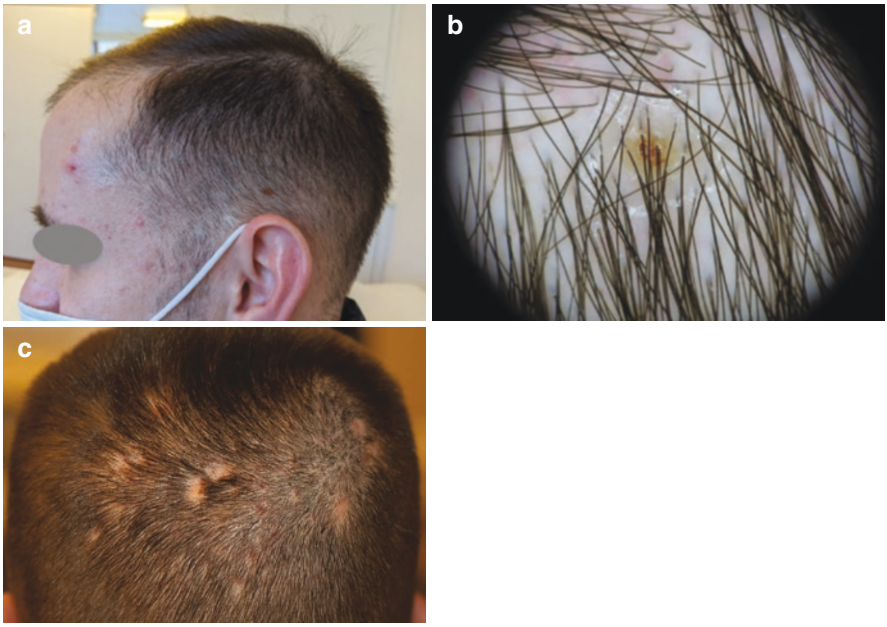


**Fig. 3.4** (**a**–**c**) Acne necrotica: (**a**) minute follicular erythematous papules of the scalp that may become crusted. The lesions concentrate along the frontal hairline, varying in number from few to numerous lesions, (**b**) dermoscopy, (**c**) varioliform scarring

Histological studies of early lesions demonstrate lymphocytes centred around a hair follicle, with keratinocytes within the external hair root sheath and surrounding epidermis showing extensive cell necrosis [3].

Besides the psychocutaneous factors, an abnormal inflammatory reaction to microbial components of the hair follicle has been postulated, particularly to commensal or pathogenic microorganisms, such as *Cutibacterium acnes*, *Malassezia* spp., *Demodex folliculorum*, and, in the more severe cases, *Staph. aureus*, while seborrhoea of the scalp promotes microbial colonization.

Additionally, mechanical manipulation of the scalp due to scratching may be to blame.

The condition usually responds well to oral antibiotics, particularly long-term tetracyclines, in combination with a topical corticosteroid cream, and a shampoo treatment alternating an antiseptic shampoo containing povidone-iodine with an antidandruff shampoo containing ketoconazole. Mild cases may be treated with topical antibiotics such 0.5–1.0 g tetracycline in 70% isopropyl alcohol (ad 100.0 g), 1% clindamycin solution, or 4% erythromycin gel. Refractory cases usually can be managed with long-term low-dose oral isotretinoin (start with 20 mg daily, and taper to the individually required minimal dosage). In particularly tense patients, addition of oral doxepin hydrochloride 10–50 mg in the evening may be helpful in alleviating the itch-scratch cycle.

### 3.1.3 Pseudofolliculitis Barbae

An important differential diagnosis of superficial folliculitis of the beard area (folliculitis barbae) is pseuodo-folliculitis barbae due to ingrowing hairs (pili incarnati) (Fig. 3.5a). Pseudofolliculitis barbae represents a foreign-body inflammatory reaction surrounding ingrown facial hairs (Fig. 3.5b), which results from shaving, particularly close shaving because the cut hair may retract beneath the skin surface. The condition is therefore also known as razor bumps in popular language.

The condition occurs mainly in people with curly hair because due to the curl of the hair, the sharp pointed end of a recently shaved hair comes out from the skin and re-enters the skin close by (pili recurvati). The injured hair follicles are highly susceptible to become infected. Besides, pseudofolliculitis barbae may co-exist with folliculitis barbae. Both folliculitis barbae and pseudofolliculitis are aggravated by co-existent dermatitis, particularly atopic and seborrhoeic dermatitis.

Involvement of the skin under the jawline is typical, since the hair follicles grow in various directions in this area. Pseudofolliculitis barbae presents with flesh-coloured or red follicular papules, which may be itchy or tender, while folliculitis barbae presents as painful pustules. Lesions may bleed when they are shaved. Deep-seated folliculitis barbae is called sycosis barbae and leads to scarring and areas of permanent hair loss.

Research has confirmed a genetic predisposition to pseudofolliculitis in the African population. A single nucleotide substitution in the hair follicle companion layer-specific keratin (K6hf) is shown to increase the chance of pseudofolliculitis barbae [4]. This sequence change leads to an amino acid substitution in the highly conserved helix initiation motif of the K6hf rod domain [5]. Carriers of the A12T polymorphism are six times more likely to develop PFB compared with people homozygous for the wild-type K6hf sequence. This suggests K6hf mutation structurally weakens the companion layer separating the inner and outer root sheath and increases the chances that a beard hair will grow inside.

Basically, pseudofolliculitis can also occur on any body site where hair is shaved or plucked, including the axilla, pubic area, and legs, and in women.

Pseudofolliculitis nuchae or dermatitis papularis nuchae is a related condition that occurs in the nape of the neck, often along the posterior hairline (Fig. 3.6a, b), when curved hairs are cut short and allowed to grow back into the skin. Left untreated, this can develop into acne keloidalis nuchae (Fig. 3.6c), a condition in which hard, dark keloid-like bumps form on the neck. Both occur frequently in black men in the military. Dermoscopy of early lesions may show dome-shaped papules and broken and tufted hairs (Fig. 3.6d).

Treatment for pseudofolliculitis barbae depends on the severity of the condition. In general, the following precautions are recommended:

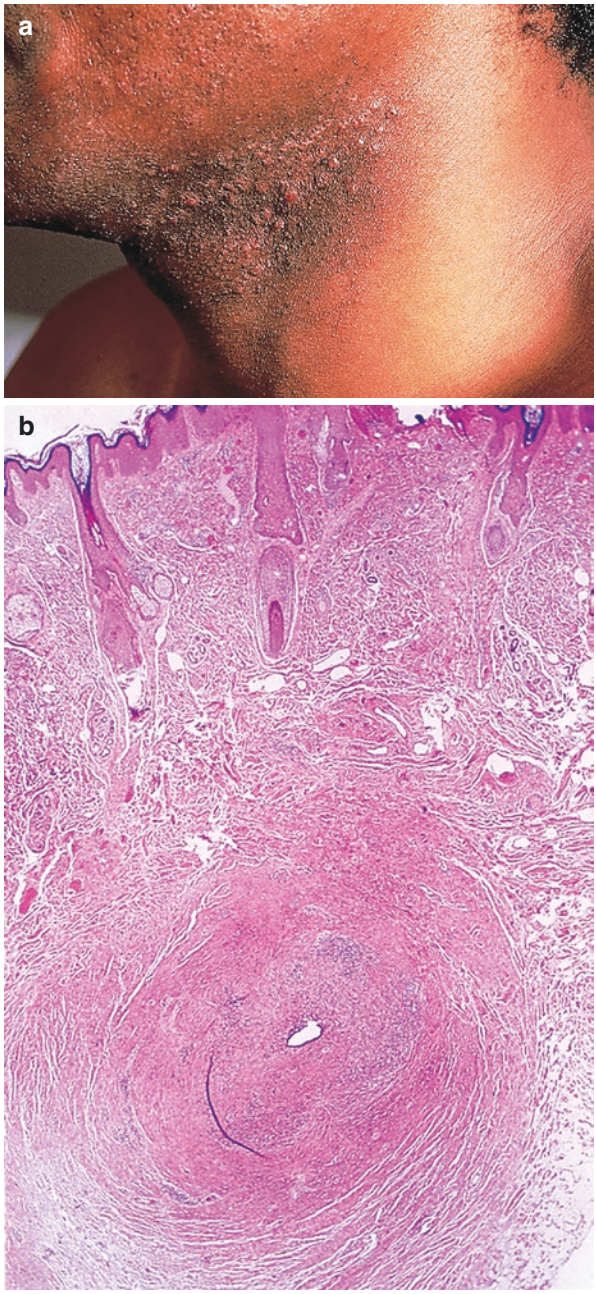


**Fig. 3.5** (**a**, **b**) Pseudofolliculitis barbae: (**a**) flesh-coloured or red follicular papules of the shaved beard area, (**b**) histopathology: foreign body reaction around an ingrowing hair

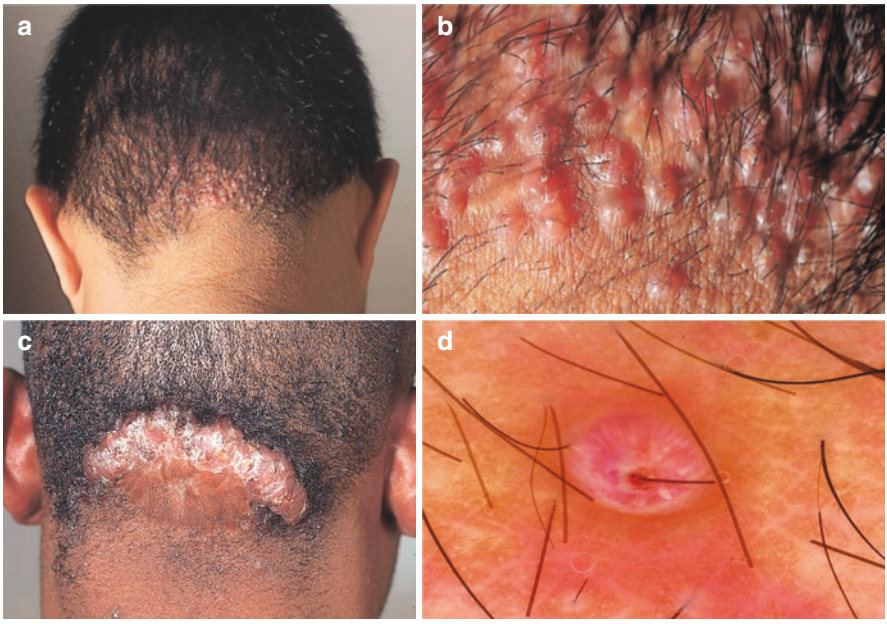


**Fig. 3.6** (**a**–**d**) Pseudofolliculitis nuchae, presenting as (**a**, **b**) dermatitis papillaris nuchae presenting as follicular papules, or (**c**) acne keloidalis nuchae presenting as keloid-like bumps, (**d**) dermoscopy

- The most efficient prevention is to grow a beard. For men who are required to, or simply prefer to shave, studies show the optimal length to be about 0.5–1 mm to prevent the hair growing back into the skin.
- For most cases, completely avoiding shaving for 3–4 weeks allows all lesions to subside. When ready to shave again, take the following precautions:
- Ensure the skin is well moisturised, for example, using a lotion containing glycolic acid to the affected areas. This exfoliates the surface skin cells and reduces the likelihood of new inflamed spots.
- Cleanse the skin using a polyester skin-cleansing pad or a moisturizing-shaving foam.
- Shave less frequently, e.g. every other day.
- Either use a single blade disposable razor or use electric hair clippers or a razor with an attachment that leaves the cut hairs long.
- Shave in the direction of the follicle, not against it. Do not stretch the skin.
- Sterilize metal hair clippers and electric razors using boiling water, and plastic items should be soaked in an antiseptic solution.

For treatment, tea tree oil, witch hazel, or hydrocortisone cream can reduce mild inflammation and itching, while topical acne treatments, such as 5% benzoyl peroxide, 1% clindamycin [6], and 0.05–0.1% tretinoin, may be used to suppress follicular hyperkeratosis. A combination of 0.025% tretinoin, low-potency topical corticosteroid, and 4–8% hydroquinone (Kligman's formula) may be selected to decrease inflammation, hyperkeratosis, and pigment production. Also, oral tetracyclines, such as doxycycline, may be used to reduce inflammation.

Clinical trials have shown glycolic acid-based peels to be an effective and well-tolerated therapy, which resulted in significantly fewer lesions on the face and neck. It is hypothesized that straighter hair growth is caused by the reduction of sulfhydryl bonds in the hair shaft by glycolic acid, which results in reduced re-entry of the hair shaft into the follicular wall or epidermis. Salicylic acid peels are also effective [7].

To prevent recurrence, follow a proper shaving regimen long term, and consider hair removal, either with a barium sulphide-based chemical depilatory or 11.5% topical eflornithine hydrochloride cream.

Permanent removal of the hair follicle by means of intense pulsed light (IPL) or laser hair removal, particularly the long-pulsed alexandrite, Nd:YAG, and diode lasers [8], is the only definitive treatment, though there remains a risk of causing white or dark marks in skin of colour. Topical eflornithine hydrochloride improves the effectiveness of laser hair removal for treating pseudofolliculitis barbae [9, 10]. Electrolysis is effective but limited by its slow pace, pain, and expense.

### 3.1.4 Folliculitis Decalvans

Folliculitis decalvans, as originally described by Quinquaud in 1888 [11], represents a chronic and recurrent pustulofollicular scalp inflammation usually of the crown area with exudative crusted areas and grouped follicular pustules at the hair-bearing margin and centrifugal progression with central scarring (Fig. 3.7a, b). Since Quinquaud's original report, further clinical variants have been described on the basis of common histopathological and microbiological findings.

Histopathology reveals a neutrophilic primary scarring alopecia (Fig. 3.7c), and microbiological studies invariably reveal pathogenic strains of *S. aureus* although a Gram-negative bacterial folliculitis may evolve in patients who have received prolonged courses of antibiotic therapy or use antibacterial topicals that selectively inhibit Gram-positive organisms [12].

In 1947, Laymon described cicatrizing seborrhoeic eczema as a condition of scarring alopecia combining clinical and histopathological features of seborrhoeic dermatitis and folliculitis decalvans [13] (Fig. 3.8a).

In 1977, Smith and Sanderson [14] and at the same time Metz and Metz [15] reported on tufted hair folliculitis (Fig. 3.8b), whereby the former considered the condition to be secondary to follicular in inflammation and destruction, while the latter deemed the inflammation to be secondary to pre-existing nevoid hair bundles. Since the original report of tufted hair folliculitis, there has been considerable controversy whether the condition represents a distinctive entity or an unspecific

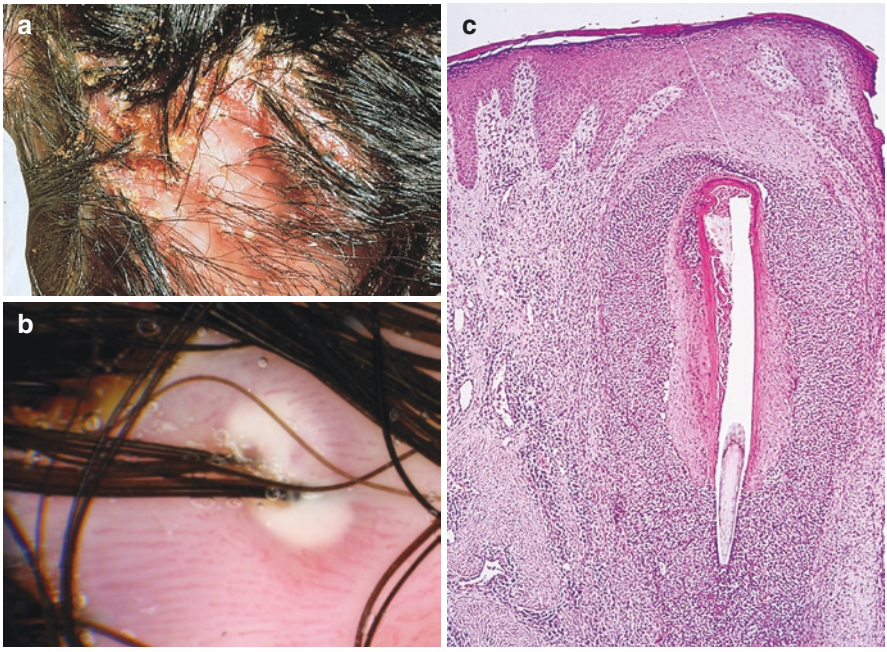


**Fig. 3.7** (**a**, **b**) Folliculitis decalvans, Quinquaud type: (**a**) crusted areas and grouped follicular pustules at the hair-bearing margin with centrifugal progression and central scarring, (**b**) dermoscopy: follicular pustules, tufting, hair pin telangiectasia; (**c**) histolopathology: neutrophilic primary scarring alopecia

finding secondary to a variety of inflammatory and scarring alopecias. Based on clinical, histopathological, and microbiological criteria, the general consensus is that the condition represents a variant of folliculitis decalvans [16–18].

Secondary tufting of hair follicles due to other inflammatory conditions of the scalp, such as lichen planopilaris, is usually less marked with <5 hair shafts per tuft, and dermoscopic features allow for differentiation [19].

Histopathological studies reveal perifollicular inflammation around the upper portions of the follicles sparing the hair root level. Within areas of inflammation, several follicles converge towards a common follicular duct with a widely dilated opening (Fig. 3.8c). It is believed that the development of atrophy with loss of adnexal structures in classical folliculitis or of hair tufts in tufting folliculitis depends on the depth and destructive potential of the inflammatory process, with sparing of the bulge area preserving an intact lower portion of hair follicles in the case of tufted hair folliculitis [20].

Very rarely, folliculitis decalvans can present with an extensive ulcerated appearance of the scalp (Fig. 3.8d) that has been reported to have been misinterpreted as a laceration of the scalp at the forensic scene [21].

We proposed adding linear circumscribed scleroderma-like folliculitis decalvans to the protean clinical manifestations of folliculitis as a further subset with a linear

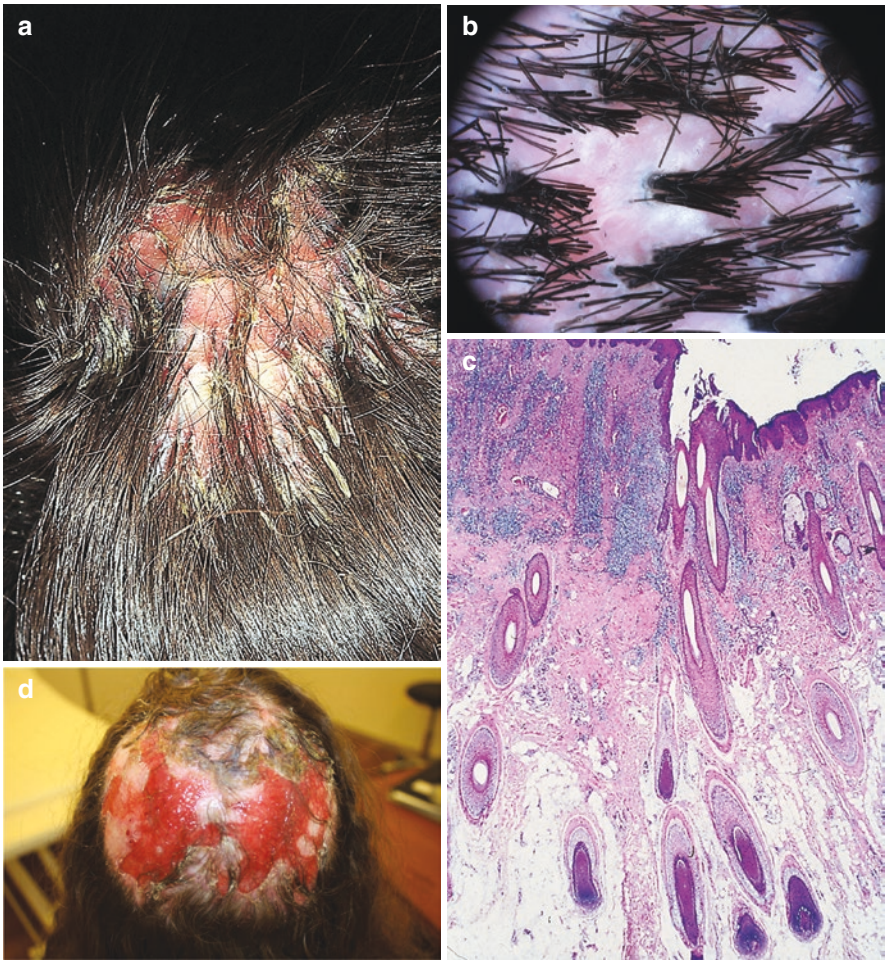


**Fig. 3.8** (**a**–**g**) Folliculitis decalvans variants: (**a**) cicatrizing seborrhoeic eczema, (**b**) hair tufting in tufted hair folliculitis, (**c**) histopathology, (**d**) ulcerative folliculitis decalvans, (**e**) linear scleroderma-like folliculitis decalvans, (**f**) folliculitis decalvans presenting frontal fibrosing alopecia-like, and (**g**) (unspecific) pseudo-peladic state resulting from end-stage folliculitis decalvans

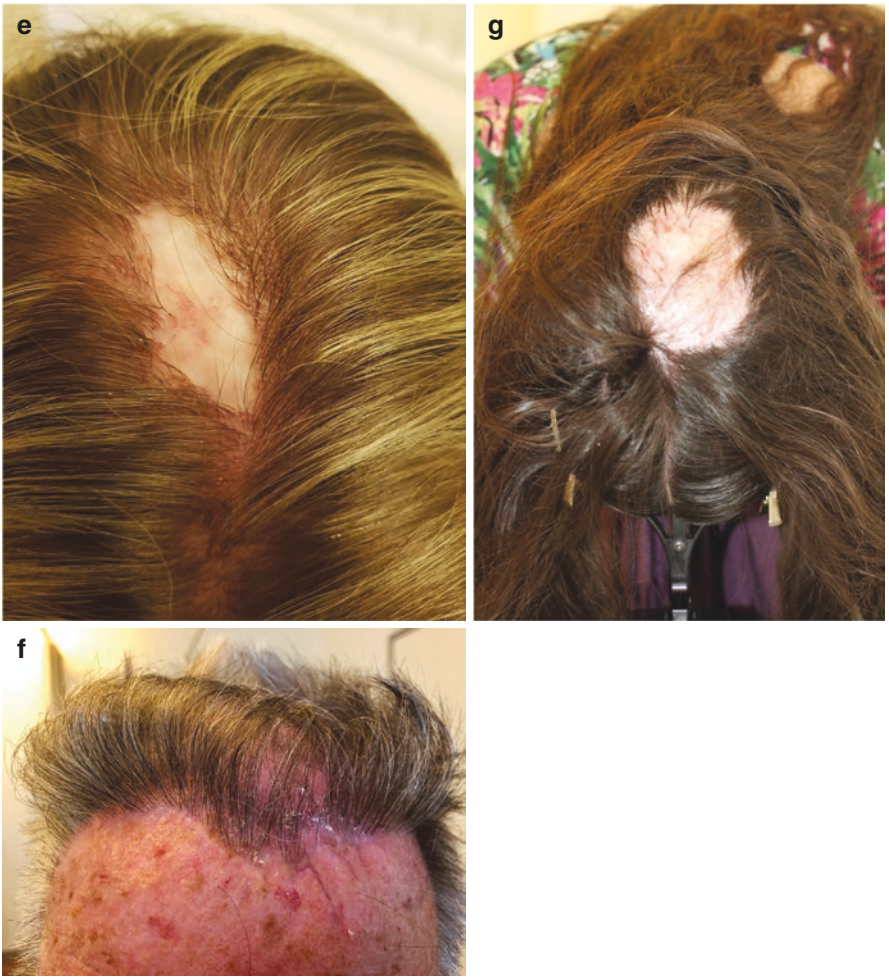


**Fig. 3.8** (continued)

circumscribed scleroderma-like white porcelain-coloured plaque of scarring alopecia with thickened skin in a linear pattern (Fig. 3.8e) [22].

Finally, Soares Pizani et al. [23] reported on folliculitis decalvans mimicking frontal fibrosing alopecia (Fig. 3.8f). Frontal fibrosing alopecia is a peculiar primary inflammatory scarring alopecia that affects the frontal hairline and frequently the eyebrows. While it has been discussed whether it represents a clinical entity of its own right or a frontal variant of lichen planopilaris, the observation of other scarring alopecias, such as folliculitis decalvans or cutaneous lupus erythematosus presenting frontal fibrosing alopecia-like, points to the alternative that the clinical presentation of frontal fibrosing alopecia is rather specific than the underlying pathology. In default of knowledge of Soares Pizani et al.'s original publication, Lobato-Berezo

et al. interpreted the condition as pustular frontal fibrosing alopecia, a new variant within the folliculitis-decalvans lichen planopilaris phenotypic spectrum [24], while in fact, it represents the chronic lichenoid phase of folliculitis decalvans. Indeed, with time, folliculitis decalvans tends to develop clinical and dermoscopic features of lichen planopilaris. More important tufting, and on histopathology, a more diffuse pattern of effaced dermal elastic fibres versus selective loss of elastic fibres at the site of selectively destroyed hair follicles [25], in combination with a more important number of plasma cells in the inflammatory infiltrate [26], helps distinguish late phases of folliculitis decalvans from lichen planopilaris. It can be assumed that through the destruction of hair follicles in the course of the primary infectious disease, follicular antigens are exposed and give rise to an autoimmune reaction. In fact, lichen planopilaris is regarded to be a T cell-mediated autoimmune reaction in response to some antigenic challenge with apoptosis of the follicular epithelial cells. Harries et al. [27] provide the first evidence that lichen planopilaris may result from an immune privilege collapse of the hair follicle's epithelial stem cell niche. Where a causal or triggering agent is identified, this is termed a lichenoid reaction rather than lichen planus; therefore, the term chronic lichenoid phase of folliculitis decalvans is proposed for this presentation of folliculitis decalvans.

Ultimately, the pseudo-peladic state as originally defined by Degos in 1954 [28] represents the non-specific end stage of a variety of at least 60 types of cicatricial alopecias, including folliculitis. It presents with a large area of scarring with irregular borders (Fig. 3.8g).

The pathogenesis and clinical presentation of folliculitis decalvans are determined by three factors:

1. The infectious pathogen
2. The incubatory microenvironment
3. The host immune response

Occasionally, folliculitis decalvans has been linked to a specific immune deficiency [29–31], ectodermal dysplasia [32], or hair transplantation, either autologous [33] or synthetic [34], impairing the immune defence mechanisms of the hair follicle.

Traditionally, the medical focus has been on the condition of either the hair or the scalp. Indeed, the proximate structural arrangement of the scalp and hair leads to an interdependent relationship between the two. The role of the scalp as an incubatory environment hair has only recently received appropriate attention [35]. In fact, seborrhoea, dandruff, and seborrhoeic dermatitis of the scalp are frequently associated with hair loss and superficial pustular folliculitis that nevertheless may eventually evolve to cicatrizing seborrhoeic eczema.

Chiarini et al. [36] proposed that the infection of hair follicles with *S. aureus* induces an intense peri- and intrafollicular migration of neutrophils, recruited by innate immunity mechanisms, involving interleukin-8 (IL-8). Furthermore,

T-lymphocytes may be activated either by microbial antigens through processing by Langerhans cells or by superantigens through the Vβ domain of the T cell receptor with consecutive release of pro-inflammatory such as interferons alpha and gamma and tumor necrosis factor-alpha and profibrotic mediators such as transforming growth factor-beta, beta-fibroblast growth factor, IL-1β, and Il-4, resulting in both inflammation and fibrosis.

The observation of simultaneous occurrence of secondary cutis verticis gyrata, folliculitis decalvans, and folliculitis keloidalis nuchae in a male patient of African origin with dreadlocks underlines a putative pathogenic role of traction or trauma and the activation of different fibroblast growth factor members [37].

According to Pujol's hypothesis [25], tufted hair folliculitis, observed in folliculitis decalvans and in folliculitis keloidalis nuchae, is secondary to follicular damage and caused by inflammatory cytokine secretion. Accordingly, tufted hair folliculitis has been reported following scalp injury (scalp laceration) [26].

A more recent study provided evidence of the presence of bacterial biofilms in the infra-infundibular part of human scalp hair follicles in folliculitis decalvans [38]. A biofilm is any group of microorganisms in which cells stick to each other on a surface. These adherent cells are frequently embedded within a self-produced matrix of extracellular polymeric substance. Biofilms form on living or non-living surfaces and in the case of folliculitis on the surfaces of the hair shaft. Bacteria living in a biofilm usually have significantly different properties from free-floating bacteria of the same species, as the dense and protected environment of the biofilm allows them to cooperate and interact in various ways. One benefit of this environment is increased resistance to antibiotics, as the dense extracellular matrix and the outer layer of cells protect the interior of the community. Biofilms have been found to be involved in a wide variety of microbial infections in the body, and more recently, it has been noted that bacterial biofilms may impair cutaneous wound healing and reduce topical antibacterial efficiency in healing or treating infected skin wounds. The presence of a bacterial biofilm at the interface of the hair shaft may provide an explanation for the chronicity and high relapse rate of folliculitis decalvans.

A summary of the clinical variants of folliculitis decalvans is reproduced in Table 3.1.

There are many different treatments available to control the inflammation of folliculitis decalvans, but unfortunately no pharmacological cure exists. Scarring, if it develops, is permanent. Treatment is aimed at reducing inflammation and preventing further scarring.

Treatment is usually a combination of the following: medicated shampoos, anti-inflammatory and antibacterial scalp solutions, and/or oral antibiotics. Combinations of antibiotics, such as clindamycin and rifampicin, are sometimes used. Steroid cream/lotion/ointment applications may be used in combination with antibiotic treatment.

There is no specific treatment licensed for folliculitis decalvans, and because the condition is not frequent, no clinical trials exist that prove the benefit of any particular therapy, specifically antibiotic protocol, over another. The majority of treatments

**Table 3.1** Clinical variants of folliculitis decalvans

- Classical folliculitis decalvans of Quinquaud (Fig. 3.7)
- Cicatrizing seborrhoeic eczema (Fig. 3.8a)
- Tufted hair folliculitis (Fig. 3.8b, c)
- Ulcerative folliculitis decalvans (Fig. 3.8d)
- Folliculitis decalvans with linear arrangement
  - Tufted hair folliculitis with linear arrangement
  - Linear scleroderma-like folliculitis decalvans (Fig. 3.8e)
- Folliculitis decalvans presenting frontal fibrosing alopecia-like (Fig. 3.8f)
- Late-stage folliculitis decalvans
  - Chronic lichenoid phase of folliculitis decalvans (folliculitis-decalvans lichen planopilaris phenotypic spectrum)
  - Pseudo-peladic state (of Degos) resulting from end-stage folliculitis decalvans (Fig. 3.8g)
- Folliculitis decalvans associated with:
  - Immune deficiency
  - Ectodermal dysplasia with clefting
  - Cutis verticis gyrata and folliculitis keloidalis nuchae
  - Hair transplantation, either autologous or synthetic

have only been tested in small numbers of patients or described in case reports. Whatever antibiotic is used, and whatever the duration of the antibiotic treatment, recurrence is common. As a general rule, antibiotics should be effective against *S. aureus* and the sensitivity of the particular strain.

The following protocols are usually effective in clearing active infection, unless bacterial resistance to the particular antibiotic as emerged:

- Oral fusidic acid 3 × 500 mg daily for 3 weeks, in combination with
- Oral zinc gluconate 30 mg daily for months
- or
- Oral rifampicin 450 mg twice daily in combination with oral flucloxacillin 500 mg four times daily for 2 weeks (induction therapy) and thereafter every 3 months for 5 days maintenance therapy)
- or
- Oral rifampicin 300 mg twice daily in combination with oral clindamycin 300 mg twice daily during 10 weeks
- or
- Oral levofloxacin 500 mg twice daily for 10 days
- Daily antiseptic shampoo treatment with 0.2–2% chlorhexidine gluconate

Folliculitis may eventually stop and burn itself out, but patients may continue to experience flares for many months or years. Folliculitis decalvans is often a condition that requires ongoing long-term treatment.

Camouflage tools such as wigs, hair fibres, hair sprays, and scalp tattoos may help with the appearance.

Trüeb et al. [39] originally proposed that punch excision or excision surgery of hair tufts may provide more sustained results than pharmacologic therapy alone.

Since structural changes in the course of scarring alopecia are irreversible, and early interventions usually fail, surgical treatments, such as reduction plasty, in combination with scalp expander technology, should be taken into consideration for more sustained results.

Together with the effectiveness of laser-assisted epilation at the active margin of folliculitis decalvans [40] (Fig. 3.9a–d), total surgical excision of the diseased area (Fig. 3.10a–d) offers a proof of concept for the pathogenicity of follicular bacterial biofilms, which are either thermally destroyed with laser or surgically removed.

Oral dapsone (75–100 mg daily) has been reported to be successful in treating folliculitis decalvans. The rational for its use is based on the dapsone antimicrobial activity and its anti-inflammatory action particularly directed to the neutrophil activity [41].

Dapsone (4,4′-diaminodiphenyl sulphone) represents a powerful therapeutic tool in many skin diseases including neutrophilic dermatosis. It has antimicrobial activity against Gram-positive cocci, such as *Staphylococcus*, including MRSA, and *Streptococcus pyogenes* [42]. In addition, dapsone has an anti-inflammatory effect that involves suppression of neutrophil chemotaxis to selected attractants, but other actions of the drug are likely also involved. Dapsone may suppress migration of neutrophils to extravascular sites through inhibition of adherence functions required

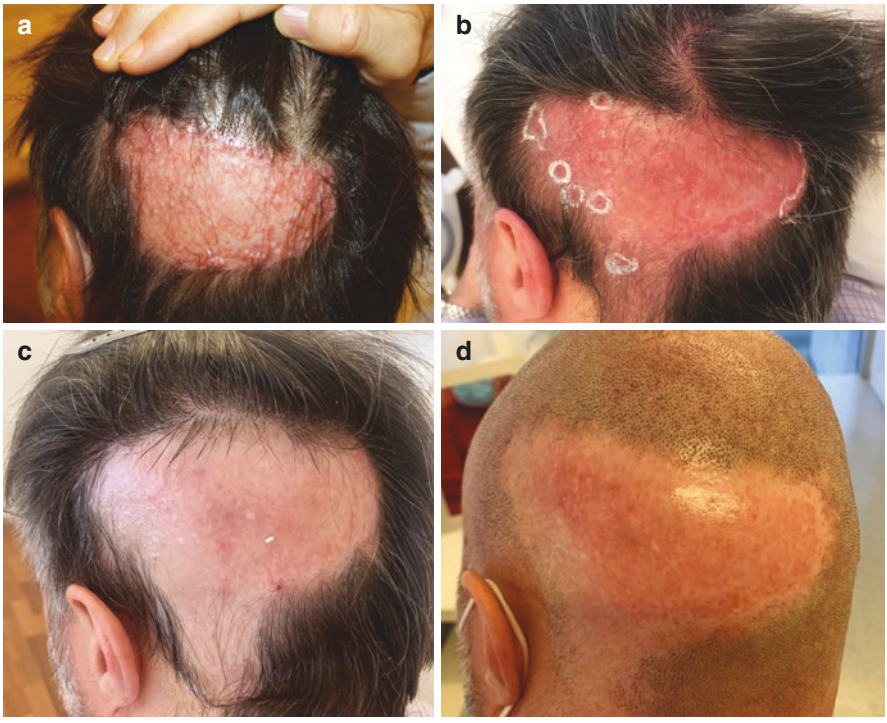


**Fig. 3.9** (**a**–**d**) Successful laser-assisted epilation of the active borders in folliculitis decalvans

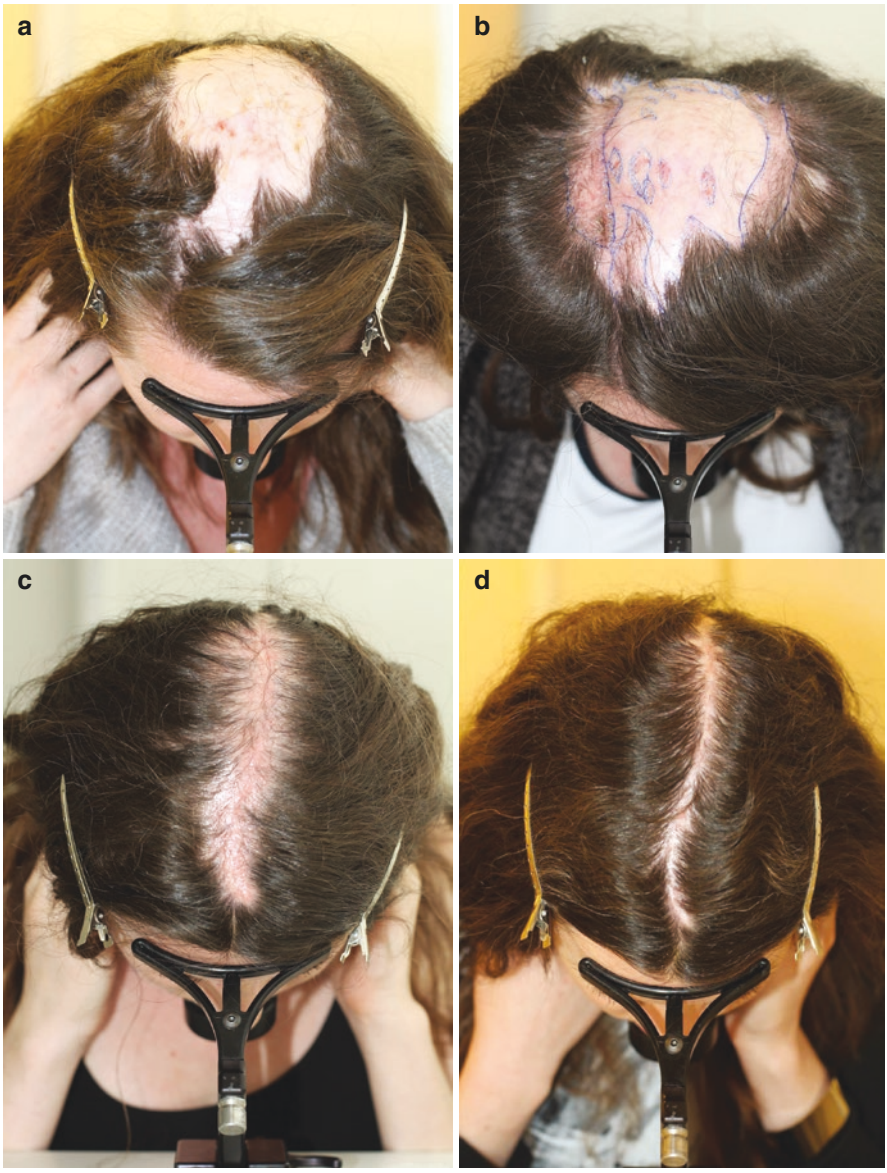


**Fig. 3.10** (**a**–**d**) Successful surgery in widespread scarring folliculitis decalvans with expander and scalp reduction plasty

for neutrophil recruitment [43]. Moreover, dapsone inhibits calcium-dependent functions of neutrophils including release of tissue-damaging oxidants and proteases in the affected skin [44].

Haematological adverse effects of dapsone are anaemia, methemoglobinemia, and rarely neutropenia. Therefore, regular hematologic controls are recommended: in case of neutropenia, the drug must be withheld. In case of decrease of Hb by >2 g/dL or increase of MetHb >15%, the dosage must be reduced.

Due to the haematological side effects of dapsone, topical dapsone has alternatively been proposed to be promising for treatment of folliculitis decalvans [45]. Topical dapsone has been approved for acne treatment. There are limited cutaneous pharmacokinetic data with topical dapsone including skin concentrations achieved with topical dapsone therapy; nonetheless, topical dapsone as a 2% nano-emulsion has shown very high local skin concentrations [43]. However, our own failed experiences with 5% dapsone gel in our patients with folliculitis decalvans led us to categorically question why positive study reports with novel therapeutic options in dermatology often fail in practice. The authors of the respective study admitted to the limitations of their study: small sample size, retrospective, uncontrolled nature of the study, and concomitant use of other treatments. Yet, clinical research ultimately aims at improving patient outcome. In fact, trials must evaluate outcomes that genuinely reflect clinical utility of drugs [46]. For this purpose, we urged for stricter criteria in dermatologic treatment trials and statistics before publication in peer-reviewed scientific journals to avoid frustrations on the part of both patients and the attending physicians.

Photodynamic therapy has been proposed to be beneficial for treatment of folliculitis decalvans [47].

Oral isotretinoin has been suggested for treatment of folliculitis decalvans [48, 49]. However, since folliculitis decalvans does not represent a follicular occlusion disorder, such as acne and dissecting cellulitis, the rationale for such a treatment remains questionable. Nevertheless, isotretinoin may reduce associated with scalp seborrhoea, which is a recognized co-factor for gram-negative infection in folliculitis decalvans [50]. Finally, isotretinoin therapy has been shown to promote *Staphylococcus* infection, with a nasal carrier rate of 64% versus 18% in a control group [51].

Subcutaneous adalimumab has been reported to be successful for treatment of recalcitrant folliculitis decalvans [52, 53]. However, again, there is no rational basis for such a treatment, since folliculitis decalvans represents a bacterial biofilm disease and usually responds well to antibiotic therapy and surgery, while anti-TNF therapies are contraindicated in infectious conditions.

Finally, lysostaphin is a 27 kDa zinc metallo antimicrobial lytic enzyme that is produced by *Staphylococcus simulans* biovar *staphylolyticus* first discovered in the 1960s. Lysostaphin is highly active against *S. aureus* strains irrespective of their drug-resistant patterns with a minimum inhibitory concentration of ranges between 0·001 and 0·064 μg $mL^{-1}$. Lysostaphin has activity against both dividing and non-dividing *S. aureus* cells and can seep through the extracellular matrix to kill the biofilm-embedded *S. aureus*. In spite of having excellent anti-staphylococcal activity, its clinical application is hindered because of its immunogenicity and reduced bio-availability.

### 3.1.5 Impetigo

Impetigo is a superficial bacterial infection of the skin. The most common presentation is a honey-coloured crusted plaque (Fig. 3.11a). Surrounding erythema may be present. Sores are not painful, but they may be itchy. Regional lymphadenopathy may be present. Impetigo most commonly affects the face, particularly the area around the nose and mouth, but it can affect any part of the body where the skin is broken. This includes the scalp. The first signs to appear are small sores forming on the skin.

Impetigo is due to either *S. aureus* or *Strept. pyogenes*. In industrial nations, *S. aureus* is the most common cause, while group A *Streptococcus* remains a common cause of impetigo in developing countries. The infection is spread by direct contact with lesions or with nasal carriers. The incubation period is 1–3 days after exposure to *Streptococcus* and 4–10 days for *Staphylococcus*. With contact, it can spread around or between people. Touching or scratching the sores may easily spread the infection to other parts of the body. Recurring infections can occur due to colonization of the nose by the bacteria. Soreness of the area is a common complaint.

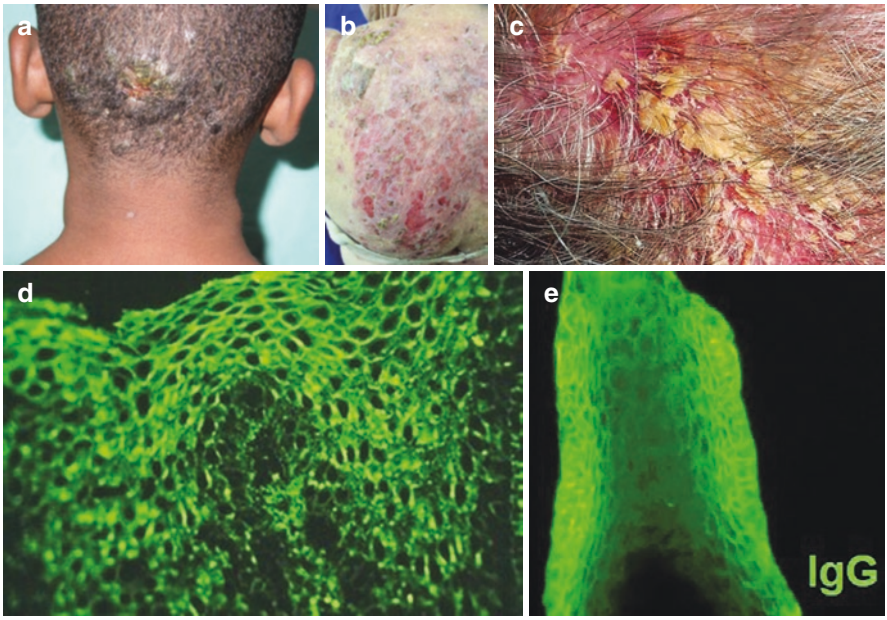


**Fig. 3.11** (**a**) Impetigo of the scalp. Honey-coloured crusted plaque with regional lymphadenopathy. (Courtesy: Prof. Fábio Francesconi, Federal University of Amazonas, Brazil). (**b**–**d**) Fogo selvagem (endemic phemphigus foliaceus) due to immunologic cross-reactivity between salivary proteins of *Lutzomyia longipalpis* and the pemphigus foliaceus antigen Dsg 1, which is also targeted by staphylococcal toxin in bullous impetigo and staphylococcal scalded skin syndrome, (**c**) scalp lesions, (**d**) direct immunofluorescence: detection of autoantibody targeted intra-epidermal intercellular antigen in the epidermis, (**e**) and in the hair root sheath of plucked hair

Impetigo can occur at any age but is most common in young children. In some places, the condition is also known as school sores. Globally, impetigo affects more than 162 million children in low- to middle-income countries. The rates are highest in countries with low available resources. Impetigo occurs more frequently among people who live in warm climates. Tropical climate and high population in lower socioeconomic regions contribute to high rates.

Risk factors include attending day care, crowding, poor nutrition, diabetes mellitus, contact sports, and breaks in the skin such as from insect bites (lice), eczema (atopic and seborrhoeic dermatitis), or herpes infection.

Complications may include cellulitis or poststreptococcal glomerulonephritis. Alopecia has been reported following impetigo of the scalp [54].

For treatment, antibiotics, either as a cream or by mouth, are usually prescribed. Mild cases may be treated with mupirocin ointments. In 95% of cases, a single 7-day antibiotic course results in resolution in children. More severe cases require oral antibiotics for 5–7 days (10 days if *Streptococci* are isolated), such as dicloxacillin (250–500 mg q.i.d.), flucloxacillin (500 mg q.i.d.), or erythromycin (250–500 mg q.i.d.). Alternatively, amoxicillin combined with clavulanate potassium (25 mg/kg/day t.i.d.), cephalosporins (first-generation), and clindamycin (15 mg/kg/day t.i.d.) may also be used as an antibiotic treatment. Alternatives for people who are allergic to penicillin or infections with methicillin-resistant *S. aureus* include doxycycline, clindamycin, and trimethoprim-sulphamethoxazole. Doxycycline should not be used in children under the age of 8 years due to the risk of drug-induced tooth discolouration. When *streptococci* alone are the cause, penicillin V is the drug of choice. When the condition presents with ulcers, valacyclovir (500 mg b.i.d. for 5 days) may be given in case a viral infection is causing the ulcer.

Oral antibiotics may be more effective for scalp impetigo since hair may hide some of the infected areas.

In very young children, there's some evidence that taking zinc supplements may reduce the risk of impetigo; particularly in one study, antenatal zinc supplementation at a dosage of 30 mg of zinc administered to mothers from 12 to 16 weeks' gestation until delivery in poor urban areas of Dhaka, Bangladesh, showed a 54% reduction in incidence rate of episodes of impetigo when compared with infants in the placebo group. The effect of zinc supplementation was more pronounced among male infants and intrauterine growth-restricted and low-birth-weight infants and among infants of mothers with increased parity or decreased socioeconomic status [55]. However, there isn't enough evidence at this point to say whether zinc is effective in older children and adults.

The best way to prevent impetigo of the skin or scalp is to avoid touching people with open skin blisters or sores, wash hands frequently, and not to share towels or other personal articles with others.

The differential diagnosis of sores on the scalp includes skin disorders such as psoriasis, eczema, ringworm, pemphigus, and scalp impetigo.

Pemphigus is an autoimmune blistering disease due to autoantibodies to the intracellular adhesion protein Desmoglein (Dsg). Blistering in bullous impetigo and staphylococcal scalded skin syndrome are due to a staphylococcal exfoliating toxin

that specifically binds and cleaves Dsg1. Pemphigus foliaceus (Fig. 3.11b, c) is due to autoantibodies aimed against Dsg 1 (Fig. 3.11d, e). It is endemic in Brazil as fogo selvagem, where it has been shown that recurring bites from the sandfly vector *Lutzomyia longipalpis* induces cross-reactive antibodies between *Lutzomyia longipalpis* salivary proteins and the pemphigus autoantigen DSg I in genetically susceptible individuals [56].

### 3.1.6 Furuncle (Boil) and Carbuncle

*S. aureus* strains first infect the skin and its structures, for example, sebaceous glands, hair follicles, or invade damaged skin (cuts, abrasions). A furuncle or boil is a deep infection of the hair follicle that is most commonly caused by *Staphylococcus aureus*, resulting in a painful swollen area on the skin caused by an accumulation of pus and necrotic tissue (Fig. 3.12a). Most are caused by coagulase-positive *S. aureus* strains, notable for the bacteria's ability to produce coagulase, an enzyme that can clot blood. *S. aureus* strains also produce enzymes and exotoxins that likely cause or increase the severity of certain diseases. Panton-Valentine leukocidin (PVL) is a cytotoxin—one of the β-pore-forming toxins. The presence of PVL is associated with increased virulence of certain strains (isolates) of *Staphylococcus aureus*. It is present in the majority of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) isolates studied and is the cause of necrotic lesions involving the skin (Fig. 3.12b, c). PVL creates pores in the membranes of infected cells. PVL is produced from the genetic material of a bacteriophage that infects *Staphylococcus aureus*, making it more virulent [57].

Furuncles present as red, pus-filled bumps arising from a hair follicle, which are tender, warm, and painful. A yellow or white point at the centre can be seen when the furuncle is ready to drain or discharge pus. When a furuncle bursts, a seemingly solid, whitish-coloured pus initially appears, and then pus and some blood follow.

Furuncles arise in hair-bearing sites, particularly in regions subject to friction, occlusion, and perspiration, such as the neck, face, armpits, and buttocks, or even in

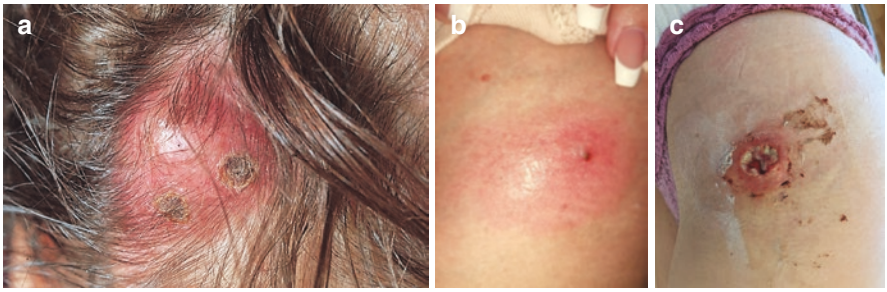


**Fig. 3.12** (**a**–**c**) Boil (furuncle) (**a**) of the scalp presenting as painful swollen area on the skin caused by an accumulation of pus and necrotic tissue. (**b**) Presence of PVL-positive strains of *S. aureus* is associated with increased virulence and cause of (**c**) necrotic lesions of the skin

the ear canal. Furuncles affecting the scalp are uncommon, and furunculoid myasis must be considered in the differential diagnosis, particularly with a respective geographic exposure history.

Other conditions to be considered in the differential diagnosis are dissecting cellulitis of the scalp (alopecic aseptic nodules of the scalp) and infected trichilemmal cysts.

Trichilemmal cysts are common benign cystic tumours that form from hair follicles and therefore occur in hairy areas, particularly the scalp, where they present as smooth, mobile, solitary masses filled with keratin (Fig. 3.13a, b). They are then easily treated by total surgical excision. Others may choose a more conservative approach involving a small punch biopsy about one-fourth the diameter of the cyst used to enter the cyst cavity. The contents of the cyst are emptied, leaving an empty sac. As the pilar cyst wall is the thickest and most durable of the many varieties of cysts, it can be grabbed with a forceps and pulled out of the small incision. This method is best performed on cysts that have formed a thick enough wall to be easily identified after the sac is emptied. Small cysts with thin walls are easily fragmented on traction. This increases the likelihood of cyst recurrence. Sometimes, trichilemmal cysts may present as multiple masses on the scalp causing cosmetic embarrassment from the un-aesthetic appearance and the foul smell of repeated recurrences of infection [58].

Recurring furuncles are called chronic furunculosis. Skin infections tend to be recurrent in many patients and may spread to other family members. Individuals who perspire excessively or who have poor hygiene are more prone to recurrent furunculosis.

Risk factors for furunculosis include bacterial carriage in the nostrils, diabetes mellitus, obesity, lymphoproliferative diseases, use of immunosuppressive drugs, malnutrition, or alcoholism.

Furuncles can be caused by other skin conditions that cause the person to scratch and damage the skin, such as atopic dermatitis.

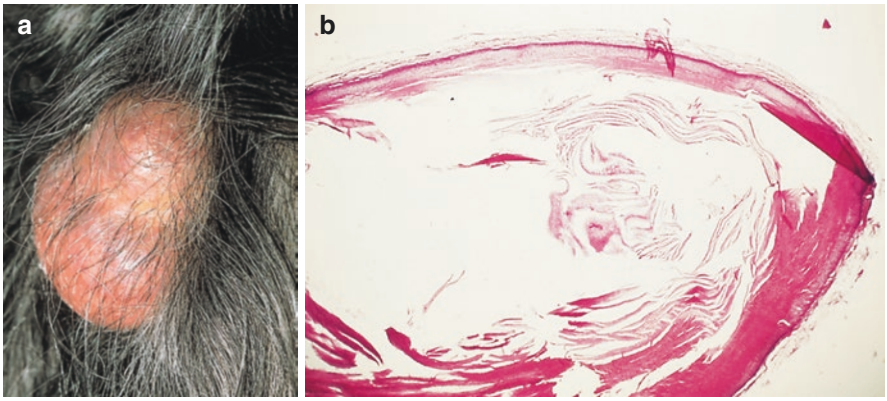


**Fig. 3.13** (**a**, **b**) Trichilemmal cyst (**a**) presenting as smooth, mobile, solitary mass, filled with keratin, (**b**) histopathology

Hyper-IgE syndrome is characterized by recurrent "cold" staphylococcal infections due to an impaired recruitment of neutrophil, unusual atopic dermatitis-like skin rashes, severe lung infections that result in pneumatoceles, and very high (>2000 IU/mL or 4800 μg/L) concentrations of the serum antibody IgE (Fig. 3.14a, b). The condition was first described by Davis et al. in 1966 who originally named the disease after the biblical figure Job, whose body was covered with boils by the Satan [59].

The most common complications of furuncles are scarring and infection or abscess of the skin. Sometimes, the infections are relatively limited, but other times, they may spread to other skin areas causing cellulitis. When these bacteria reach the bloodstream (bacteraemia), they may end up in many different body sites, causing serious infections (osteomyelitis, endocarditis, pneumonia). Fever and chills are signs of sepsis and indicate immediate treatment is needed. Squeezing or cutting boils in the danger triangle of the face can be particularly dangerous if done outside a medical setting, as blood vessels in this area drain into the brain and can carry serious infections there.

A furuncle may clear up on its own without bursting, but more often, it will need to be opened and drained. This will usually happen spontaneously within 2 weeks. Regular application of a warm moist compress, both before and after a furuncle opens, can help speed healing. The area must be kept clean, hands washed after touching it, and any dressings disposed of carefully, in order to avoid spreading the bacteria. A doctor may cut open or lance a boil to allow it to drain, but squeezing or cutting should not be attempted at home, as this may further spread the infection. Antibiotic therapy may be recommended for large or recurrent boils or those that occur in sensitive areas, such as the groin, breasts, armpits, around or in the nostrils, or in the ear. A semi-synthetic penicillin is recommended; in the penicillin-allergic patient, clindamycin (150–300 mg q.i.d.) or erythromycin (250–200 mg q.i.d.) is given. Antibiotics should not be used for longer than 1 month, with at least 2 months (preferably longer) between uses; otherwise, it risks to lose its effectiveness.

The diagnostic and therapeutic approach to a patient with a suspected staphylococcal infection should include a thorough medical history, clinical examination, and specific microbiological and biochemical investigations. This is particularly

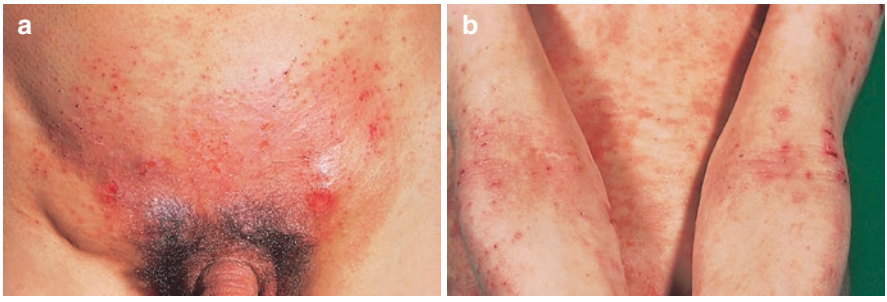


**Fig. 3.14** (**a**, **b**) Hyper-IgE or Job's syndrome is characterized by recurrent (**a**) "cold" staphylococcal abscesses and (**b**) unusual atopic dermatitis-like skin rashes

important in recurrent cases where culture swabs from the patient, family members, and close contacts are mandatory to identify and ultimately control the chain of infection. Focus on personal, interpersonal, and environmental hygiene issues is crucial to reduce the risk of contamination and recurrences.

Finally, *Staphylococcus aureus* has the ability to acquire antimicrobial resistance easily, making treatment difficult. Therefore, knowledge of the antimicrobial resistance of *S. aureus* is important in the selection of appropriate antimicrobials for treatment.

Furuncles frequently recur and can be prevented by applying liquid soap containing 2% chlorhexidine gluconate with isopropyl alcohol.

Ultimately, patients with recurrent furunculosis should be treated for predisposing factors such as obesity, diabetes, occupational or industrial exposure to inciting factors, and nasal carriage of *S. aureus* or MRSA colonization [60].

Intranasal application of 2% mupirocin ointment in a white soft paraffin base for 5 days has been effective in eliminating *S. aureus* nasal carriage in 70% of healthy individuals for up to 3 months; a 5-day course of nasal mupirocin ointment every month for one ear resulted in positive nasal cultures in only 22% of patients compared to 83% in the placebo group [61]. Oral rifampicin, 600 mg daily for 10 days, has also been effective in eradicating *S. aureus* from most nasal carriers for periods of up to 3 months [62]. However, selection of rifampicin-resistant strains can occur rapidly, which is why the addition of a second antibiotic, such as dicloxacillin, trimethoprim-sulfamethoxazole, ciprofloxacin, or minocycline for MRSA, is recommended to reduce the emergence of resistance [63].

A carbuncle is a cluster of several boils, which is typically filled with purulent material. Fluid may drain freely from the carbuncle, or intervention involving an incision and drainage procedure may be needed. Carbuncles may develop anywhere, but they are most common on the back and the nape of the neck.

A carbuncle is palpable and can range in size to be as large as a golf ball. The surrounding area is indurated. Typically, the lesion is extremely painful. The skin on the centre of the carbuncle softens, and peripheral satellite pustules appear, which rupture discharging pus and give rise to a cribriform appearance. Sometimes, systemic symptoms may occur, such as fatigue, fever, chills, and general malaise. Permanent scarring that is readily evident is usually the result of a carbuncle.

Triggers that make carbuncle infections more likely include recent incidence of folliculitis, friction from clothing or shaving, having hair pulled out at sites where clothing or furniture grab at hairs, generally poor hygiene, poor nutrition, or weakened immunity. Poor health may be a predisposing factor; particularly persons with diabetes are more likely to develop infections.

Currently, infection involving MRSA has become more common in carbuncles and may be the source of respective bacteraemia [64].

Abscesses are incised and drained. Intermittent hot compresses are used to facilitate drainage. Antibiotics, when used, should be effective against MRSA, pending culture and sensitivity test results. Systemic antibiotics are recommended for the following:

- Lesions >5 mm or <5 mm that do not resolve with drainage
- Multiple lesions
- Evidence of expanding cellulitis
- Immunocompromised patients
- Patients at risk of endocarditis
- Fever

Treatment choices include trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg to 320/1600 mg orally two times a day, clindamycin 300–600 mg orally every 6–8 h, or doxycycline or minocycline 100 mg orally every 12 h.

## 3.2 Soft Tissue Infections

Soft tissue infections are a broad category of microbial disease that can involve some or all layers of soft tissue, with cellulitis, abscesses, necrotizing fasciitis, and gas gangrene the most frequently encountered. Infections can range from mild cutaneous infections to severe necrosis of the skin, muscle, and fascia. Although cellulitis and abscesses are often treated with oral antibiotics or local drainage, respectively, necrotizing fasciitis and gas gangrene represent surgical emergencies with high morbidity and mortality. A comprehensive history and physical examination are crucial, while laboratory and imaging studies are available and can aid the clinician in the workup [65].

### 3.2.1 Cellulitis

Cellulitis is an acute, spreading bacterial infection of the skin involving primarily the inner layers of the skin, specifically the dermis and subcutaneous fat. *Staphylococcus aureus* and group A *streptococci* are the most common etiologic agents. The legs and face are the most common sites involved, although cellulitis can occur on any part of the body. Bacterial cellulitis of the scalp is rare and has been reported following trauma, i.e. after internal foetal monitoring [66], in association with infected cephalhematoma [67], from intravenous "scalp-vein" needles [68], as a post-procedural complication of 5-aminolevulinic acid photodynamic therapy in the treatment of actinic keratosis [69], and following a camel bite [70]. Massive cellulitis of the scalp has been reported in persons with diabetes [71].

Symptoms include an area of redness, which increases in size over a few days, while the borders of the area of redness are generally not sharp, and the skin may be swollen. The area of infection is usually painful.

In contrast to cellulitis, erysipelas is a bacterial infection involving the more superficial layers of the skin, with a marked lymphatic-vessel involvement and fever, produced by group A *streptococci*. Rarely, a similar clinical picture may be

due to infection with *S. aureus*. Group B streptococci may cause erysipelas in the newborn. Erysipelas-like scalp cellulitis has also been reported due to *haemophilus influenzae* type b [72].

The diagnosis is usually based on the presenting signs and symptoms, while a cell culture is rarely possible. Before making a diagnosis, more serious infections such as an underlying necrotizing fasciitis should be ruled out.

Treatment is with systemic antibiotics, such as cephalexin, amoxicillin, or cloxacillin [73]. Those who are allergic to penicillin may be prescribed erythromycin or clindamycin as alternative. When MRSA is a concern, doxycycline or trimethoprim/sulfamethoxazole may, in addition, be recommended [74]. Potential complications include abscess formation. Those with diabetes often have worse outcomes [75].

While bacterial cellulitis of the scalp is rare, dissecting cellulitis of the scalp is not uncommon.

Dissecting cellulitis of the scalp (DCS), also known as perifolliculitis capitis abscedens et suffodiens, or Hoffmann's disease, is a well-characterized chronic inflammatory disease of the scalp leading to scarring alopecia. Most of those affected are young black males; about 10% of cases involve white males. Association with acne conglobata was described as early as in 1903. Today, the condition is considered to be part of the follicular occlusion (or acne) triade, along with acne conglobata and hidradenitis suppurativa (acne inversa), or the acne tetrade along with a pilonidal sinus (Fig. 3.15a), though isolated scalp disease frequently occurs.

Deep inflammatory nodules develop on the occipital scalp or vertex and can evolve to extensive confluent boggy plaques with sinus tract formation (Fig. 3.16a). Hairs overlying the nodules can be easily plucked, and sinus tracts may discharge purulent material. Ultimately, a multifocal scarring alopecia ensues that is potentially disfiguring.

Histopathology reveals a neutrophilic primary scarring alopecia. Pathogenetically, a defect in follicular keratinization is implicated, leading to poral obstruction and accumulation of sebaceous and keratinous material within dilated pilosebaceous units. Subsequently, follicles burst and an intense neutrophilic inflammatory reaction with abscess and sinus tract formation follow (Fig. 3.16b).

Treatment recommendations for DCS have been oral isotretinoin 1 mg/kg body weight daily for at least 6 months, in combination with sustained, pathogen-specific, systemic antibiotic (according to antibiogram), and oral prednisone 1 mg/kg body weight with subsequent tapering or oral dapsone 100–200 mg daily, in combination with oral zinc gluconate 30 mg daily, and intralesional triamcinolone acetonide 5–10 mg/mL and in severe and refractory cases, large-scale surgical excision in combination with reconstructive surgery or subcutaneous adalimumab 40 mg every 2 weeks (Fig. 3.17) [76]. The inflammation responsible for scarifying tissue destruction is directly targeted by adalimumab at the level of tumour necrosis factor. Histopathologic characteristics demonstrate marked improvement of inflammation, despite persistence of underlying structural disease. Relapse on discontinuation of therapy can therefore be expected depending on persisting structural disease. Therefore, continuous treatment or combined surgical resection of involved areas could be necessary for definitive resolution of disease (Fig. 3.17a–g).

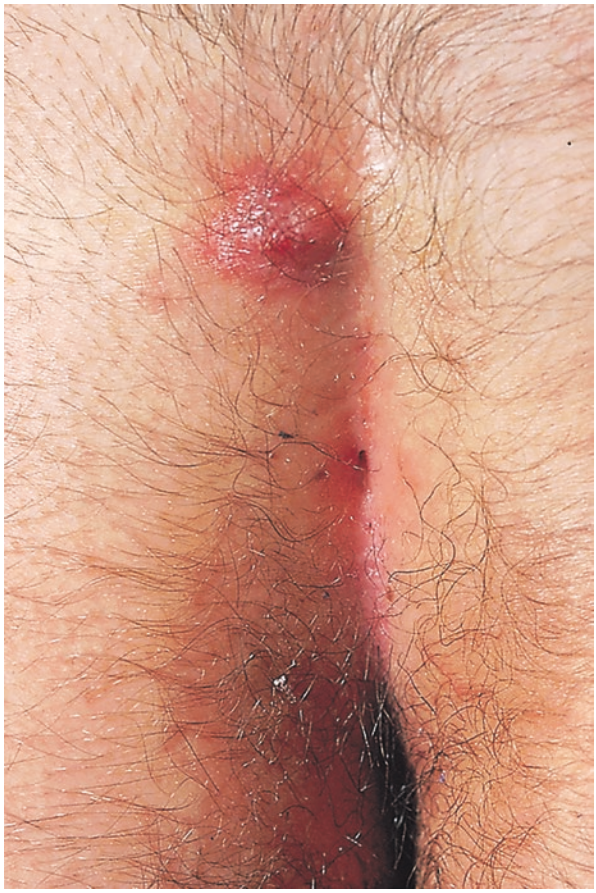

**Fig. 3.15** Pilonidal sinus

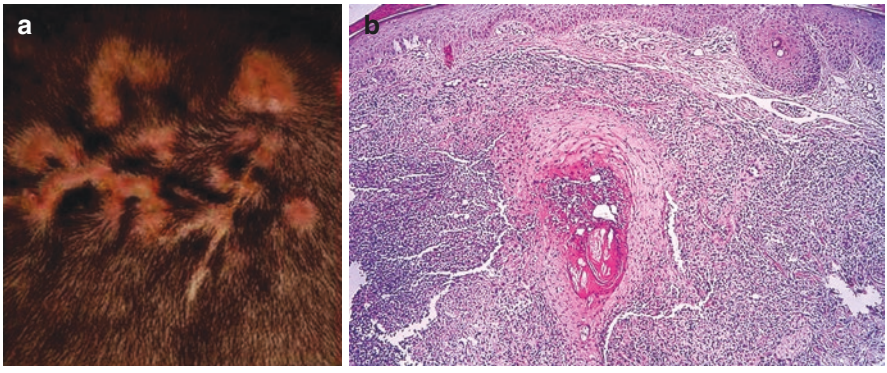


**Fig. 3.16** (**a**, **b**) Dissecting cellulitis of the scalp. (**a**) Deep inflammatory nodules of the vertex region evolving to extensive confluent boggy plaques with sinus tract formation. (**b**) Histopathology: defect in follicular keratinisation with accumulation of keratinous material within dilated pilosebaceous unit and follicular burst with an intense neutrophilic inflammatory reaction with abscess formation

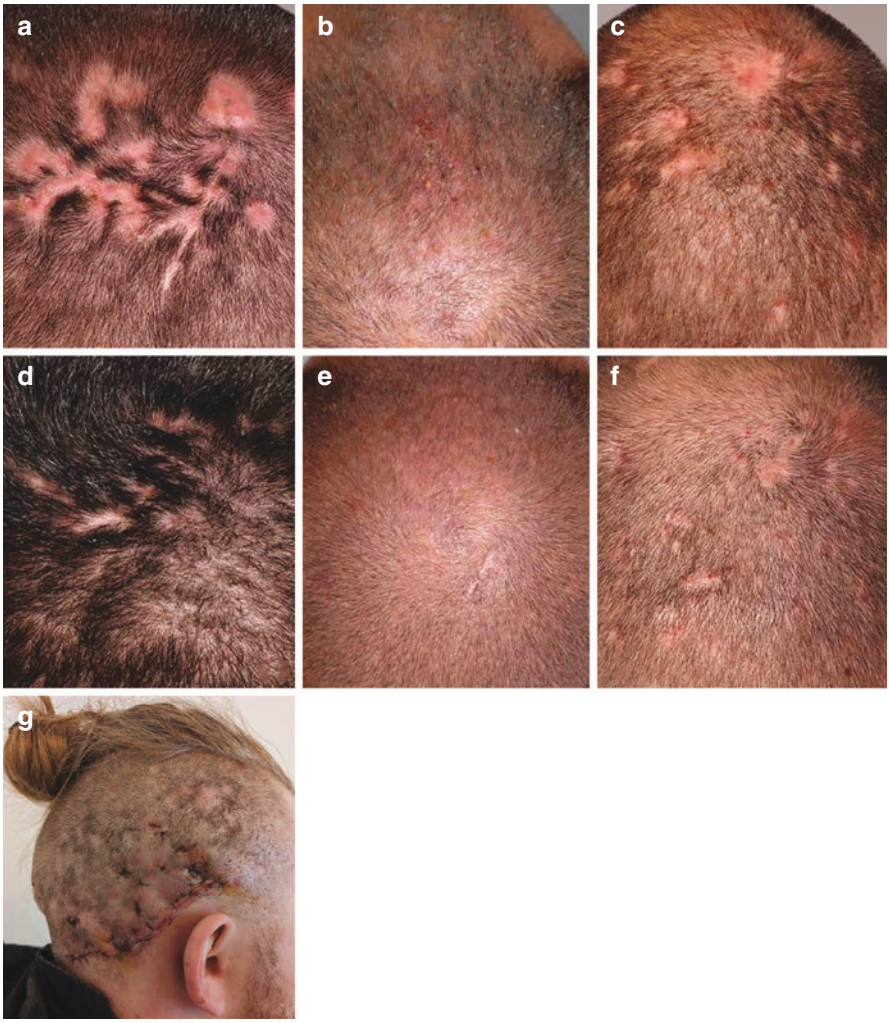


**Fig. 3.17** (**a**–**g**) Management of dissecting cellulitis of the scalp: (**a**–**f**) three cases successfully treated with subcutaneous adalimumab 40 mg every other week, (**a**–**c**) before and (**d**–**f**) after treatment. (**g**) Combined pharmacological and surgical management of dissecting cellulitis of the scalp. The patient was treated with subcutaneous adalimumab prior to surgery

In 1992, Iwata et al. originally reported 19 Japanese patients with pseudocysts of the scalp with inflammatory granulation tissue presenting as solitary painful subcutaneous tumour associated with alopecia [77]. It was not until 1998 that Chevallier reported three cases of non-infectious abscesses of the scalp with alopecia on the occasion of the French Federation for Continuing Medical Education in Dermatology and questioned whether it represented a new nosological entity [78]. In 2005, Tsuruta et al. reported four additional cases of the so-called pseudocyst of the scalp

under the assertion that there were no reports of such lesions in the Western literature for lack of acquaintance with the French language [79]. Ultimately, Abdennader and Reygagne coined the term alopecic and aseptic nodules of the scalp (AANS) for the condition in a retrospective review of 18 cases seen over a period of 12 years at the Saint-Louis-hospital in Paris [80]. Subsequently, Abdennader et al. reported a prospective study of 15 cases of AANS and demonstrated that the disorder affected predominantly young men of Caucasian origin [81]. The main location of the nodules was occipital. Microbiological cultures of material from the puncture were negative. The histopathology showed a deep granuloma. Pseudocysts were not always present. The condition responded well to oral doxycycline therapy with recovery of hair. Subsequent single case reports and case series did not add any new insight of pertinence to the nomenclature and nosology of the condition.

The condition received its designation based on the clinical presentation with either one or few dome-shaped, firm, fluctuating, or soft alopecic nodules of the scalp on the vertex (Fig. 3.18a) or occipital area (Fig. 3.18b), which when punctured drain a sterile purulent or blood-tinged fluid (Fig. 3.18c). Histopathology shows a non-specific mixed inflammatory infiltrate in the deep dermis; however, a granulomatous infiltrate with multi-nucleated foreign body giant cells and pseudocyst formation may be found [81, 82]. Dermoscopic features are black and yellow dots, fine vellus hairs, and broken hair shafts (Fig. 3.18d), with none of these being pathognomonic for the condition [83]. Bourezane et al. reported the "Eastern pancake sign" (Fig. 3.18e), referring to dilated follicular orifices and comedo-like structures [84]. Ultrasonographic studies demonstrated well-defined hypoechoic or anechoic subcutaneous nodular lesions [83]. The course of disease is chronic relapsing with partial or total regrowth of the hair. Doxycyline 100–200 mg/day for 8–12 weeks was the most used treatment, followed by intralesional triamcinolone acetonide injections [85].

Except for ethnicity and the extent and severity of disease, there is no single feature that justifies distinguishing AANS as a nosological entity in its own right from DCS. Apart from the lesser degree of severity and extent, AANS does not present any features distinct from DCS, including dermoscopic findings [86], histopathology [87], and microbiologic studies. With respect to pathogenesis, in fact, the dermoscopic feature of comedo-like structures suggests the potential role of follicular occlusion. Finally, also treatment is the same, with oral doxycycline or isotretinoin associated with intralesional triamcinolone acetonide and oral isotretinoin [88] being effective. We therefore consider AANS a disease manifestation of DCS at the minor end of its clinical spectrum. Particularly, AANS is more frequently observed in non-Africans. Indeed, due to peculiarities of hair anatomy and hair-grooming habits, environmental factors, and maybe genetic factors [89], a number of inflammatory scalp conditions tend to be more severe in patients of African origin, such as DCS, folliculitis keloidalis nuchae, and central centrifugal cicatricial alopecia.

While large-scale surgical excision in combination with reconstructive surgery may be necessary in severe cases of DCS, surgery is not warranted in AANS because of its favourable prognosis.


**Fig. 3.18** (**a–d**) Alopecic and aseptic nodules of the scalp: (**a**) dome-shaped, firm, fluctuating, or soft, alopecic nodules of the scalp on the vertex or (**b**) occipital area, which (**c**) when punctured drain a sterile purulent fluid; (**d**) dermoscopy, (**e**) Eastern pancake

### 3.2.2 Abscess

An abscess is a localized collection of pus that has built up within the tissue of the body, lined by an abscess wall or pyogenic membrane, and represents a defensive reaction of the tissue to prevent the spread of the infection. The final structure of the abscess is an abscess wall or capsule, which is formed by the adjacent healthy cells in an attempt to keep the pus from infecting neighbouring structures. However, such encapsulation tends to prevent immune cells from attacking bacteria in the pus or from reaching the causative organism or foreign object. Nevertheless, even without treatment, skin abscesses rarely are fatal, as they naturally break through the skin.

Signs and symptoms of abscesses include redness, pain, warmth, and swelling (rubor, dolor, calor, tumour). The swelling may feel fluid-filled when pressed. The area of redness often extends beyond the swelling.

Abscesses caused by *S. aureus* commonly occur in folliculocentric infections (furuncle, carbuncle). Abscesses can also occur at sites of trauma, foreign bodies, or sites of insertion of intravenous catheters. An incisional abscess is one that develops as a complication secondary to a surgical incision. It presents as redness and warmth at the margins of the incision with purulent drainage from it. If the diagnosis is uncertain, the wound should be aspirated with a needle, with aspiration of pus confirming the diagnosis and availing for bacterial culture.

The organisms or foreign materials injure the local cells, resulting in the release of cytokines. These trigger an inflammatory response, which draws large numbers of neutrophils to the area and increases the regional blood flow.

Standard treatment for most skin or soft tissue abscesses is cutting it open and drainage (ubi pus ibi evacuat). Sucking out the pus with a needle is often not sufficient.

Antibiotics in addition to standard incision and drainage are recommended in persons with severe abscesses, many sites of infection, rapid disease progression, the presence of cellulitis, symptoms indicating systemic bacterial disease, or a health condition causing immunosuppression. Also, individuals who are very young or very old may also need antibiotics. If the abscess does not heal only with incision and drainage or if the abscess is in a place that is difficult to drain such as the face, hands, or genitals, then antibiotics are also indicated. Finally, the draining of an abscess is not enough to address MRSA. However, antibiotic therapy alone without surgical drainage of the abscess is seldom effective due to antibiotics often being unable to get into the abscess and their ineffectiveness at low pH levels. Finally, the abscess should be inspected to identify if foreign bodies are a cause, which require removal.

Abscesses of the scalp are a rare event and have primarily been observed in neonates [90], in the immunocompromised [91], secondary to spread from frontal sinusitis (Pott's puffy tumour) [92–95], as a sequel from infected scalp sebaceous cysts [96], associated with a postsurgical scalp ulcer [97], from scalp-vein needles [98], and as a complication of mesotherapy [99].

Neonatal scalp abscesses are a rare but serious condition, with meningitis as a potential complication. The emergency practitioner should recognize that a neonate

with a scalp abscess needs to be evaluated for potential serious complications and treated empirically to cover for organisms of vaginal origin [90]. Very rarely, neonatal scalp abscess may result from infection of a cephalhaematoma [100]. More frequently, it is related to neonatal monitoring with a spiral foetal electrode [101, 102]. Factors associated with infection are duration of monitoring and high-risk indications for monitoring [103]. The lesions are usually single and localized. Bacterial cultures will usually reveal aerobic and/or anaerobic bacteria similar to the cervical flora of the late trimester of pregnancy. However, since herpes simplex virus infection has been reported to start as vesicles around the site of electrode implantation, careful attention to the maternal history must be given [104]. Also, neonatal gonococcal scalp abscess may have to be taken into consideration with a respective maternal history [105]. Gonococcal infection in caesarean delivered babies is very rare and is usually limited to ophthalmia neonatorum. In one reported case, the mother had rupture of membranes 14 h before the caesarean section. The infection was most likely introduced by the foetal scalp electrode probes applied 2 h before delivery. Finally, neonatal scalp abscesses may also be due to retention of a fragment of an electrode [106].

The rich blood supply of the head makes widespread infection from a scalp wound an unlikely occurrence. Most acute infections of the scalp result in complete resolution with adequate early management. And yet, extensive purulent fibrosis of the scalp remains a potentially serious complication. Infection due to *Chromobacterium violaceum*, a large motile gram-negative bacillus, is a rare entity that typically starts with a localized skin infection after contact with stagnant water or soil. It can progress to fulminating septicaemia, with necrotizing metastatic lesions and multiple abscesses in the liver, lung, spleen, skin, lymph nodes, and brain. One case report involves a young male with a history of falling from a bike into stagnant water who subsequently developed *C. violaceum* infection at the site of the sutured scalp wound [107].

The differential diagnosis of scalp abscesses includes sebaceous cysts, aseptic alopecic nodules (pseudocysts) respectively dissecting cellulitis of the scalp [77], tinea capitis of the kerion type [108], and furuncular myaisis [109], and only exceptionally atypical presentation of temporal arteritis [110] or inflammatory myofibroblastic tumour [111].

### 3.2.3 Necrotizing Fasciitis

Necrotizing fasciitis is an uncommon but often fatal bacterial infection of the skin, subcutaneous fat, superficial fascia, and deep fascia. It is characterized by marked tissue oedema, rapid spread of inflammation, and signs of systemic toxicity. Symptoms usually include red or purple skin in the affected area, severe pain, fever, and vomiting. The most commonly affected areas are the limbs and perineum (Fournier gangrene), though necrotizing fasciitis can occur at any part of the body [112]. Neonatal necrotizing fasciitis has been reported from foetal scalp monitoring [113].

Typically, the infection enters the body through an injury of the skin such as a cut or burn. Risk factors include poor immune function such as from diabetes obesity, alcoholism, and intravenous drug abuse.

Wound cultures are predominantly polymicrobial, and the location of initial involvement depends on the underlying etiologic factor. In streptococcus gangrene, *Streptococcus* species produce M protein, which acts as a superantigen, stimulating a massive systemic immune response, which is not effective against the bacterial antigen, precipitating shock. *Vibrio vulnificus*, a bacterium found in saltwater, is a rare cause of this infection.

Trauma is the usual cause of the infection, such as from intravenous drug injection, insulin injection, animal and insect bites, catheter insertion over the skin, or injury. Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the rates of necrotizing infections due to the modification of immune response in the body, because NSAIDs inhibit the cycloxygenase-1 and cycloxygenase-2 enzymes, which are important in producing thromboxane and prostaglandin E2. Prostaglandin has been responsible for fever, inflammation, and pain. The inhibition of prostaglandin E2 production reduces inflammatory response and leukocyte adhesion and thus reduces immune response against bacterial invasion, giving rise to soft tissue infection.

The initial skin changes are similar to cellulitis or abscess, thus making the diagnosis at early stages difficult. Symptoms may include fever, swelling, and complaints of excessive pain. Medical imaging is often helpful to confirm the diagnosis [114]. The gold standard for diagnosis is a surgical exploration in a setting of high suspicion. When in doubt, a small incision can be made into the affected tissue, and if a finger easily separates the tissue along the fascial plane, the diagnosis is confirmed, and an extensive debridement should be performed. A white blood cell count greater than 15,000 cells/mm$^3$ and serum sodium level less than 135 mmol/L have a sensitivity of 90% in detecting the necrotizing soft tissue infection.

High index of suspicion, prompt aggressive surgery, appropriate antibiotics, and supportive care are the mainstays of management. Aggressive wound debridement should be performed early. Antibiotics should be started as soon as this condition is suspected. Empiric antibiotics are usually initiated as soon as the diagnosis has been made and then later changed to culture-guided antibiotic therapy. The empiric antibiotics are broad spectrum, covering gram-positive (including MRSA), gram-negative, and anaerobic bacteria. Tissue cultures, rather than wound swabs, are taken to determine appropriate antibiotic coverage, and antibiotics may be changed in light of results. Supportive therapy, including intravenous hydration, wound care, anticoagulants to prevent thromboembolic events, pain control, etc., is provided to patients as needed. Skin grafting may be required in case of large post-operative skin defects.

### 3.2.4 Gas Gangrene

Gas gangrene, also known as anaerobic myonecrosis, is a bacterial infection that produces tissue gas in gangrene. Myonecrosis is a condition of necrotic damage, specific to muscle tissue. It is often seen in infections with *C. perfringens* or any of a number of soil-borne anaerobic bacteria (*Bacteroides* spp., *Peptostreptococcus* spp., *Prevotella* spp.). Usually it occurs in a setting of a traumatic dirty wound with extensive muscle and soft tissue damage.

A case of gas gangrene of the scalp has been reported [115].

Bacteria cause myonecrosis by specific exotoxins. These microorganisms are opportunistic and usually enter the body through significant skin breakage. Common virulence factors associated with gas gangrene include alpha toxin and theta toxin. *Clostridium perfringens* causes 80–90% of infections and produces both these toxins. Alpha toxin is associated with haemolysis, thus restricting blood flow towards the area of infection. As the surrounding circulatory system collapses, neutrophils, monocytes, eosinophils, and basophils cannot reach target areas of infection. The haemolytic activity of alpha toxin produces an anaerobic environment essential for the proliferation of the bacteria. Theta toxin promotes vascular degradation. A platelet-activation factor is employed, which triggers an acute inflammatory response in nearby tissues [116]. This inflammatory response leads to constriction of surrounding arteries, again promoting an anaerobic environment for *Clostridium perfringens* growth and pathophysiology.

A multitude of symptoms is associated with gas gangrene. Typically, black lesions on the skin appear in a bubble form, which allows visualization of bacterial gas production. Symptoms include pain following site of trauma, swelling, air in subcutaneous tissues (crepitation), a foul sweet-smelling discharge from lesions, fever, light-headedness, and a rapid heart rate.

Due to a low incidence of gas gangrene, it is easy to miss. Diagnostic methods include microscopy identification of strain of bacteria sampled from fluids of inflicted area, Gram stain, cultures of fluids from inflicted area, biopsy of affected tissue, X-rays for air pockets in affected tissues, and resonance imaging to visualize necrotized subcutaneous tissues.

Treatment is debridement and excision. Water-soluble antibiotics, such as penicillin, alone are not effective because they do not penetrate ischemic muscles sufficiently to be effective. Skin grafts are often required following removal of necrotic tissues.

## 3.3 Gram-Negative Infections

Gram-negative bacteria are bacteria that do not retain the crystal violet stain used in the Gram staining method of bacterial differentiation. They are characterized by their cell envelopes, which are composed of a thin peptidoglycan cell wall sandwiched between an inner cytoplasmic cell membrane and a bacterial outer membrane. Gram-negative bacteria are found in virtually all environments on earth that

support life. They are an important medical challenge, as their outer membrane protects them from many antibiotics, detergents that would normally damage the inner cell membrane, and lysozyme that forms part of the innate immune system. Additionally, the outer leaflet of this membrane comprises a complex lipopolysaccharide (LPS) whose lipid A component can cause a toxic reaction when bacteria are lysed by immune cells. Platelet depression, disseminated intravascular coagulation, and possibly the dermal or generalized Shwartzman reaction may produce varied haemorrhagic cutaneous manifestations. Gram-negative bacteria include the model organism *Escherichia coli*, as well as many pathogenic bacteria, such as *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Salmonella* spp., *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp., and *Serratia marcescens*. With regard to the skin and hair, *Pseudomonas aeruginosa* is the most prevalent of pathogens. These ubiquitous gram-negative bacilli can cause serious infections in individuals with altered immunity, receiving intense antibiotic therapy, or in hospital settings. The cutaneous manifestations of *Pseudomonas* infection are common and characteristic. They may represent the only overt findings in septicaemia (ecthyma gangrenosum) or be the localizing focus in serious infections of the ear in elderly diabetics (malignant external otitis), or they may present as trivial infections of the nails (green nail), toe webs, skin, and hair (*Pseudomonas* folliculitis).

### 3.3.1 Gram-Negative Folliculitis

Gram-negative folliculitis occurs in the setting of exposure to warm water in a whirlpool (whirlpool dermatitis) [117] (Fig. 3.19), hot tub (hot tub folliculitis) [118], some recreational spa for swimming, or a water slide; following epilation [119, 120] (Fig. 3.20); from other sources of contaminated water, such as a loofah sponge [121]; rubbing skin with nylon towels placed in the bathroom during bathing [122], as so-called non-recreational *Pseudomonas* folliculitis [123]; or as a complication of antibiotic therapy of either acne or folliculitis decalvans, particularly with oral tetracyclines. Nosocomial outbreak of gram-negative folliculitis has also been reported associated with a physiotherapy pool [124]. A classification of gram-negative folliculitis is found in Table 3.2.

*Pseudomonas aeruginosa* is frequently found in whirlpools and hot tubs, sometimes in 94–100% of those tested at concentrations of <1–2400 CFU/mL. The high concentrations found probably result from the relatively high temperatures of whirlpools, which favour the growth of *P. aeruginosa*, and the aeration, which also enhances its growth. The organism is usually found in whirlpools when the chlorine concentrations are low, but it has been isolated even in the presence of 3.00 ppm residual free chlorine [125].

The factors that affect the host's susceptibility to whirlpool-related infection are the anatomic and physiologic defences of normal skin, the microecology of the skin surface, factors intrinsic to the individual host, and behavioural factors. The structural components of the skin maintain an environment at the skin surface that makes

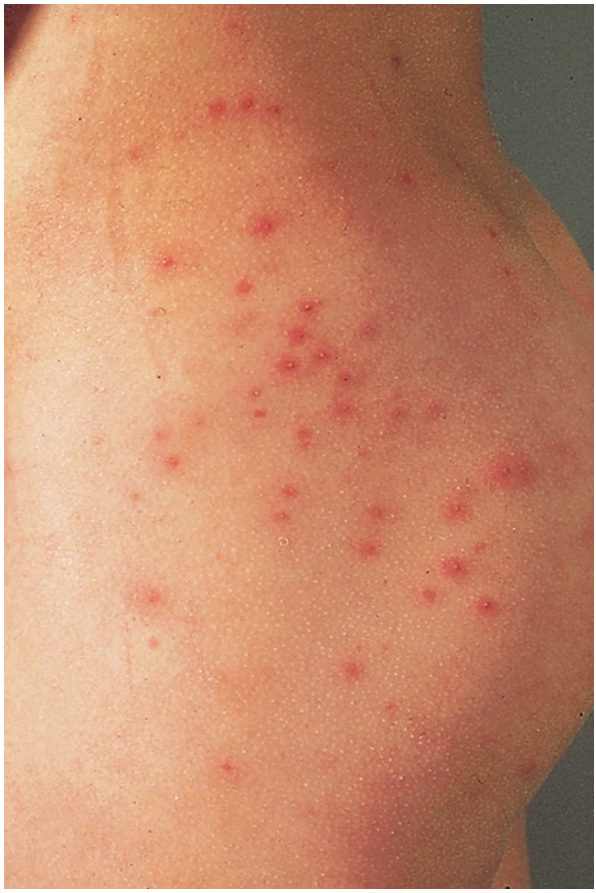

**Fig. 3.19** Pseudomonal folliculitis of the whirlpool dermatitis type. Widespread eruption of follicular papules and pustules

human skin an inhospitable habitat for microflora. However, natural and experimental models of *P. aeruginosa* skin infection suggest that immersion in whirlpools may negate many of the body's normal host defences. Associations have been made between pseudomonal folliculitis and behaviours in pools or hot tubs. Of these, the length of time in the water has the greatest association with skin infection [126]. Bacterial invasion into the skin is facilitated by the enhanced permeability of the stratum corneum after immersion in water, while it is hypothesized that water absorption of the stratum corneum increases proportionally with time submerged in water. Differences in gender can also influence the risk of pseudomonas folliculitis. In studies of pseudomonal folliculitis outbreaks, there were more women affected than men. Hypotheses to explain this disparity include intrinsic gender-specific differences in skin flora and differing topical product use, such as lotions and deodorants [127].

Transient colonization of the skin with *P. aeruginosa* may lead to elaboration of toxins in vivo, resulting in the characteristic dermatitis [126].

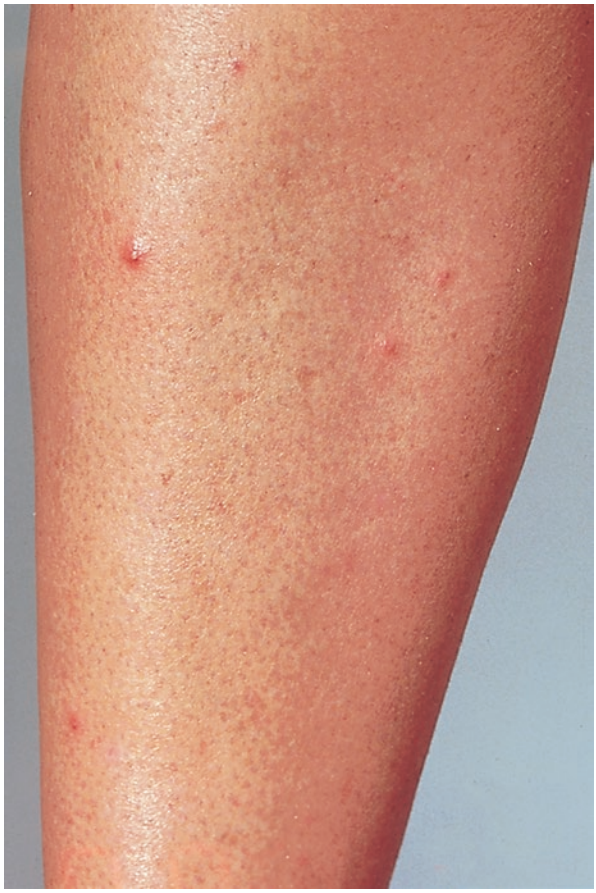

**Fig. 3.20** Post-epilation pseudomonal folliculitis. The follicular lesions are localized to the area of epilation

**Table 3.2** Gram-negative folliculitis: classification

- Recreational (whirlpool dermatitis, hot tub folliculitis)
- Non-recreational (post-epilation, associated with a wet contamination source)
- As a complication of antibiotic treatment (in acne, rosacea, folliculitis decalvans)

The clinical presentation is that of a rash that is localized to the body parts that have been immersed in contaminated water [128] or more generalized in distribution in swimsuit and intertriginous areas. The rash begins as papules and evolves to papulopustules before healing with a fine desquamation. Pruritus and pain may accompany the lesions and, occasionally, mastitis, external otitis, and systemic symptoms. Also, urinary tract infections with *P. aeruginosa* have been reported from exposure to whirlpools [129]. While recreationally acquired *Pseudomonas* folliculitis tends to be acute, non-recreational *Pseudomonas* folliculitis tends to be chronic recurrent with continued exposure, as long as the source of infection is not identified and eliminated [123].

Management of pseudomonas folliculitis varies with severity of the infection. In most cases, lesions are self-limited and resolve without management in 1–2 weeks [130]. Despite the discomfort caused by the rash, usually no treatment is necessary.

Home treatments can provide symptomatic relief and help speed up the healing. These treatments include:

- Applying warm compresses, which can help reduce itching and improve healing
- Using anti-itching creams or lotions to help relieve discomfort
- Applying antibacterial creams like gentamycin to the affected areas to prevent secondary infection
- Applying apple cider vinegar or acetic acid 5% for 20 min twice to four times a day to the affected area, either directly or by soaking in a bath containing apple cider vinegar

In cases in which the folliculitis does not self-resolve, a culture and antibiotic susceptibility testing can provide guidance on appropriate therapy. *Pseudomonas aeruginosa* is resistant to nearly all common topical and oral antibiotics. Antipseudomonal agents include [131]:

- Antipseudomonal penicillins (ticarcillin and piperacillin)
- Beta-lactamase inhibitor combinations (ticarcillin-clavulanate and piperacillin-tazobactam)
- Carbapenems (doripenem, imipenem, and meropenem)
- Cephalosporins (ceftazidime and cefepime)
- Colistin
- Fluoroquinolones (ciprofloxacin or levofloxacin)
- Monobactams (aztreonam)

Studies of *P. aeruginosa* found in public pools demonstrate considerable antibiotic resistance to agents such as aztreonam and imipenem [132]. The oral antibiotic group least associated with resistance and most commonly recommended is fluoroquinolones, specifically ciprofloxacin.

Gram-negative folliculitis also occurs in patients who have had moderately inflammatory acne for long periods and have been treated with long-term antibiotics, mainly tetracyclines, a disease in which cultures of lesions usually reveal a species of *Klebsiella*, *Escherichia coli*, *Enterobacter*, or, from the deep cystic lesions, *Proteus*.

In a study of 34 subjects with folliculitis decalvans who had bacterial cultures, the majority of cultures were positive for *staphylococci*; however, gram-negative bacteria were found in up to 33% (Fig. 3.21). The most frequently detected gram-negative bacteria were *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter*

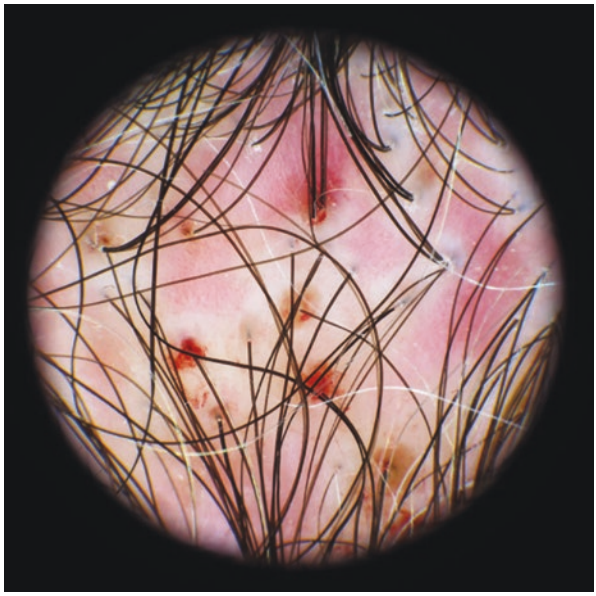

**Fig. 3.21** Gram-negative folliculitis of the scalp

*aerogenes*, and enteric gram-negative rods. Other gram-negative bacteria, such as *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Citrobacter koseri*, and *Serratia marcescens*, were found at a less frequent rate. This pattern corresponds to findings of previous studies in patients with gram-negative folliculitis [133–135]. Presence of *Cutibacterium acnes* and coagulase-negative staphylococci characterizes the normal subepidermal microbiota of scalp skin. Their presence helps maintain the integrity of the hair follicle. Similar to gram-negative folliculitis, gram-negative infection in folliculitis decalvans is believed to be a complication of long-term antibiotic treatment, the aetiology of which has been hypothesized to be the result of suppression of the normal commensal flora. In addition, overproduction of sebum and sweat may create a favourable environment for gram-negative infections. In this cohort, the rate of gram-negative rod infections was high and likely represents a referral bias of patients who did not respond to standard treatment. Potential causes for these infections include long-term antibiotic use and presumably nosocomial/environmental exposure and disruption of the normal epidermal barrier related to ongoing inflammation. The authors concluded that awareness of the incidence of these infections may lead to better therapeutic outcomes, and regular bacterial cultures should be considered in patients who have ongoing/active folliculitis decalvans to evaluate for the presence of non-staphylococcal bacterial infections, specifically gram-negative rod infections. Ultimately, treatments including appropriate antibiotics (e.g. trimethoprim or fluoroquinolones, such as ciprofloxacin or levofloxacin), eradication of the potential source of the infection, possibly retinoids to suppress sebum production, and re-establishment of the epidermal barrier may be necessary for disease control [50].

### 3.3.2 Ecthyma Gangrenosum

Ecthyma gangrenosum is a well-recognized though uncommon cutaneous infection classically associated with pseudomonal sepsis, typically secondary to neutropenia. The characteristic lesions are haemorrhagic vesicles or pustules that evolve into necrotic ulcers with a tender erythematous border. The lesions may be single or multiple. They are most commonly seen in perineum and under the armpit. However, they can occur in any part of the body, including the head [136]. Ecthyma gangrenosum was originally described in association with *Pseudomonas* septicaemia by Canadian pathologist Dr. Lewellys Barker in 1897 [137]. Not all cases have been associated with sepsis [138]. There is increasing recognition that a broader definition is warranted, as numerous causative organisms and predisposing conditions are being reported. It mostly occurs in patients with underlying immunocompromise, e.g. malignancy or HIV. A retrospective study of all cases of ecthyma gangrenosum from 2004 to 2010 in a university hospital in Mexico shows that neutropenia in immunocompromised patients is the most common risk factor [139]. Other bacteria, including *Escherichia coli*, *Citrobacter freundii*, *Klebsiella pneumoniae*, various other *Pseudomonas* spp., and *Morganella morganii*, have been implicated in similar lesions [140, 141].

A nosocomial outbreak of *Pseudomonas* folliculitis occurred in neutropenic patients in a cancer treatment centre, while the sinks and faucets in the patient's rooms proved to be the source of *P. aeruginosa*. In contrast to normal individuals with swimming pool folliculitis, in these patients, the lesions rapidly became widespread and progressed to ecthyma gangrenosum-like lesions, unless systemic antibiotic treatment was initiated immediately [142].

Prompt recognition and empiric therapy with broad-spectrum antipseudomonal agents (anti-pseudomonal penicillin such as piperacillin, aminoglycosides fluoroquinolones, third-generation cephalosporins, aztreonam) are of critical importance. While awaiting culture results, piperacillin is usually given in combination with an aminoglycoside. Once microbiology results identify the causative pathogen and sensitivities are available, antimicrobial coverage should be narrowed accordingly. Ecthyma gangrenosum indicates a poor prognosis, particularly in immunocompromised individuals with neutropenia. Progression of the process may be extremely rapid and therefore an indication for prompt surgical debridement in addition to antimicrobial therapy and, where indicated, granulocyte colony-stimulating factor (G-CSF).

## 3.4 Corynebacterial Infections

*Corynebacterium* is a genus of mostly aerobically growing bacteria that are Gram-positive bacilli (rod-shaped), and in some phases of life, they are, more specifically, club-shaped, which inspired the genus name (*coryneform* meaning "club-shaped"). Unlike gram-negative bacteria, the gram-positive *Corynebacterium* species lack lipopolysaccharides that function as antigenic endotoxins in humans.

Corynebacteria are widely distributed in nature in the microbiota of animals, including the human microbiota, and are mostly innocuous, most commonly existing in commensal relationships with their hosts [143]. Others can cause human disease, including most notably diphtheria, which is caused by *C. diphtheriae*. As with various species of a microbiota, they usually are not pathogenic but can occasionally opportunistically capitalize on atypical access to tissues via wounds or weakened host defences. *Corynebacterium* endocarditis is seen most frequently in patients with intravascular devices [144].

Skin infections caused by coryneform bacteria are common dermatological conditions.

The normal human skin is colonized by huge numbers of bacteria that live harmlessly as commensals on its surface and within its follicles. A warm and moist environment under occlusion facilitates increased colonization of these bacteria [145]. The diseases caused by coryneform bacteria include pitted keratolysis, erythrasma, and trichobacteriosis (formerly called trichomycosis).

This group of infections does not present with diagnostic difficulties because of its distinctive clinical appearance and odour.

The coexistence of these three corynebacterial diseases has been documented in the literature as the corynebacterial triad [146].

Knowledge of the predisposing factors that promote bacterial growth is essential as their removal ensures effective and long-term treatment.

### 3.4.1 Trichobacteriosis Palmellina

Trichobacteriosis (formerly trichomycosis) palmellina or Paxton's disease [147] is a usually asymptomatic superficial bacterial colonization of the hair shaft with *Corynebacterium tenuis* [148, 149], which is clinically characterized by yellow, red, or black, 1–2 mm granular nodules or concretions surrounding hair shafts in the axillary (trichobacteriosis axillaris) or pubic region including the scrotal hair [150]. Atypical presentation of trichobacteriosis involving head hair in children has also been reported [151–153].

The concretions surrounding hair shafts make the hairs appear beaded. These nodules are firmly attached to the hair shaft and difficult to remove. The most common nodule colour is yellow (trichobacteriosis flavus) (Fig. 3.22), although red (trichobacteriosis rubra) and black (trichobacteriosis nigra) are the most common colours in tropical climates. Discoloured axillary sweat (chromhidrosis) may stain clothing. A rancid acid smell in the axillae (bromhidrosis) may be first noted, and patients may report sweaty malodorous armpits. A history of poor hygiene and axillary hyperhidrosis is frequently elicited. Other corynebacterial-related conditions may also be seen on examination, including pitted keratolysis and erythrasma, the so-called corynebacterial triad [146]. In a prospective study, evaluating the prevalence of trichomycosis axillaris and erythrasma in Korean soldiers presenting with pitted keratolysis, 14 of 108 patients (13%) had the full triad of pitted keratolysis, erythrasma, and trichomycosis axillaris. Twenty-two patients (20.4%) had

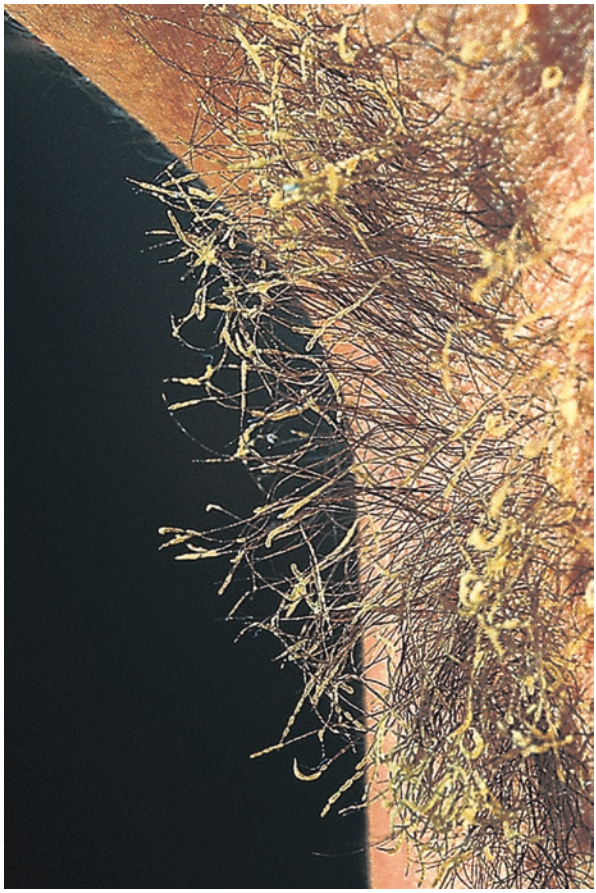

**Fig. 3.22**
Trichobacteriosis palmellina (axillaris). Yellow, 1–2 mm granular nodules or concretions surrounding hair shafts

trichomycosis axillaris and pitted keratolysis. This study supports the notion that these three corynebacterial infections may frequently coexist [154].

Corynebacteria produce a cement-like substance, which facilitates bacterial adherence to hair [155]. The rancid odour is due to the ability of the corynebacteria to metabolize testosterone and other hormones found in the apocrine sweat into several malodorous compounds.

Clinically, trichobacteriosis may be confused with piedra, a hair disease caused by fungi (*Trichosporon*, *Piedraia hortae*), which cause formation of nodules on the hair shaft.

Wood's light examination will show a dull yellow or grey-white fluorescence. A potassium hydroxide (KOH) preparation, followed by light microscopic examination, will show the causative bacteria in the concretions. A gram stain will also show slender purple rods under light microscopy.

The most rapid and effective treatment is to shave hairs in the affected areas and prevent further recurrences with daily use of antibacterial soaps or benzoyl peroxide washes. Triclosan and triclocarban are the most common compounds used as

**Table 3.3** Treatment options for trichobacteriosis palmellina

| | |
|---|---|
| Physical | • Shaving hairs in the affected area |
| Medical-topical | • 5% Benzoyl peroxide gels or washes<br>• Topical 1% clindamycin or 2% erythromycin b.i.d. |
| Medical-systemic | • Oral erythromycin 4 × 250 mg for 2 weeks |
| Prevention | • Antibacterial soaps<br>• Antiperspirants (20% aluminium chloride in anhydrous ethyl alcohol)<br>• Drying powders |

antibacterials in soaps; others include benzalkonium chloride, benzethonium chloride, and chloroxylenol. Use of antiperspirants after bathing is important to reduce sweating. Antiperspirants with 20% aluminium chloride in anhydrous ethyl alcohol are particularly helpful because they reduce hyperhidrosis and are bactericidal. Drying powders may also reduce moisture in the area. Attention to hygiene measures alone is usually sufficient to treat trichobacteriosis. Patients who do not wish to shave the axillary hair can still achieve clearance within a few weeks with daily washing with an antibacterial soap or benzoyl peroxide wash.

To promote more rapid resolution of the condition, a topical antibiotic or 5% benzoyl peroxide gel is frequently prescribed, in addition to the above hygiene measures. Twice daily use of topical 1% clindamycin lotion or 2% erythromycin lotion is effective and leads to clearance within 2 weeks. Benzoyl peroxide may be irritating to some individuals and may bleach hair. Oral erythromycin at 250 mg four times daily for 2 weeks can be prescribed if compliance is an issue.

The rancid odour may remain in clothing, and patients should be prompted to adequately wash or dry clean clothing.

Although treatment of trichobacteriosis is rapid and effective, preventive measures are essential to reduce recurrence. Continuous use of antibacterial soaps, followed by use of an antiperspirant, is recommended. Treatment options are summarized in Table 3.3.

### 3.4.2 *Corynebacterium*, *Cutibacterium*, Scalp, and Gut Microbiota in Health and Disease

A microbiome (from Ancient Greek μικρός = small and βίος = life) is the community of microorganisms that can usually be found living together in any given habitat. It was originally defined in 1988 by Whipps et al. as "a characteristic microbial community occupying a reasonably well-defined habitat which has distinct physiochemical properties. The term thus not only refers to the microorganisms involved but also encompasses their theatre of activity" [156].

The microbiota consists of all living members forming the microbiome. Whipps's "theatre of activity" includes the essential role secondary metabolites play in mediating complex interspecies interactions and ensuring survival in competitive environments. The ability of microbes to detect and respond to cell population density by gene regulation (quorum sensing) allows bacteria to control cooperative

activities and adapt their phenotypes to the biotic environment, resulting, e.g., in cell-cell adhesion or biofilm formation.

The development of new techniques and equipment boosted microbiological research in understanding health and disease. Sequencing technologies, PCR, and cloning techniques have enabled the investigation of microbial communities using cultivation-independent approaches. Accumulated sequence data have highlighted both the ubiquity of microbial communities in association within higher organisms and the critical roles of microbes in human health.

When the first microscopes led to the discovery and identification of microorganisms, the infectious diseases became the earliest focus of research. However, only a small proportion of microorganisms are associated with disease. The overwhelming majority of microbes are essential for healthy ecosystem functioning and known for beneficial interactions with other microbes and organisms. The concept that microorganisms exist as single cells began to change as it became increasingly obvious that microbes occur within complex assemblages in which species interactions and communication are critical [156].

The emergence in publications on opportunistic pathogens and pathobionts has produced a shift towards a more universal approach in the co-evolutionary theory. This approach sees the host and its associated microbiota as one unit, the so-called holobiont, which co-evolves as one entity. The holobiont's disease state is linked to dysbiosis, low diversity of the associated microbiota, and their variability: a so-called pathobiome state. The healthy state, on the other hand, is accompanied with eubiosis, high diversity, and uniformity of the respective microbiota [157].

Humans are colonized by many microorganisms, with approximately the same order of magnitude of non-human cells as human cells [158]. Some microorganisms that colonize humans are commensal, meaning they co-exist without harming or benefiting humans; others have a mutualistic relationship with their human hosts. Conversely, some non-pathogenic microorganisms can harm human hosts via the metabolites they produce.

The skin surface microbiome and its role in health and disease has increasingly gained the attention of investigative dermatology. The scalp surface provides a distinct microenvironment to the microbes, primarily arising from the host physiological conditions, which include sebum content, moisture, pH, and topography. In addition, environmental factors such as climatic conditions, hygiene, and use of cosmetics play a role. Within the scalp, hair follicles provide unique anatomical niches. Particularly, scalp hair follicles form large tubular invaginations in a high density, which extend deep into the skin and harbour a variety of microorganisms. The distinct immunology of the hair follicle with enhanced immune cell trafficking in superficial compartments in juxtaposition to immune-privileged sites crucial for hair follicle cycling and regeneration, such as the stem cell niche, makes this site highly susceptible to the microbiota. Depending on composition and penetration depth, microbiota may contribute to a pro-inflammatory environment or may cause infections, such as folliculitis decalvans [159]. Involvement in hair cycle regulation and immune cell maturation has also been postulated [160].

Compared to the skin surface microbiome, which has been the subject of extensive research, the specific microbiome of the human hair follicles has been relatively under-investigated beyond pathogen-induced folliculitis. Human hair follicles carry complex microbial communities that differ from skin surface microbiota.

So far, scalp microbiome studies have revealed *Malassezia restricta*, *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and *Staphylococcus epidermidis* as the prominent microbial genera [161]. Coryneform bacteria account for nearly 50% of the natural skin microflora [162]. At times, overgrowth of some of these resident organisms may cause minor disease of the skin or its appendages, as illustrated above. However, it often remains unclear whether the associated dysbiosis is a secondary phenomenon or primary cause of the pathologic condition.

Nevertheless, there is a case report of scalp pustules due to *Corynebacterium acnes* [163].

One explanation for how healthy hair follicles manage and control their microbiome is the production of antimicrobial peptides with different microbial specificities by hair follicle keratinocytes in defined epithelial compartments, such as cathelicidin, psoriasin, RNAse7, and dermcidin. In addition, the specific composition and metabolic activities of the resident microbes likely create a local milieu that inhibits the growth of hair follicle pathogens. Finally, in case of excessive microbial hair follicle colonization or dysbiosis, outer root sheath keratinocytes can recruit inflammatory cells to keep the hair follicle microbiome under control.

The association of the prominent fungal and bacterial genera, particularly a higher incidence of *M. restricta* and *S. epidermidis* and a lower incidence of *Cutibacterium acnes* in dandruff and seborrhoeic dermatitis, suggests that these are linked to the balance between bacteria and fungi of the host scalp surface [164].

*Cutibacterium acnes* is a relatively slow-growing, typically aerotolerant anaerobic, gram-positive bacterium (rod). The species is largely commensal and part of the skin flora present on most healthy adult humans' skin. It is usually just barely detectable on the skin of healthy preadolescents. It lives, among other things, primarily on fatty acids in sebum secreted by sebaceous glands in the follicles. Originally identified as *Bacillus acnes*, it was later named *Propionibacterium acnes* for its ability to generate propionic acid and association with acne. In 2016, *P. acnes* was taxonomically reclassified as a result of biochemical and genomic studies. In terms of both phylogenetic tree structure and DNA G + C content, the cutaneous species was distinguishable from other species. As part of restructuring, the novel genus *Cutibacterium* was created for the cutaneous species, including those formerly identified as *Propionibacterium acnes*.

*Cutibacterium acnes* predominantly reside deep within follicles and pores, although they are also found on the surface of healthy skin. In these follicles, *Cutibacterium acnes* utilize sebum, cellular debris, and metabolic by-products from the surrounding skin tissue as their primary sources of energy and nutrients. Elevated production of sebum by hyperactive sebaceous glands or blockage of the follicle can cause *Cutibacterium acnes* to grow and multiply.

*Cutibacterium acnes* secrete many proteins, including several digestive enzymes involved in the digestion of sebum and the acquisition of other nutrients. They can

also destabilize the layers of cells that form the walls of the follicle. Cellular damage, metabolic by-products, and bacterial debris produced by the rapid growth of *Cutibacterium acnes* in follicles can trigger inflammation [165]. This inflammation can lead to the symptoms associated with some common skin disorders, such as acne and folliculitis.

Ultimately, the damage caused by *Cutibacterium acnes* and the associated inflammation make the affected tissue more susceptible to colonization by opportunistic bacteria, such as *Staphylococcus aureus*.

*Cutibacterium acnes* is susceptible to a wide range of antimicrobial molecules, from both pharmaceutical and natural sources. The antibiotics most frequently used to treat acne are erythromycin, clindamycin, doxycycline, and minocycline. However, the emergence of antibiotic-resistant *Cutibacterium acnes* bacteria represents a growing problem worldwide [166]. Also, *Cutibacterium acnes* is susceptible to a number of antimicrobial chemicals found in over-the-counter antibacterial products, such as benzoyl peroxide, triclosan, chloroxylenol, and chlorhexidine gluconate. Furthermore, the elements silver, sulphur [167], and copper have been demonstrated to be toxic towards many bacteria, including *Cutibacterium acnes*. Also, several naturally occurring molecules and compounds are toxic to *Cutibacterium acnes*, specifically some essential oils, such as rosemary [168], tea tree [169], clove oil [170], and citrus oils [171]. Natural honey has also been shown to have some antibacterial properties against *Cutibacterium acnes* [172].

*Cutibacterium acnes* glows orange when exposed to blacklight, probably due to the presence of endogenous porphyrins. It is also killed by ultraviolet light. *Cutibacterium acnes* is especially sensitive to light in the 405–420 nm range due to an endogenic porphyrin—coproporphyrin III. A total irradiance of 320 J/cm$^2$ inactivates this species in vitro. Its photosensitivity can be enhanced by pre-treatment with aminolevulinic acid (photodynamic therapy) [173]. Red fluorescence of comedones has also been interpreted as evidence of porphyrin production by *Corynebacterium acnes* [174].

It has also been hypothesized that the production of porphyrins in the pilosebaceous duct by *Cutibacterium* and *Corynebacterium* spp. and their photoactivation through ultraviolet radiation (UVR) may lead to oxidative tissue injury and microinflammation at the level of the putative site of the hair follicle stem cells, contributing to hair loss from androgenetic alopecia [175]. Fluorescent studies performed on the extrusions from pilosebaceous follicles showed emission spectra with close resemblance to those from cultured *Cutibacterium acnes* with dominant peaks due to at least three porphyrins [176]. Accordingly, Pierard et al. proposed and found the use of topical antimicrobials to be beneficial in the management of androgenetic alopecia [177].

Finally, a putative role of the gut microbiota is a current line of investigation into the pathogenesis and management of alopecia areata [178]. The determinants of the development of autoimmune diseases, such as alopecia areata, have been allocated to genetics, environmental triggers, and chance. The immune system is tightly coupled to the gut microbiome, which develops from the flora present at birth and matures through environmental exposure and in response to diet. An imbalance of

the gut microbiome can cause inflammation, increased intestinal permeability, and drive priming and dysregulation of immune cells in genetically susceptible individuals. The detection of an altered gut microbiome in patients with alopecia areata [179, 180] and the report of cases of alopecia areata with long-term regrowth of hair after faecal microbiota transplants [178] support the hypothesis of a role of the intestinal microbiome in alopecia areata.

Chronic non-scarring folliculitis of the scalp is yet another proposed entity with recurrent follicular pustules of the scalp without obvious necrosis or residual scarring, as in acne necrotica. The most common age at onset is 20–40 years. The sex ratio (M/F) is 3:1. A minority of patients have concomitant acne vulgaris on the face. Most of the patients treated topically with steroids experience little or no effect. Histopathology discloses a neutrophilic folliculitis. Bacteriological examinations show only the usual resident microflora of the scalp, with *Cutibacterium acnes* being the most frequent species. Oral low-dose tetracyclines usually have a symptomatic effect [181].

Infantile eosinophilic pustular dermatosis of the scalp (Fig. 3.23) is a pruritic relapsing pustulosis of the scalp beginning in infancy or early childhood that is unresponsive to antibiotic therapy. Although secondary infection may occur, the lesions are primarily sterile, while smears of pustules show a variable proportion of eosinophils. Histopathologic findings suggested a major role for eosinophils because dermal eosinophilia is noted in all patients. There may be associated transient blood eosinophilia. Topical steroids usually relieve inflammatory episodes. The cause is unknown [182].

Erosive pustular dermatosis of the scalp represents yet another pustular dermatosis of the scalp. It presents with localized areas of pustules, lakes of pus, or crusts, which overlie eroded plaques, and mainly affects the sun-damaged, bald scalp of older individuals [183] (Fig. 3.24a ). Histopathology is unspecific. However, a biopsy is important to exclude some of the differential diagnoses that may need different treatment. Histopathology shows sub-corneal pustules, epidermal hypertrophy, or atrophy and erosions (Fig. 3.24b). The pustules, when present, are not of the follicular type, an important difference to bacterial folliculitis. These findings can be accompanied by a polymorphous dermal inflammatory infiltrate composed of neutrophil leukocytes, lymphocytes, and some plasma cells. Microbial investigations are usually negative. The cause of erosive pustular dermatosis of the scalp is unknown. However, it appears to relate to sun damage. It is often triggered by a minor injury to the affected skin, including a surgical procedure (pathergy phenomenon), and faulty wound healing may be involved. Infection is not considered the primary cause, as the condition does not clear with antibiotics. Interestingly, erosive pustular dermatosis has been reported as an adverse effect of epidermal growth-factor receptor inhibitor treatment for cancer, such as gefitinib [184]. Treatment is usually successful with either high-potency topical corticosteroids or topical calcineurin inhibitors [185]. The latter have the advantage over topical corticosteroids of not causing additional skin atrophy.

The characteristics of the human skin microbiome are summarized in Table 3.4.

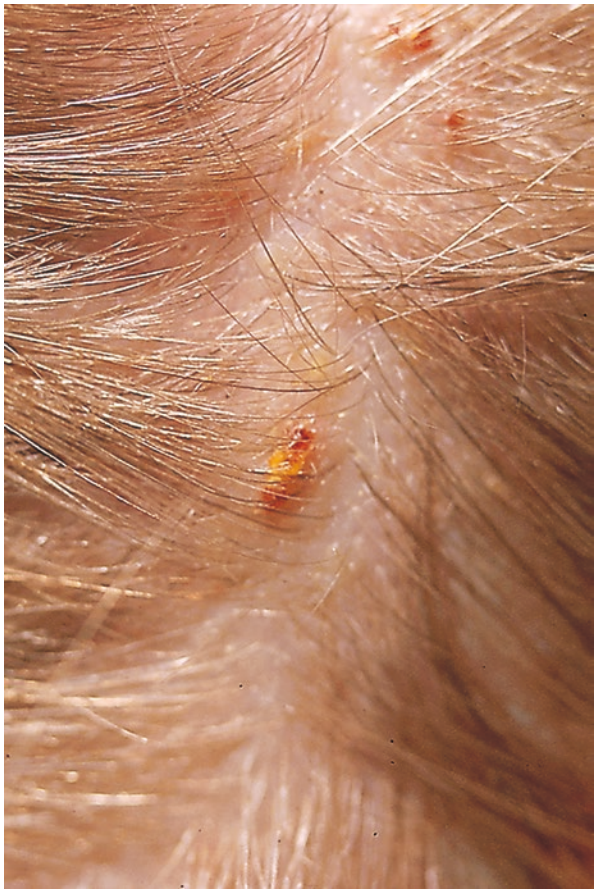

**Fig. 3.23** Infantile eosinophilic pustular dermatosis of the scalp

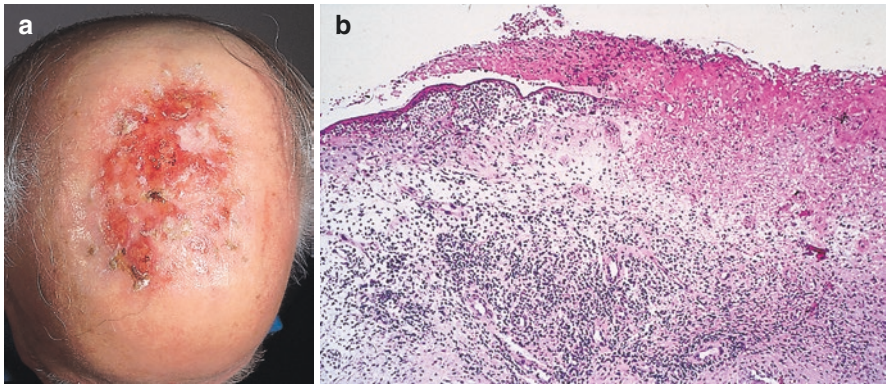


**Fig. 3.24** (**a**, **b**) Erosive pustular dermatosis of the scalp. (**a**) Localized area of pustules, lakes of pus, or crusts overlying eroded plaques and mainly affecting the sun damaged, bald scalp of an older individual. (**b**) Histopathology: subcorneal pustules, epidermal hypertrophy, or atrophy and erosions

**Table 3.4** The human skin microbiome: key points from [186]

- Skin microorganisms have adapted to utilize the sparse nutrients available on the skin
- Many cutaneous microorganisms can produce molecules that inhibit the colonization of other microorganisms or alter their behaviour
- The skin microbiota of a healthy adult remains stable over time, despite environmental perturbations
- Skin microorganisms have important roles in educating the innate and adaptive arms of the cutaneous immune system
- Some skin diseases are associated with an altered microbial state; reversion of this dysbiosis may help prevent and/or treat the disease

## 3.5 Tuberculosis

German novelist and 1929 Nobel prize laureate Thomas Mann (1875–1955) set a monument to tuberculosis with his epic *Der Zauberberg* (*The Magic Mountain*, 1924) on the occasion of his visit to the Waldsanatorium in Davos, Switzerland, in 1912, where Mann became acquainted with the team of doctors and patients in this cosmopolitan institution for patients with lung diseases, particularly tuberculosis. The disease rules the daily routines, thoughts, and conversations of the patients and ends fatally for many. As yet, it is widely considered to be one of the most influential works of twentieth-century German literature.

Tuberculosis was for centuries associated with poetic and artistic qualities among those infected and was also known as the romantic disease. Major artistic figures such as the poets Novalis (1772–1801), Friedrich Schiller (1759–1805), John Keats (1795–1821), Frédéric Chopin (1810–1849), Charlotte Brontë (1816–1855), Anton Chekhov (1860–1904), Aubrey Beardsley (1872–1898), Franz Kafka (1883–1924), and others suffered of tuberculosis. A widespread belief was that tuberculosis assisted artistic talent. Physical mechanisms proposed for this effect included the slight fever and toxaemia that it caused, allegedly helping them to see life more clearly and to act decisively.

Tuberculosis is an infectious disease usually caused by the bacteria *Mycobacterium tuberculosis*.

*Mycobacterium tuberculosis* is a small, aerobic, non-motile bacillus. The high lipid content of this pathogen accounts for many of its unique clinical characteristics. It divides every 16–20 h, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour. Mycobacteria have an outer membrane lipid bilayer. If a Gram stain is performed, the microorganism either stains very weakly or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall. Using histological stains on expectorated samples, *Mycobacterium tuberculosis* can be identified under a microscope. Since the microorganism retains certain stains even after being treated with acidic solution, it is classified as an acid-fast bacillus (Fig. 3.25a, b). The most common acid-fast staining techniques are the Ziehl-Neelsen stain and the Kinyoun stain, which dye acid-fast bacilli a bright red that stands out against a blue background. Auramine-rhodamine staining and fluorescence microscopy are also used.

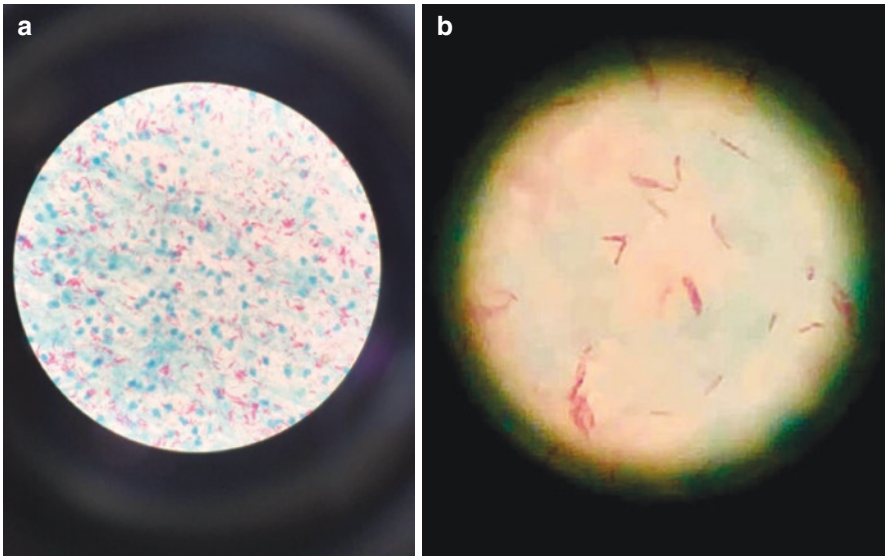


**Fig. 3.25** (**a**, **b**) Acid-fast bacilli of tuberculosis. (Courtesy of Prof. Remberto Mauricio Vilte, Fluminense Federal University)

Tuberculosis is classified as one of the granulomatous inflammatory diseases. Macrophages, epithelioid cells, T lymphocytes, B lymphocytes, and fibroblasts aggregate to form granulomas, with lymphocytes surrounding the infected macrophages. When other macrophages attack the infected macrophage, they fuse together to form a giant multinucleated cell in the alveolar lumen. The granuloma may prevent dissemination of the mycobacteria and provide a local environment for interaction of cells of the immune system. However, the bacteria may also use the granulomas to avoid destruction by the host's immune system. Macrophages and dendritic cells in the granulomas are unable to present antigen to lymphocytes; thus, the immune response is suppressed. Bacteria inside the granuloma can become dormant, resulting in latent infection. Another feature of the granulomas is the development of necrosis in the centre of tubercles. To the naked eye, this has the texture of soft, white cheese and is termed caseous necrosis.

Tuberculosis generally affects the lungs but can also affect other parts of the body, including the skin. Most infections show no symptoms, in which case it is known as latent tuberculosis. About 10% of latent infections progress to active disease, which, left untreated, proves fatal in about half of those affected. Typical symptoms of active tuberculosis are a chronic cough with blood-containing mucus, fever, night sweats, and weight loss (consumption) (Fig. 3.26).

In many people, the infection waxes and wanes. Tissue destruction and necrosis are often balanced by healing and fibrosis. Affected tissue is replaced by scarring and cavities filled with caseous necrotic material. During active disease, some of these cavities are joined to the air passages, and this material can be coughed up. It contains living bacteria and thus can spread the infection.

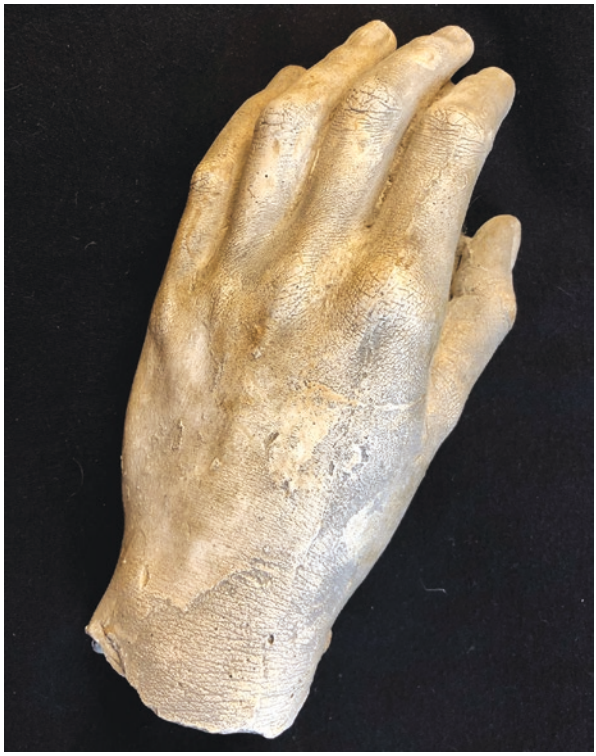

**Fig. 3.26** Dead hand from consumption, dating 31.10.1919, plaster cast, from the author's personal collection. The BCG vaccine was first used on humans in 1921. Only in 1946, the development of the antibiotic streptomycin made effective treatment and cure of tuberculosis a reality. Nevertheless, by the 1950s, mortality in Europe had decreased about 90%, thanks to improvements in sanitation, vaccination, and other public-health measures. In 2014, the WHO adopted the "End Tuberculosis" strategy, which aims to reduce tuberculosis incidence by 80% and TB deaths by 90% by 2030

Infection of other organs can cause a wide range of symptoms. In 15–20% of active cases, the infection spreads outside the lungs, causing other kinds of tuberculosis, collectively called extrapulmonary tuberculosis. Extrapulmonary TB occurs more commonly in people with a compromised immune system, including HIV, and young children. Notable extrapulmonary infection sites include the pleura (tuberculous pleurisy), the central nervous system (tuberculous meningitis), the lymphatic system (scrofula of the neck), the genitourinary system (urogenital tuberculosis), and the bones and joints (Pott's disease of the spine), among others.

If tuberculosis bacteria gain entry to the bloodstream from an area of damaged tissue, they can spread throughout the body and set up many foci of infection, all appearing as tiny, white tubercles in the tissues. This severe form of tuberculosis, most common in young children and those with HIV, is called miliary tuberculosis. People with this disseminated TB have a high fatality rate even with treatment (about 30%).

Tuberculosis of the skin is subclassified depending on the mode of infection and the immunologic state of the host, with more or less distinct disease forms (Table 3.5).

Primary inoculation tuberculosis (tuberculous chancre) typically follows a penetrating injury that results in the direct introduction of *mycobacterium* into the skin of an individual with no previous tuberculosis infection. Within 2–4 weeks, an

**Table 3.5** Classification of cutaneous tuberculosis

| Mode of infection | Immunologic state of the host | |
|---|---|---|
| **Exogenous infection** | **Non-immune host** | **Immune host** |
| | Primary inoculation tuberculosis (Tuberculous chancre) | Tuberculosis verrucosa cutis (Warty tuberculosis) |
| **Endogenous spread** | **Normoergic host** | |
| Hematogenous | Lupus vulgaris (tuberculosis luposa) | |
| Contiguous | Scrofuloderma (tuberculosis colliquative cutis) | |
| Hematogenous | **Hypoergic host** | |
| | Acute miliary tuberculosis (tuberculosis cutis miliaris disseminata) | |
| | Metastatic tuberculous abscess (tuberculous gumma) | |
| Contiguous | Orificial tuberculosis (tuberculosis ulcerosa cutis et mucosae) | |
| **Tuberculids** | **Hyperergic host** | |
| | Papulonecrotic tuberculid | |
| | Lichen scrofulosum | |
| Facultative | Erythema induratum Bazin (nodular vasculitis) | |
| | Erythema nodosum | |

inflammatory papule develops at the inoculation site and evolves into a firm, shallow, non-tender, non-healing, undermined ulcer with a granulomatous base (Fig. 3.27a). Painless, regional lymphadenopathy is frequently apparent around the time, and the tuberculin skin test (Mantoux) converts to positive. The pioneer work of Austrian pathologist Anton Ghon (1866–1936) [187] and others resulted in the establishment, on an anatomic basis, of the character of the lesion produced by first infection tuberculosis. As originally described, the lesion consisted of a primary focus at the site of inoculation plus an always present regional lymphadenitis. To this combination of primary focus and regional lymphadenitis, German pulmonologist Karl Ernst Ranke (1870–1926) gave the name primary complex of tuberculosis, a term generally used today [188]. In the lung, the Ghon complex undergoes progressive fibrosis, often followed by radiologically detectable calcification (Ranke complex), and despite seeding of other organs, no lesions develop. Although they are often confused, Ranke complex and Ghon complex are not synonymous. The Ranke complex is an evolution of the Ghon complex resulting from further healing and calcification of the lesion. A Ghon complex retains viable bacteria, making them sources of long-term infection, which may reactivate and trigger secondary tuberculosis later in life [189].

A case of posttraumatic inoculation tuberculosis of the scalp has been reported in a scalp wound [190].

Calvarial tuberculosis is tuberculosis of the flat bones of the vault of the skull (tuberculous osteitis). It was first reported by Reid in 1842. The condition is reported to occur in only 0.01% of patients with mycobacterial infections [191]. Although rare, the incidence of calvarial tuberculosis is on the rise in developing countries because of malnutrition, poor socioeconomic conditions, and immunodeficiency syndromes. It usually occurs secondary to hematogenous spread from a primary focus elsewhere in the body that may not always be evident. Most cases occur in the first two decades. The frontal and the parietal bones are usually involved [192]. Trauma and surgery can result in direct inoculation of the organism [193]. It has

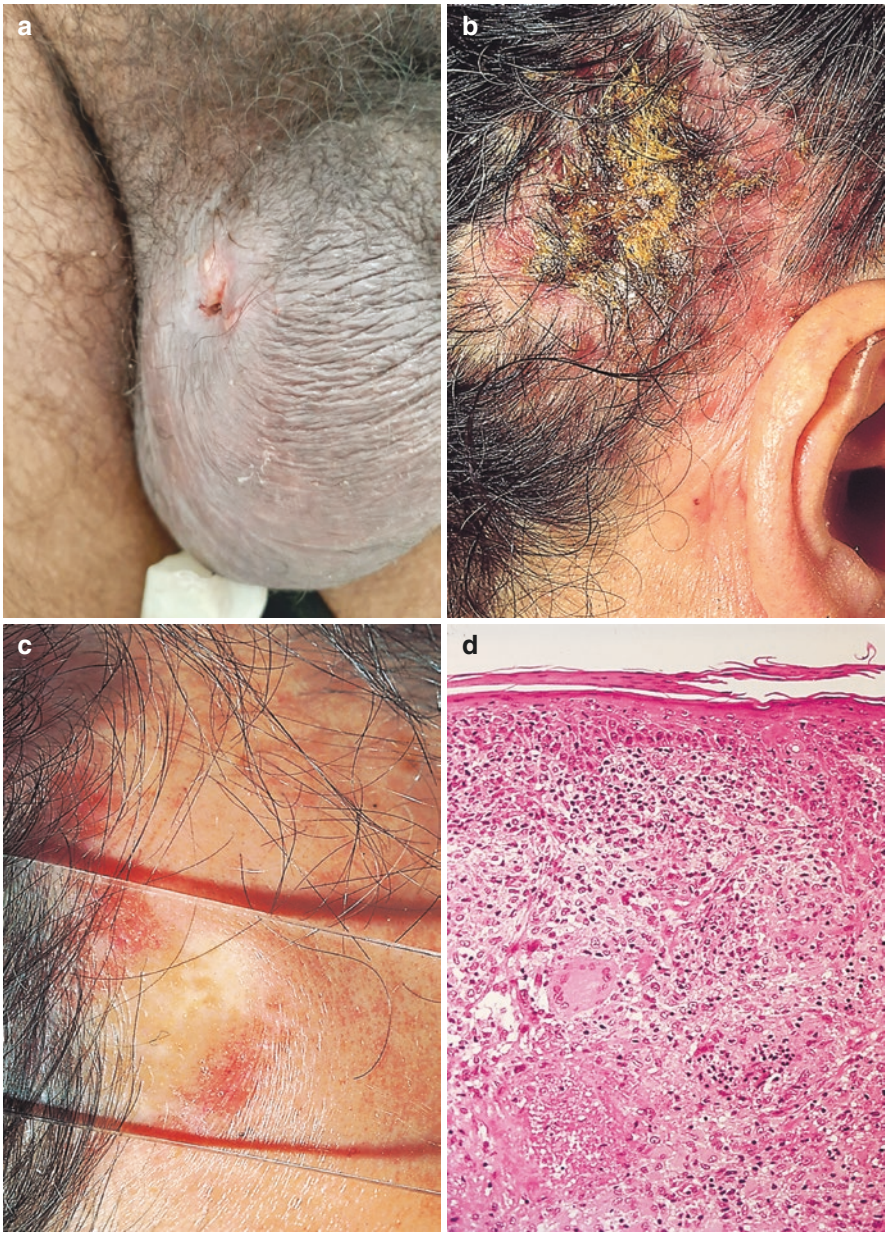


**Fig. 3.27** (**a–d**) Cutaneous tuberculosis: (**a**) tuberculous chancre, (**b–d**) lupus vulgaris (tuberculosis luposa) of the scalp: (**b**) brownish red friable patch, (**c**) diascopy, (**d**) histopathology showing non-caseating granuloma with Langhans giant cell

been also proposed that the increased vascularity and transient decreased resistance at surgery may result in specific homing of bacilli, as the inflammatory cells are attracted to the site of trauma and act as vectors for the bacilli [194]. The type of clinical presentation possibly depends on the immunity of the host [195]. A solitary discrete round or oval punched-out osteolytic defect with minimal surrounding sclerosis in the frontoparietal bones is the commonest presentation. When multiple, they are of diffuse type with geographical defects of extensive bone loss [196]. Once the marrow of the diploe is seeded with the inoculum, the infection spreads towards the inner and outer table of the skull bone, causing bone destruction and formation of granulation tissue. Involvement of the outer table is usually associated with scalp swelling or a discharging sinus of the scalp. The differential diagnosis of multiple osteolytic lesions of the skull would include metastases, multiple myeloma, and histiocytosis. A high index of suspicion and biopsy result in early diagnosis of the condition, before the central nervous system is involved. Conventional radiographs of the skull show focal bone destruction often with accompanying soft tissue opacity. CT helps in assessing the extent of bone destruction, scalp swelling, and degree of intracranial involvement [197]. Prompt treatment with an adequate antituberculous therapy, along with appropriate surgical intervention as indicated, may result in cure with no morbidity.

The most common cutaneous manifestation of tuberculosis is lupus vulgaris or tuberculosis luposa originating from endogenous spread of tuberculosis elsewhere in the body by hematogenous, lymphatic, or contiguous spread, most often from cervical adenitis, or pulmonary tuberculosis, and sometimes from an old, apparently quiescent primary complex. This presents as usually asymptomatic skin lesions with nodular appearance, most often on the face around the nose, lips, cheeks, ears, and neck. The earlobes are often affected, and solitary patches may be encountered on the scalp. The initial lesion is characterized by a brownish-red colour and a soft, friable consistency (Fig. 3.27b). Upon diascopy, the infiltrate exhibits a typical apple-jelly colour (Fig. 3.27c). Chrobak's probe is a thin steel sound with a bulbous head that is useful to distinguish between a caseating granuloma (tuberculosis) (Fig. 3.27d) and non-caseating granuloma (sarcoidosis). In tuberculosis luposa, the probe breaks through the skin versus encountering an elastic resistance. Progression of disease is characterized by elevation of the lesions and a deeper brownish colour. Involution in one area and simultaneous expansion in another result in plaques with a gyrate outline. If left untreated, the lesions may ultimately develop into disfiguring skin ulcers with scarring. The most serious complication of long-standing lupus vulgaris is the development of squamous cell carcinoma with a surprisingly high incidence of metastases [198].

Histologically, lupus vulgaris shows presence of epithelioid cell granulomas with Langhans giant cells and central caseation necrosis in the dermis (Fig. 3.27d). Secondary changes may be superimposed: epidermal thinning and atrophy or acanthosis with excessive hyperkeratosis or pseudoepitheliomatous hyperplasia. Older lesions are composed of epithelioid cells and may be impossible to distinguish from sarcoidal infiltrates.

Cutaneous tuberculosis of the scalp has repeatedly been reported [199–201].

Metastatic tuberculous abscess (tuberculous gumma) is a form of cutaneous tuberculosis, which is characterized by cold abscesses that are usually located on the trunk or extremities without involvement of the underlying tissue. It represents a multibacillary variant of cutaneous tuberculosis that is caused by the metastatic, hematogenous spread of *Mycobacteria* during a period of immunosuppression or malnutrition. The clinical manifestations of the condition vary widely depending on the virulence of the organism, route of infection, and immunity status of the host. Single or multiple, tender, cold abscesses with ulceration or fistulae are the common features. Drainage of pus or caseous material is also frequently observed [202]. A review of 49 case reports of metastatic tuberculous abscess revealed that in almost one fourth of the cases, the condition was the sole presentation of tuberculosis, and search for a primary location had been given emphasis [203].

A case of metastatic tuberculous abscess of the scalp is illustrated in Fitzpatrick's textbook of *Dermatology in General Medicine* [204].

A tuberculid represents a hypersensitivity reaction of the skin in association with tuberculosis elsewhere in the body. *Mycobacterium tuberculosis* organisms cannot be isolated from the respective skin lesions. It is thought to be due to hematogenous spread of mycobacterial antigens to the skin resulting in a type III or type IV hypersensitivity reaction. The following types of tuberculid are generally recognized as such: papulonecrotic tuberculid, lichen scrofulosorum, and erythema induratum (Bazin disease). Tuberculids develop in patients with a tuberculosis infection, either overt or silent, as an allergy to or a medium-high level of cell-mediated immunity against the tubercle bacillus. They can sometimes appear after initiating anti-tuberculous treatment as a Jarisch-Herxheimer reaction or after starting antiretroviral treatment for AIDS. Tuberculids are mostly seen in countries where tuberculosis remains common, such as China, the Indian subcontinent, and sub-Saharan Africa. Clinically, papulonecrotic tuberculid presents as recurring crops of clustered dusky or erythematous papules that can become pustular or necrotic to form small ulcers that heal with varioliform scarring after about 6 weeks. The skin lesions develop symmetrically mostly on the limbs of children and young adults before the age of 30. Histopathology shows a lymphohistiocytic small vessel vasculitis with thrombosis, ulceration, and wedge-shaped necrosis. The tuberculin test is usually strongly positive, and the interferon-gamma release assay such as QuantiFERON-TB gold is positive. A comprehensive examination, including chest X-ray, to detect tuberculosis of internal organs is warranted.

A case of papulonecrotic tuberculid affecting the scalp has been reported [205].

Essentially, the treatment of cutaneous tuberculosis is that of tuberculosis in general. A full anti-tuberculous regimen is administered, even in apparently localized form of cutaneous tuberculosis, where a primary focus or evidence underlying organ or lymphonodular tuberculosis exists.

Treatment of tuberculosis consists of a combination of 5 mg/g body weight (max. 300 mg) isoniazid, 600 mg/day rifampicin, 1.5–2.0 g/day pyrazinamide, and 15–25 mg/kg body weight ethambutol or 1–2 g/day streptomycin for 2 months, followed by 4 months of isoniazid and rifampicin [206].

Special considerations may apply to tuberculosis verrucose cutis and localized forms of lupus vulgaris without evidence of associated internal tuberculosis, for which isoniazid may be given alone with a high cure rate. Prolonged treatment, extending up to 12 months, is also necessary in these forms of lupus vulgaris. Small lesions of tuberculosis verrucose cutis or lupus vulgaris are also best excised; however, tuberculostatics should be given concomitantly.

Isoniazid should be given together with pyridoxin to prevent neuropathy. In a dosage of 2.0 g/day over 60–120 days, streptomycin causes ototoxicity in 75% of patients.

Isoniazid-induced anagen effluvium has been reported [207].

Non-tuberculous mycobacteriosis, also known as atypical mycobacteriosis, and mycobacteriosis other than tuberculosis (MOTT), is caused by mycobacteria that do not cause tuberculosis or leprosy. They occur in many animals (including fish), including humans, and are commonly found in soil and water, which is why they are also known as environmental mycobacteriosis. Non-tuberculous mycobacteria are all the other mycobacteria that can cause pulmonary disease resembling tuberculosis, lymphadenitis, skin disease, or disseminated disease. Although over 150 different species of nontuberculous mycobacteria are known, skin infections are most commonly due to *Mycobacterium marinum*, *M. ulcerans*, *M. kansasii*, *M. scrofulaceum*, *M. avium-intracellulare*, *M. fortuitum*, *M. chelonae*, *M. abscessus* (the latter three are also grouped in the *M. fortuitum* complex).

Disseminated mycobacterial disease was common in US and European AIDS patients in the 1980s and early 1990s, though the incidence has declined in developed nations since the introduction of highly active antiretroviral therapy. It can also occur in individuals after having renal transplantation.

Treatment of atypical mycobacteriosis represents a challenge for clinicians, due to the scarcity of the disease and an increasing drug resistance of the mycobacteria. In a Colombian series of 350 patients with post-injection abscesses due to *M. abscessus*, surgical excision of the lesions in combination with 3–6 months of clarithromycin resulted in a 95% cure rate, while either of the measures alone was successful in less than 30% of patients [208].

A case of atypical mycobacteriosis of the scalp due to *M. marinum* in a 70-year-old Caucasian presenting as a persistent erythematous plaque affecting the occipital region successfully treated with photodynamic therapy (PDT) has been reported. The patient had already been treated with oral rifampicin in combination with clarithromycin for 6 months with only slight improvement. Using the photosensitizing agent methyl aminolevulinate (MAL) left under occlusion for 3 h, PDT was performed with a red light-emitting diose lamp (wave length 630 nm) performed once a month, at increasing dosages from 37 to 60 J/cm$^2$. Complete remission was observed after five sessions of MAL-PDT, and the patient showed no signs of recurrence at 1 year follow-up [209].

Sarcoidosis is a multisystem inflammatory disease of unknown aetiology that manifests as noncaseating granulomas, predominantly in the lungs and intrathoracic lymph nodes. The presentation in sarcoidosis varies with the extent and severity of

organ involvement. About 20% of people who get sarcoidosis develop signs of the disease on their skin.

Sarcoidosis was first described in 1877 by the English physician Jonathan Hutchinson (1828–1913) as a non-painful skin disease [210]. As yet, the cause of sarcoidosis has remained unknown. Some believe it may be due to an immune reaction to an as yet unknown antigen of microbial or chemical origin in those who are genetically predisposed [211]. Several infectious agents have appeared to be significantly associated with sarcoidosis, but none of the known associations is specific enough to suggest a direct causative role [212]. Cases of sarcoidosis have also been reported as part of the immune reconstitution syndrome of HIV, that is, when people receive treatment for AIDS, their immune system rebounds, and the result is that it starts to attack the antigens of opportunistic infections caught prior to said rebound, and the resulting immune response starts to damage healthy tissue [213].

Although cutaneous involvement is common, sarcoidosis of the scalp remains uncommon, with so far 55 reported cases in the literature. The pattern of scalp involvement rages from annular plaques to infiltrated papules coalescing to form plaques (Fig. 3.28a), discoid plaques, nodules, psoriasiform plaques, and scarring alopecia [214]. Sarcoidosis has also been reported to present as non-scarring alopecia in an area other than the scalp [215]. Dermoscopy of the lesions shows decreased hair density associated with perifollicular and follicular yellowish to pale orange round spots or a diffuse orange discoloration with prominent telangiectasia [216]. Biopsies demonstrate a non-necrotizing granulomatous inflammation (Fig. 3.28b). Periodic acid-Schiff and Grocott are negative for fungi, and no acid-fast bacilli are detected on Ziehl-Neelsen.

Cutaneous sarcoidosis is acknowledged as a great imitator in dermatology, because it can mimic a vast variety of cutaneous lesions, including discoid lupus erythematosus, psoriasis, and tuberculosis (Fig. 3.29). A case of sarcoidosis presenting with a 2-year history of progressively enlarged lepromatous leprosy-like nodules and plaques on the back, chest, and scalp and treated with anti-lepromatous drugs for 1 year was reported [217]. The diagnosis of sarcoidosis is made by exclusion and is supported by the recognition of specific clinical features, the detection of classic histopathologic findings, and the exclusion of other granulomatous diseases.

Considering the fact that cutaneous sarcoidosis is often associated or a precursor of systemic disease, including sarcoidosis of the scalp [218], it is mandatory to diagnose correctly. Essential standard investigations, accompanied by physical examination and a complete medical history, should include chest X-ray, pulmonary function tests, ophthalmologic evaluation, electrocardiogram, full blood count, serum immunoglobulins, serum-soluble interleukin-2 receptor [219], delayed cutaneous hypersensitivity testing [220], serum calcium levels, and a 24-h urinary calcium assay [221]. Ga-67 scintigraphy should be performed in all patients suffering from cutaneous sarcoidosis as being the most sensitive method to demonstrate systemic involvement [222].

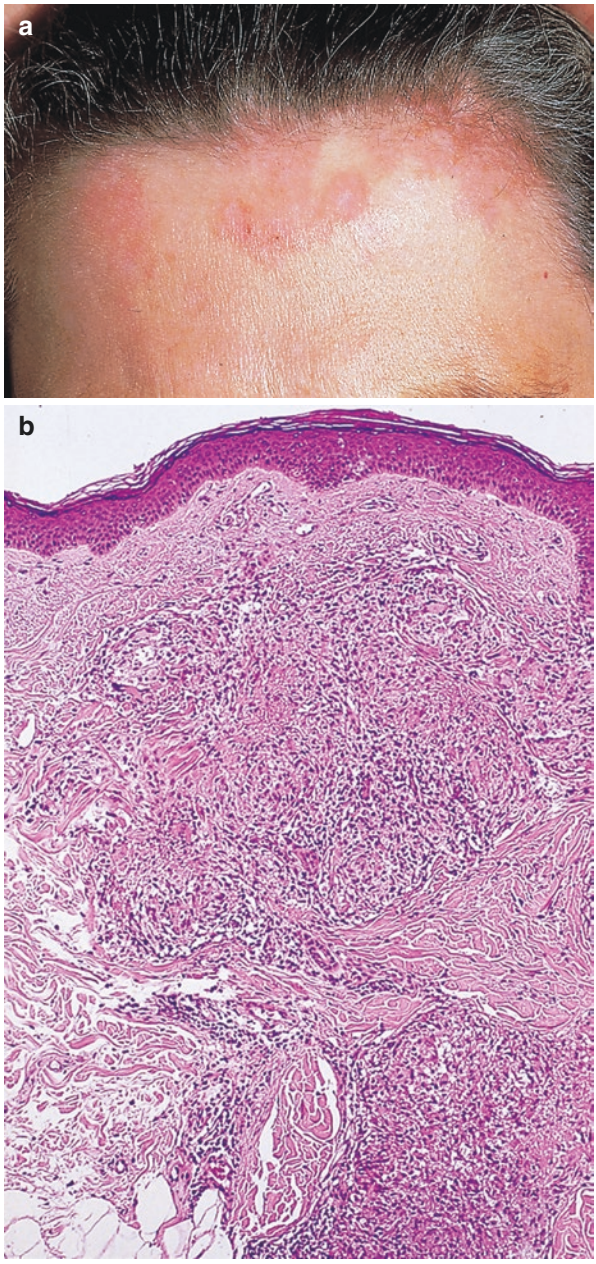


**Fig. 3.28** (**a**, **b**) Sarcoidosis of the scalp: (**a**) erythematous plaques. (**b**) Histopathology: non-caseating granuloma

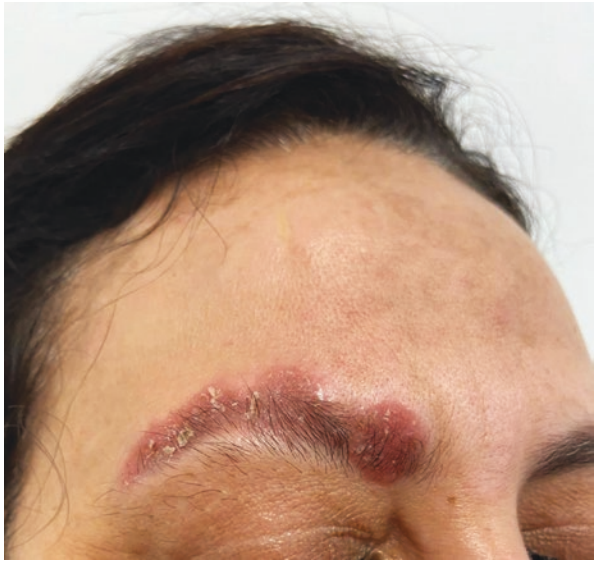

**Fig. 3.29** Sarcoidosis of the eyebrow region. Cutaneous sarcoidosis is a great imitator of other dermatologic diseases

Treatment modalities include intralesional corticosteroids, oral antimalarials (hydroxychloroquine, chloroquine), oral corticosteroids, subcutaneous methotrexate, and the TNF antagonists (adalimumab, infliximab) [223].

Other non-infectious granulomatous diseases that may involve the scalp are granuloma annulare (Fig. 3.30), necrobiosis lipoidica or Miescher's granulomatosis disciformis chronica at progressive (Fig. 3.31a, b), and annular elastolytic giant cell granuloma.

These entities are histopathologically distinguished by palisading granuloma, a histological variety of a granuloma, characterized by the presence of macrophages and giant cells arranged in a tier-like fashion on the border of an area of necrobiosis [224]. Little is known about the aetiology of the granulomatous skin diseases; however, studies have revealed a critical role of tumour necrosis factor α (TNF-α), as concentrations in sera of patients with in necrobiosis lipoidica and granuloma annulare are significantly higher than in healthy controls [225].

Granuloma annulare (Fig. 3.30) is a common skin condition, which presents as erythematous papules on the skin arranged in a circle or ring. The condition is usually seen in otherwise healthy people. It can initially occur at any age, though two-thirds of patients are under 30 years old, and it is seen most often in children and young adults. Most lesions of granuloma annulare disappear in pre-pubertal patients with no treatment within 2 years, while older patients (50+) have rings for upwards of 20 years. Granuloma annulare microscopically consists of dermal epithelioid histiocytes around a central zone of mucin.

The condition was originally described in 1895 by Thomas Colcott Fox (1848–1916) as a ringed eruption of the fingers, though it can present as localized, generalized, subcutaneous granuloma annulare or arcuate dermal erythema, and on the scalp [226] and elsewhere.

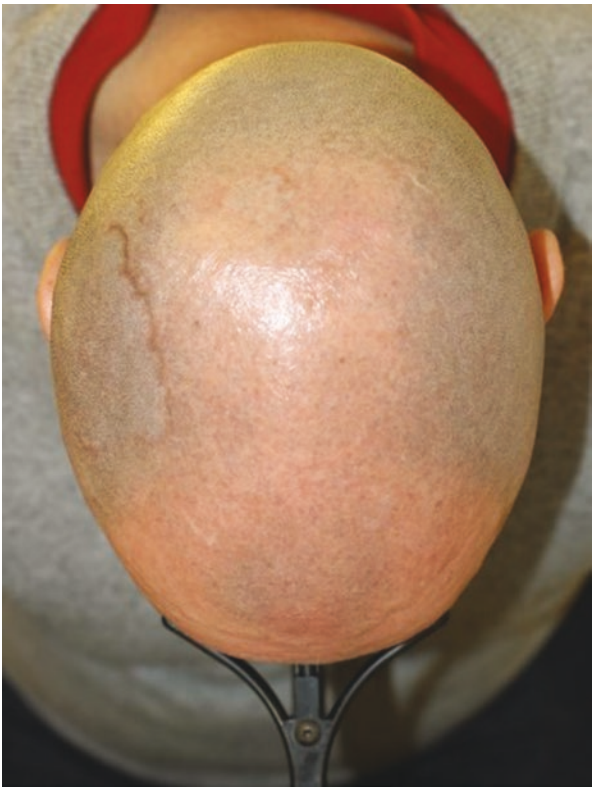

**Fig. 3.30** Granuloma annulare

Necrobiosis lipoidica is a necrotizing skin condition that usually occurs in patients with diabetes mellitus (necrobiosis lipoidica diabeticorum) but can also be associated with rheumatoid arthritis. Necrobiosis lipoidica most frequently appears on the patient's shins but may occur at any body site, including the scalp [227], where it frequently affects the scalp and face [228] (Fig. 3.31a). The lesions are often asymptomatic but may become tender and ulcerate when injured. The first symptom of necrobiosis lipoidica is often a bruised appearance that is not necessarily associated with a known injury. Necrobiosis lipoidica appears as a hardened, raised area of the skin. The centre of the affected area usually has a yellowish tint, while the area surrounding it is a dark pink. It is possible for the affected area to spread or turn into an open sore. When this happens, the patient is at greater risk of developing ulcers. If an injury to the skin occurs on the affected area, it may not heal properly, or it will leave a dark scar. Although the exact cause of this condition is not known, it is an inflammatory disorder characterized by collagen degeneration, combined with a granulomatous response. It always involves the dermis diffusely and sometimes also involves the deeper fat layer. Commonly, dermal blood vessels are thickened (microangiopathy). Histopathology demonstrates superficial and deep perivascular and interstitial mixed inflammatory cell infiltrate including lymphocytes, plasma cells, mononucleated and multinucleated histiocytes, and eosinophils

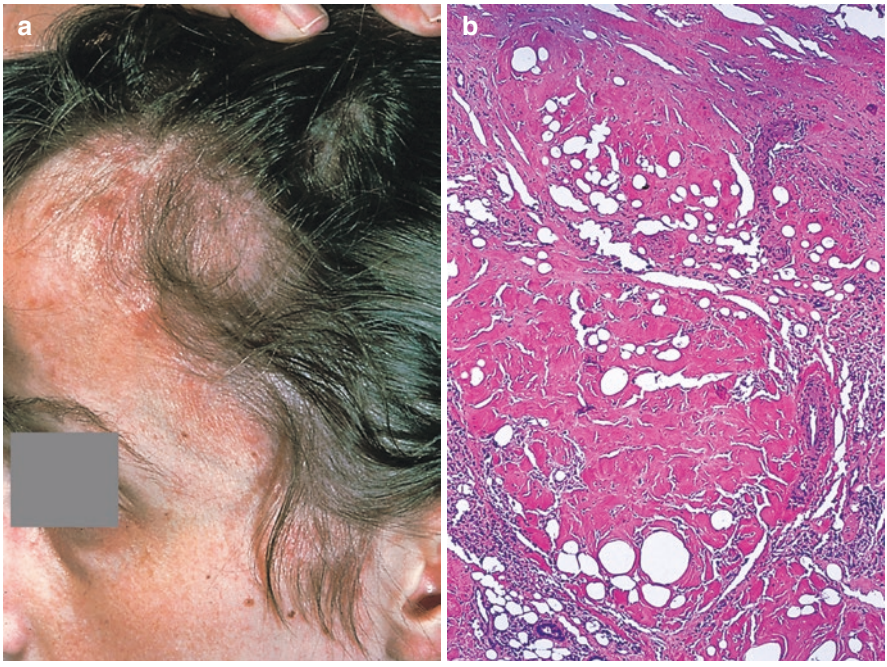


**Fig. 3.31** (**a**, **b**) Granulomatosis disciformis chronica et progressive Miescher (necrobiosis lipoidica of the scalp): (**a**) hardened, raised area of the skin. The centre of the affected area usually has a yellowish tint, while the area surrounding it is a dark pink. (**b**) Histopathology: palisading granuloma with central necrobiosis. Commonly, dermal blood vessels are thickened

in the dermis and subcutis, as well as necrotizing vasculitis with adjacent necrobiosis and necrosis of adnexal structures. Areas of necrobiosis are often more extensive and less well defined than in granuloma annulare (Fig. 3.31b). Presence of lipid in necrobiotic areas may be demonstrated by Sudan stains. Cholesterol clefts, fibrin, and mucin may also be present in areas of necrobiosis.

Miescher's granulomatosis disciformis chronica progressiva most likely represents the same nosological entity as necrobiosis lipoidica [229].

Annular elastolytic giant cell granuloma is another granulomatous skin disorder of uncertain etiopathogenesis presenting with annular erythematous plaques predominantly on the sun-exposed areas. Histopathologically, it is characterized by elastin degeneration, multinucleate giant cells, and elastophagocytosis. Histopathological hallmarks also include absence of mucin deposition as in granuloma annulare and of collagen necrobiosis as in necrobiosis lipoidica [230].

A case of annular elastolytic giant cell granuloma of the scalp presenting with multiple asymptomatic annular plaques in a 67-year-old male was reported [231], as well as annular elastolytic giant cell granuloma of the scalp with re-pigmentation of grey hair within the lesions [232].

Finally, hair granulomas (Fig. 3.32a) are an unspecific finding in a variety of inflammatory alopecias. They represent foreign body-type granulomas in response

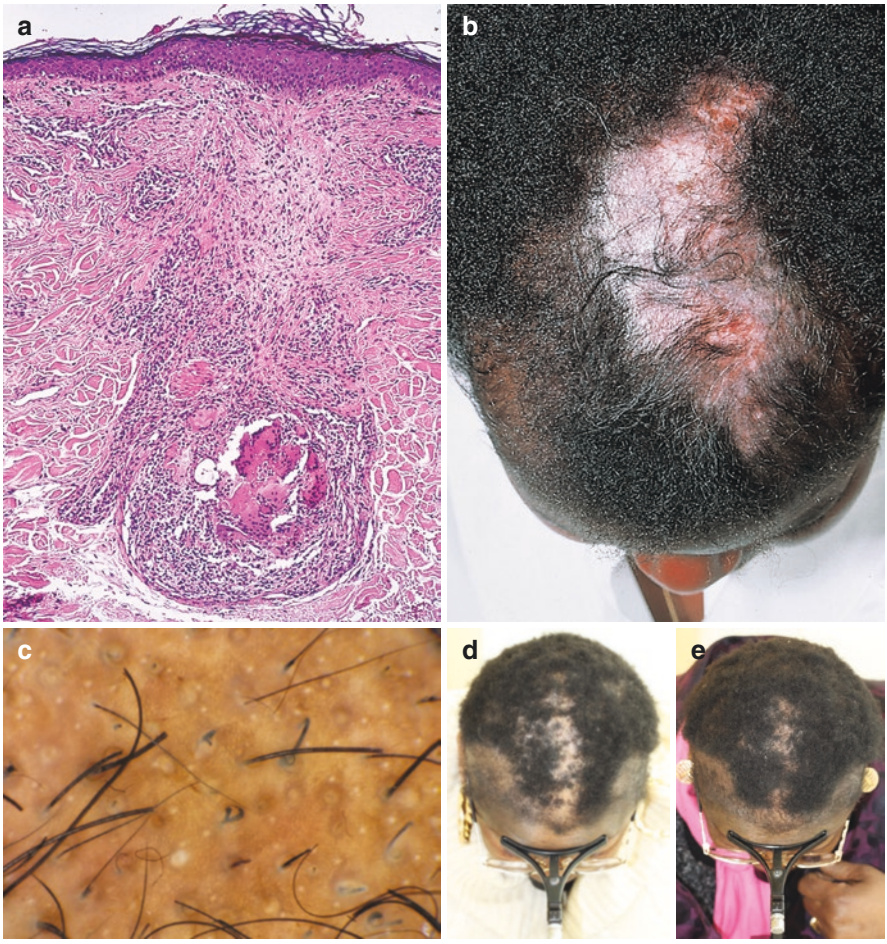


**Fig. 3.32** (**a**) Hair granuloma. (**b**–**e**) Central centrifugal cicatrizing alopecia: (**b**) scarring alopecia of the centroparietal scalp; (**c**) dermoscopy: interfollicular and perifollicular erythema, peripilar white halo, pinpoint white dots, terminal and vellus hairs, broken hairs, and increased interfollicular distance; (**d**, **e**) successful treatment with 100 mg oral doxycycline and a compound of topical 5% minoxidil and 0.2% triamcinolone acetonide, avoidance of traction, chemical hair treatments, and heat exposure

to either the introduction of exogenous material to the skin, such as in barber's interdigital pilonidal sinus of the hand [233], or in response to modified endogenous material that the immune system identifies as foreign, such as naked hair shafts in the inflammatory scarring alopecias, or ruptured cysts. Naked hair shafts are free-floating hair shafts devoid of surrounding epithelium, supporting structures, and/or embedded in inflammation that may result from destruction of hair follicles by scarring processes such as inflammation and fibroplasia. In a study of 622 scalp biopsies of alopecia, 345 cicatricial alopecias (central centrifugal cicatricial alopecia, lichen

planopilaris, discoid lupus erythematosus, acne keloidalis nuchae, and folliculitis decalvans), and 277 non-cicatricial alopecias (alopecia areata, androgenic alopecia, telogen effluvium, and psoriatic alopecia), naked hair shafts were detected in 20% of cicatricial alopecias (27/118 of central centrifugal cicatricial alopecia, 29/109 of lichen planopilaris, 2/75 of discoid lupus erythematosus,11/16 of acne keloidalis nuchae, and 3/27 of folliculitis decalvans) and in 0.72% of non-cicatricial alopecias (1/102 of alopecia areata, 1/150 of androgenic alopecia, 0/17 of telogen effluvium, and 0/8 of psoriatic alopecia). This variation is understood to result from destruction of hair follicles by the inflammatory and scarring processes [234].

In fact, central centrifugal cicatricial alopecia represents a peculiar inflammatory scarring disease of the African scalp. It classically affects the vertex scalp, although it may manifest as patchy hair loss beyond the vertex (Fig. 3.32b). Its etiopathogenesis has so far remained elusive. One hypothesis involves pressure exerted on the internal root sheath leading to damage, which leads to the recruitment of inflammatory cells and the end result of scarring. Dermoscopic features include interfollicular and perifollicular erythema, peripilar white halo, pinpoint white dots, terminal and vellus hairs, broken hairs, and increased interfollicular distance (Fig. 3.32c). African Americans are found to be at increased risk because of the curled hair shaft, distinct styling practices, and chemical processing techniques. Risk factors so far identified include diabetes mellitus type 2, bacterial scalp infections, and hair styles associated with traction. Alternatively, it may be interpreted as an unspecific variant of cicatricial pattern hair loss with the clinical presentation being related to peculiarities of African hair and hair grooming habits. The condition tends to present itself in the 20s and progresses over the following 20–30 years. Prevalence has been found to be highest in women over 50 years (6.7%). Treatment is with a combination of oral tetracyclines, topical corticosteroids, and oral minoxidil, preferably before significant permanent hair loss has occurred for better results (Fig. 3.32d, e).

Barber's interdigital pilonidal sinus of the hand or trichogranuloma is an occupational disease of male hair barbers. Customers' hairs penetrate the interdigital skin and cause a sinus and later a cyst. As with any foreign body, there is a propensity for infection. Surgical excision is the preferred method of treatment to prevent recurrence. Primary closure or closure with a flap, instead of secondary healing, should be the first choice of management of the defect due to the excision [235].

## 3.6 Leprosy

In 1873, G.H. Armauer Hansen (1841–1912) in Norway discovered the causative agent of leprosy, *Mycobacterium leprae*. This was the first bacterium to be identified as causing disease in humans. Norway was the location of a progressive stance on leprosy tracking and treatment and played an influential role in European understanding of the disease.

The earliest documented record of leprosy and its cure can be found in the Mahavamsa (The Great Chronicle of Sri Lanka). It was composed by a Buddhist monk at the Mahavihara temple in Anuradhapura about the fifth century AD. In

2021, a petition was made to declare the original leaf book a UNESCO heritage. The Mahavamsa relates the history of Sri Lanka from its legendary beginnings up to the reign of Mahasena of Anuradhapura (AD 302), covering the period between the immigration of Prince Vijaya from India with his retinue, recounting wars, succession disputes, building of stupas and reliquaries, and other notable incidents. It refers to a period at least earlier than 700 BC, before the birth of Gautama Buddha (563–483 BC). According to the report, two ancestors of Gautama Buddha, Princess Priya and King Rawma, contracted the disease and lived in the wilderness until they were cured with the help of herbal medicine.

Historians have made persistent claims that symptoms of leprosy are described among skin afflictions in ancient Greece, Middle Eastern, and Indian documentary sources. Scholars acknowledge that it is difficult to make retrospective diagnoses of leprosy from symptoms described in ancient writings.

Many English translations of the Bible translate *tzaraath* as leprosy, a confusion that derives from the use of the koine cognate Λέπρα, which can mean any disease causing scaly skin, in the Septuagint. While the condition may sometimes be a symptom of Hansen's disease, it has many other causes as well. In addition, ancient sources such as the Talmud (Sifra 63) make clear that *tzaraath* refers to various types of lesions or stains associated with ritual impurity and occurring on cloth, leather, or houses as well as skin.

Skin infections causing symptoms similar to leprosy were likely common in the ancient world. In particular, tinea capitis and related infections on other body parts caused by *Trichophyton violaceum* are abundant in the late twentieth century throughout North Africa and the Middle East. They may also have been common in Biblical times. Likewise, the disfiguring skin disease favus is caused by *Trichophyton schoenleinii*, which appears to have been common throughout Africa and Eurasia before the advent of modern medicine.

The use of the term leprosy before the mid-nineteenth century, when microscopic examination of skin for medical diagnosis was first developed, can seldom be correlated reliably with leprosy as it is understood today.

Nevertheless, there is abundant evidence of notable cases of leprosy in history, such as Baldwin IV of Jerusalem (1161–1185); Christian king of Latin Jerusalem; Henry IV of England (1367–1413); Japanese daimyo Ōtani Yoshitsugu (1558–1600); Vietnamese poet Francis Nguyễn Trọng Trí (1912–1940); Belgian Roman Catholic priest Saint Damien De Veuster (1840–1889), who ministered to lepers placed under a government-sanctioned medical quarantine on the island of Moloka'i in the Kingdom of Hawai'i; and Josephine Cafrine of Seychelles (1877–1907), who suffered from leprosy from the age of 12 and kept a personal journal that documented her sufferings finally published as an autobiography in 1923. Her wounds were said to have miraculously healed upon her death. A committee from the Roman Catholic Diocese of Port Victoria was formed in 2010 to collect information and accounts regarding possible miracles performed by Cafrine so that she can be considered for beatification.

Leprosy or Hansen's disease is a chronic bacterial infection primarily affecting the skin and peripheral nerves usually caused by *Mycobacterium leprae*. The form

the disease takes depends on the person's immune response to the infection and ranges over a spectrum from multibacillary lepromatous leprosy showing limited or low immunity to *M. leprae* to paucibacillary tuberculoid leprosy with a strong immune response (Table 3.6).

**Table 3.6** Classification of leprosy

| Classification | Bacterial load | Immunity | Features |
|---|---|---|---|
| **Tuberculoid** | Paucibacillary | Lepromin test positive | One or more (1–2) hypopigmented skin macules where skin sensations are lost. Affected nerves are thickened and tender on palpation. Formation of epithelioid cell granulomas with a large number of epithelioid cells. *Mycobacterium leprae* are either absent from the lesion or occur in very small numbers. The most benign type of leprosy |
| **Borderline** | Multibacillary | | Skin lesions resemble tuberculoid leprosy but are more numerous (5–20), larger, and irregular with asymmetrical distribution and satellite lesions. Large patches may affect a whole limb, and peripheral nerve involvement with weakness and loss of sensation is common. This type is unstable and may become more like lepromatous leprosy (borderline lepromatous) or may undergo a reversal reaction, becoming more like the tuberculoid form (borderline lepromatous). Of intermediate severity and the most common form of leprosy |
| **Lepromatous** | | Lepromin test negative | Early symptoms of nasal stuffiness, discharge, and bleeding. Swelling and thickening of limbs with subsequent ulceration. Widespread poorly defined hypopigmented erythematous macules with a shiny surface and normal sensation. Progression to widespread infiltration of skin forming nodules and plaques. Characteristic leonine facies with thickening of the forehead, loss of eyebrows and eyelashes (madarosis), distortion of the nose, and thickening of the earlobes. Involvement of other systems: eyes, testes, liver, kidneys, and bones. Absence of epithelioid cells in the lesions. *Mycobacterium leprae* are found in lesions in large numbers. The most unfavourable clinical variant of leprosy |
| **Lepra reactions** | **Type I** | | Reversal reactions. May occur before, or, more often, after the start of treatment. These are sudden responses resulting from the release of immunologically active bacilli or its products leading to localized or systemic symptoms and signs. Such reactions are responsible for most of the nerve damage, deformity, and disability |
| | **Type 2** | | Erythema nodosum leprosum |

*Mycobacterium leprae* has a high predilection for the skin and peripheral nerves. In over 90% of patients, the first symptom noticed is numbness. Temperature is the first sensation lost, followed by light touch, pain, and then deep pressure. This may precede the development of cutaneous lesions by years. The initial skin lesions are usually of the indeterminate type, presenting as a solitary or small number of hypopigmented patches before evolving into borderline tuberculoid or lepromatous types.

Leprosy (Fig. 3.33a–d) is said to mainly affect those areas of the skin which have a relatively low temperature and are more exposed to trauma. Therefore, certain zones like scalp, palms and soles, genitalia, groins, axillae, eyelids, transverse band of skin over the lumbosacral area, the midline of the back, and the perineum have been described to be resistant to the development of lesions of leprosy [236].

The scanty reports of scalp involvement in leprosy have been mostly on the bald areas of the scalp [237]. Hairy scalp has higher skin temperature than the other parts by approximately 5 °C. Alopecia secondary to leprosy is mild and unusual. The low occurrence of alopecia may explain the apparent rarity of scalp involvement. Also, the scalp's anatomical peculiarities may obscure the prominence of the lesions so that they cannot be easily detected. Besides temperature, other anatomical characteristics of the scalp are considered to obstruct the spread of inflammatory infiltrates, particularly the tension system among the cleavage lines, subcutaneous tissue, aponeuroses, and muscles. Tension lines are particularly rich in adipose tissue, and the fat lobes are compressed by fibrous septa along the dermis and aponeurosis.

However, in 1938, Muir states that lesions on the scalp are quite common, though the denseness of the hair and the covering provided by it renders the lesions on the scalp less obvious [238]. Infiltration, papules, and nodules are the most common lesions when the hair is intact. While earlier authors did not think that the mycobacteria affected the scalp, with the advents of the investigational techniques, this is now widely accepted.

Skin biopsies from clinically normal skin of the scalp, axillary, and groin regions in 20 lepromatous leprosy patients revealed significant histopathological findings in up to 25% of patients. Positive findings could, perhaps, be enhanced by studying larger skin materials from these body areas. Indeed, no skin area appears to be immune from invasion by *M. leprae* [239].

Finally, slit smears form 16 lepromatous leprosy and 4 borderline leprosy patients were taken from the scalp, axilla, inguinal regions, and apparently involved skin patch. The bacilli were found in 100% of lepromatous leprosy patients and in 75% of borderline leprosy patients at all sites. Scalp showed acid-fast bacilli in all lepromatous leprosy and in 3 out of 4 borderline leprosy cases. No lesions were seen on the scalp. Contrary to belief, no immune zones were found on the skin as judged by results of bacteriological examination. These studies do not support the view that the leprosy bacillus has a predilection for sites with relatively low temperature as far as human leprosy is concerned [240].

Scalp involvement in leprosy can been classified into:

- Leprotic alopecia
- Involvement of the bald area of the scalp
- Extension of anaesthesia from neighbouring lesion
- Apparently normal skin showing acid-fast bacilli in histopathological sections or slit-skin smear examination
- Involvement of the hairy area of the scalp

Leprotic alopecia seen in Japanese patients suffering from lepromatous leprosy has been well illustrated by Mitsuda [241]. The most common area affected in the scalp is temporal region. Interestingly, an area overlying the temporal artery was said to be spared.

In a clinical-pathological study of 270 patients admitted to the El Rincón Leprosary in Cuba, the incidence of scalp alopecia, its localization on the skull, and its association with the polar form of lepromatous leprosy are stressed [242].

A few cases of leprosy involving the scalp, especially the frontal region and in patients with lepromatous leprosy, have been reported [243–246].

Two cases with tuberculoid lesion on the hairy occipital area of the scalp, well inside the hairline, were reported [247, 248].

The hairy scalp can be involved in borderline tuberculoid leprosy, while hair growth may appear normal [246, 249, 250].

Plaques and nodules over the scalp in lepromatous leprosy patients have been reported [237, 251].

Finally, a case of borderline tuberculoid leprosy of the scalp mimicking alopecia areata-vitiligo overlap has been reported. Hair loss was limited to the scalp, and other body sites remained uninvolved. Skin examination showed three patches of alopecia with depigmented skin on the occipital region of the scalp extending down to the nape of the neck. The follicular openings were patent, and there was no evidence of inflammation or atrophy. Previously a private practitioner had performed local corticosteroid injections once a month with a provisional diagnosis of alopecia areata with no effect. Only a biopsy with histopathological examination revealed epithelioid cell granulomas with Langhans giant cells in the dermis, also involving the nerves. Sensations of pain, touch, and temperature were decreased over the bald patches. In conclusion, the possibility of leprosy must be kept in mind in cases of unexplained progressive alopecia unresponsive to treatment, especially in an endemic country, like India in this case [252].

The term madarosis, originally described eyelash loss secondary to destruction of the hair follicles (Fig. 3.33e), but in contemporary usage, describes the loss of eyelashes from any cause, and it is also used to describe the loss of eyebrows [253]. Deep cutaneous infections, such as leprosy, may infiltrate the lid margin. In non-institutionalized leprosy patients in the USA, 46% had scarring madarosis, noted more commonly in the lepromatous disease (68%), as compared to the tuberculoid disease (25%), and also more common in patients with longer disease duration [254, 255]. In non-institutionalized leprosy patients in India, madarosis was the

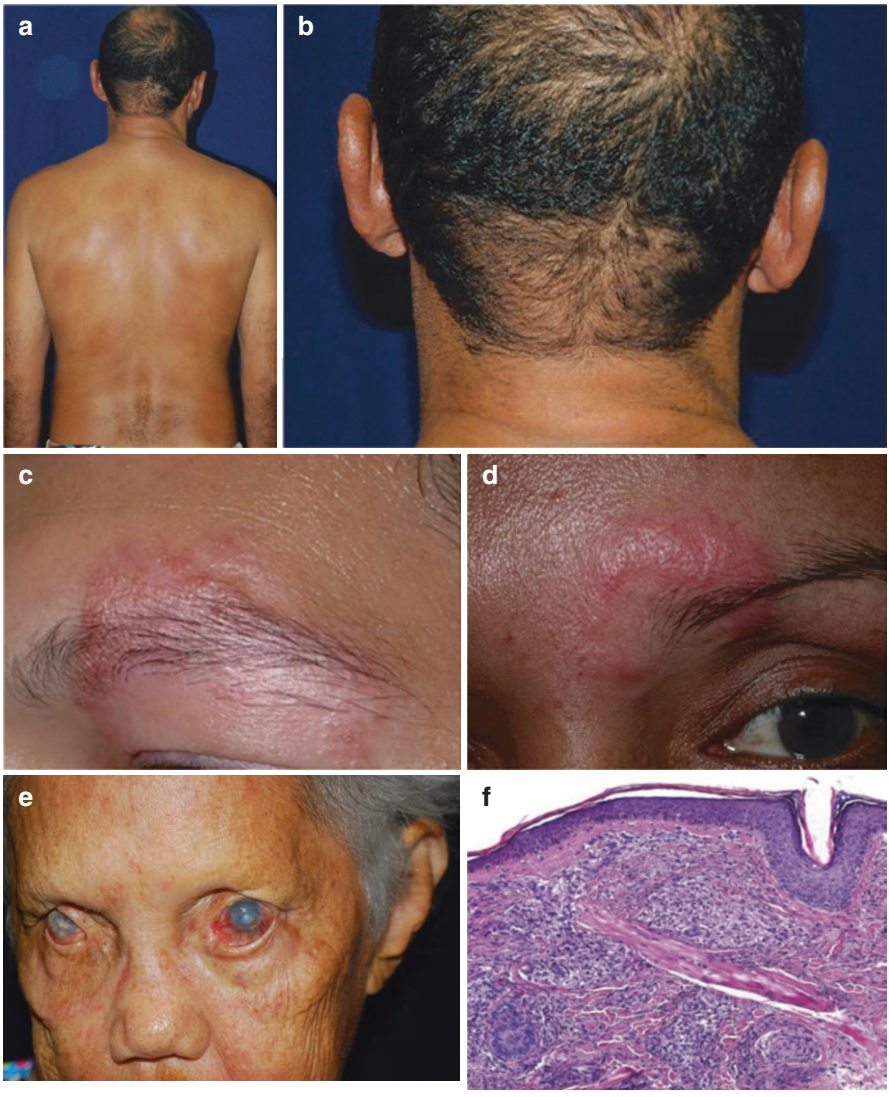


**Fig. 3.33** (**a**–**f**) Leprosy: (**a**) widespread lepromatous leprosy, with (**b**) scalp involvement (leprotic alopecia). (Courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil). (**c**, **d**) Involvement of eyebrow region with solitary lesions of tuberculous leprosy. (Courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil). (**e**) Madarosis of long-standing lepromatous leprosy. (Courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil). (**f**) Histopathology: histiocytic infiltrates in the dermis. A grenz zone of sparing is usually present in the papillary dermis. The histiocytes are arranged in poorly circumscribed masses. Lymphocytes are scarce. Histiocytes may show vacuolated or frothy cytoplasm with a greyish-blue tinge (on H&E) due to clusters of leprosy bacilli. With modified Ziehl-Neelsen stain (Wade-Fite stain), the bacilli can be visualized. (Courtesy of Prof. Werner Kempf, kempf und pfaltz histologische diagnostic, Zurich, Switzerland)

most common eye lesion (76%), and it was seen in lepromatous and borderline lepromatous leprosy. Approximately 90% of the patients with madarosis had a disease duration longer than 10 years.

Lepra reactions are acute episodes occurring during the disease process of leprosy and are of two types: type 1 or reversal reaction and type 2 reaction or erythema nodosum leprosum. In the episodes of lepra reaction, several parts are affected including the face like the oral cavity and extremities.

A rare case of lepromatous leprosy with necrotic erythema nodosum leprosum involving the scalp apart from the usual sites was reported [256].

In another report of borderline tuberculoid leprosy involving the scalp and the right side of the face, the patient also had features of type 1 lepra reaction with facial palsy on the right side [257].

There is evidence that there are distinct clinical variations of leprosy in different world areas. The role of host susceptibility or resistance, ethnic factors, or climatic and other geographical conditions in producing these variations may all play a role.

Cleve [258] proposed an interesting correlation between alopecia leprotica and the religious customs and folklore of shaving the heads of the newborn in countries influenced by Buddhism. Evidence is presented to show that leprosy is contracted during infancy or childhood and not primarily in maturity. Leprosariums in Japan, Korea, and Formosa were visited to determine whether the incidence of alopecia leprotica was greater in relation to the total number of patients in the leprosariums of these countries than in other countries where the practice of shaving the scalp of newborns is not observed. In the final count of 1369 persons with leprosy examined in three countries (Japan, Korea, and Formosa) where shaving of the newborn's scalp is practiced, 479 patients (35%) were found to have alopecia leprotica. The highest incidence, 49% and 38%, was found in the Japanese. Statistics from 11 countries where the custom of shaving the heads of infants is not present (Mexico, Venezuela, the Philippine Islands, Sumatra, Egypt, Palestine, Norway, South Africa, Argentina, the USA, and Hawaii) have been used in establishing the control group. Of 12,585 patients examined, only 34 were found to have alopecia leprotica. This is an incidence of less than 0.3%. These data suggest that the incidence of alopecia leprotica among patients with leprosy is far greater in those countries where shaving of the scalp of the newborn is a common practice than where it is not. The scalp invasion among the natives of Japan, Korea, and Formosa might theoretically be due to a greater virulence of the organisms, lesser resistance of the scalp, or greater dosage of the organism. The common factor in all cases appears to be the larger dosage of the organism, for trauma (shaving) with complete removal of the natural protecting barrier of the hair and the inevitable production of small nicks and cuts would appear to predispose to heavy infection. It is evident that scalp infection is external in origin and not vascular from a central focus.

In fact, the natural history of the transmission of leprosy was given considerable elucidation by the work of Brazil investigators and of Lara in the Philippines. The former found that the disease developed in over 70% of the children affected prior to the third year. At the Culion leper colony in the Philippines, Lara repeatedly examined 770 children over a period of years in an effort to determine the

pathogenesis of leprosy in these cases. The children ranged in age from 1 to 9 years. Lara estimated that at least 50% of exposed children of leprous persons would show manifestations of the disease by the time they were 5 years old [259]. Environmental factors are felt to influence the transmission of leprosy. Such variants as a hot, humid climate, overcrowding, poor housing, and insufficient food and clothing have been implicated.

Leprosy has very characteristic clinical features. Diagnosis should be confirmed by one of the following investigations:

- Slit-skin smear: a small slit is made using a sharp blade over the skin of the earlobe, forehead, or lesional skin; then a smear is made by scraping the exposed dermis onto a glass slide and examining for acid-fast bacilli under the microscope; useful for multibacillary leprosy only.
- Lepromin test: an intradermal test for delayed type hypersensitivity to *M. leprae* antigens; although not specific, it is helpful for classifying the type of leprosy.
- Skin biopsy (Fig. 3.33f): may show typical features, depending on the type of leprosy. Special stains may be required to demonstrate the bacilli.
- *M. leprae* DNA PCR is very specific for detecting leprosy organisms.

The treatment objective of leprosy is to stop active infection and minimize complications and deformity.

Most of the endemic countries follow the WHO recommended multi-drug therapy of antibiotics. First-line antibiotics used in the treatment of leprosy are dapsone, rifampicin, and clofazimine. The combination of drugs selected and the duration of treatment depends on the type of leprosy. The WHO guidelines recommend three drugs including clofazimine for 6 months in paucibacillary leprosy and 12 months for multibacillary disease.

Once appropriate treatment has been commenced, skin lesions slowly subside. However, nerve damage cannot be reversed. Residual disabilities may require corrective reconstructive surgery.

Also, loss of eyebrows, which may be particularly stigmatizing for patients with leprosy, has been successfully treated by reconstructive surgery [260].

## 3.7 Actinomycosis

Actinomycosis is a rare subacute or chronic bacterial infection caused by Gram-positive, anaerobic, or microaerophilic bacilli. The microorganism is ubiquitous and occurs in soil and in the microbiota of animals and humans. In humans, actinomyces are commonly found in the oral cavity (tonsillar crypts, gingivodental crevices), the gastrointestinal tract (colon, caecum, appendix), and the female genital tract (IUD).

The name refers to ray-like appearance of the organisms in the granules. About 70% of infections are due to either *Actinomyces israelii* or *A. gerencseriae*. Infection can also be caused by *Streptomyces somaliensis* and *Propionibacterium propionicus*. The condition is likely to be a polymicrobial anaerobic infection. Infection depends on other bacteria (Gram-positive, Gram-negative, and cocci) to aid in invasion of tissue.

The infection is characterized by formation of hardened swelling with sinuses, which may drain pus containing granules to the skin surface. Actinomycosis abscesses grow larger as the disease progresses, often over months.

The most common sites of infection are cervico-facial (50%) (Fig. 3.34), abdominal (20%), thoracic (15%), and the rest (15%): pelvic and cutaneous [261].

Cutaneous actinomycosis commonly manifests as abscess, tissue fibrosis, draining sinuses, and classical sulphur granules, which are pathognomic. Presentation as pseudo-tumorous masses is rare.

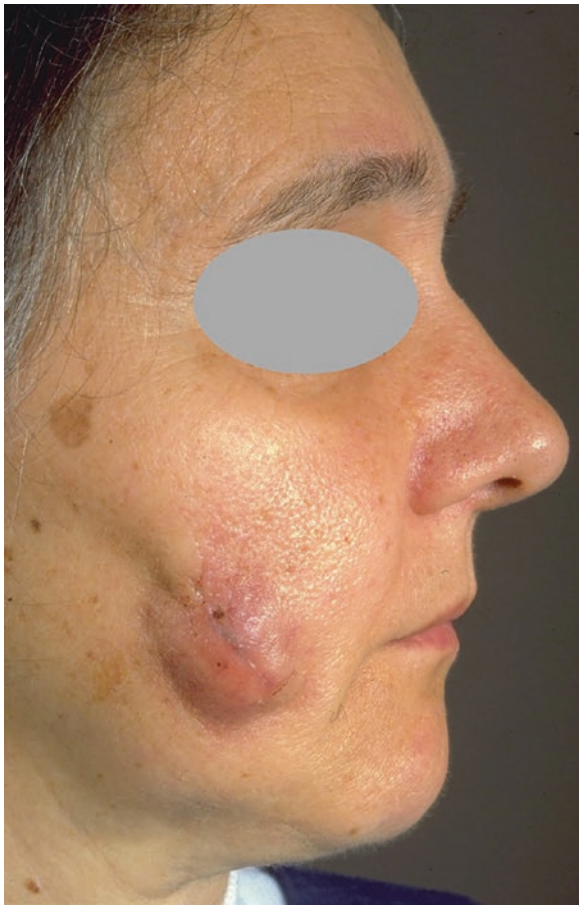

**Fig. 3.34** Actinomycosis

Actinomyces are unable to penetrate healthy tissue, and in order to become invasive, disruption of epithelial or mucosal barrier is mandatory.

An affected human often has recently had dental work, poor oral hygiene, periodontal disease, radiation therapy, or trauma causing local tissue damage to the oral mucosa, all of which predispose the person to developing actinomycosis. This is not an exogenous infection; therefore, no person-to-person spread occurs.

Scalp actinomycosis is a rare event and has been reported presenting as a soft tissue tumour with trauma as a preceding event [262]. Another case was reported presenting with two soft tissue masses located at the upper segment of the right posterior neck space and extended to the occipital region and parietal scalp [263]. Finally, a case was reported with multiple, painless, greenish pus draining sinuses at the same site of a previous road traffic accident with multiple bruises to the scalp. Skull radiograph showed a thickened parietal vault and intact inner table but multiple defects in the outer table suggestive of chronic osteomyelitis. A punch biopsy from the granulation tissue done showed foci of sulphur granules comprising of filamentous basophilic radiating fungal-like structures in the dermis surrounded by acute and chronic inflammatory cells, namely, neutrophils, plasma cells, and foamy macrophages intervened with fibroblasts representing actinomyces [264].

Actinomycosis of the scalp may be misdiagnosed as neoplasm or tuberculosis. High index of suspicion in such lesions not resolving with antibiotics therapy and small biopsy being inconclusive, a diagnosis of actinomycosis of skin should be considered, and the patient should be put on high dose of antibiotics trial.

Histopathological confirmation is mandatory with visualization of sulphur granules, which is seen only in 25% cases and can be missed in small biopsy specimen. Pus culture is not a reliable investigation as positive cultures are present in 25–50% cases only.

The management of cutaneous actinomycosis is high-dose IV antibiotics for 4–6 weeks followed by oral penicillin or amoxycillin for 6–12 months. Surgical resection is a useful adjuvant therapy, particularly in large masses not responding to treatment, and excisional biopsy is helpful in establishing histopathological confirmation. Surgery alone is not curative.

Cutaneous granular bacteriosis is the term proposed for the clinically and histologically actinomycosis-like presentation of infections of other origin.

A young man presented with a large multilobulated tumour of the scalp, which had been relapsing for years. Histological examination of a lesional biopsy revealed chronic inflammation with granulation tissue and presence of granules with eosinophilic periphery, which was positive for Gram, Grocott, and periodic acid-Schiff stains. A large excision was performed. Cultures grew *Staphylococcus aureus*. The patient was treated with penicillin G, but 4 weeks after the start of treatment, new small nodules appeared over the same area. All these new nodules disappeared within 2 weeks of addition of clindamycin and cotrimoxazole. This triple antibiotic treatment was carried on for 18 months, and the patient remained disease-free after a follow-up of 4 years. Although the lesions were suggestive of actinomycosis, culture revealed that they were caused by a different pathogen. The authors suggested

grouping such lesions under a single term granular bacteriosis and combining surgery with broad-spectrum antibiotics covering both *Actinomyces* species and botryomycosis-causing organisms, mainly *Staphylococcus* [265].

## 3.8 Hidradenitis Suppurativa

Hidradenitis suppurativa (HS), also known as Verneuil's disease and acne inversa, is a long-term dermatological condition characterized by the occurrence of inflamed and swollen lumps that are typically painful and break open, releasing fluid or pus. The condition typically involves areas of friction that are rich in (but not limited to) apocrine glands, such as the axilla, groin, inframammary area, and other intertriginous areas [266]. Occlusion of hair follicles is considered as the primary pathogenic factor, and therefore the condition is nosologically classified as follicular occlusion disease, as is acne vulgaris and related conditions, including dissecting cellulitis of the scalp. Risk factors for HA include obesity and smoking. The condition is not primarily caused by an infection, nor do poor hygiene, or the use of deodorant play a role. Patients experience cycles of inflammation, which alternates between frank disease activity and scar tissue formation [267–269].

The condition may severely impair patients' quality of life by limitation of everyday activities, such as walking, hugging, moving, and sitting down. Sitting disability may occur in patients with lesions in sacral, gluteal, perineal, femoral, groin or genital regions.

The estimated prevalence of HS shows wide variations, with a point prevalence ranging from 0.3% in Germany to 4.1% in Denmark, owing to heterogeneous measurement methods and populations that have been studied [270]. In Caucasian patients, women outnumber men by a ratio of 3:1, and African Americans seem to be disproportionately affected. However, our understanding of race-specific prevalence is limited by under-reporting of ethnicity in many HS studies [270].

So far, there has not been concordance in the literature regarding an association between early disease onset and a family history of HS [271]. Nevertheless, genetic factors have been proposed [272]. In fact, some cases have been found to result from mutations in the NCSTN, PSEN1, or PSENEN genes. The genes produce proteins that are all components of a complex called gamma- (γ-) secretase. This complex cuts apart (cleaves) many different proteins, which is an important step in several chemical signalling pathways. One of these pathways, known as notch signalling, is essential for the normal maturation and division of hair follicle cells and other types of skin cells. Notch signalling is also involved in normal immune system function. Studies suggest that mutations in the NCSTN, PSEN1, or PSENEN gene impair notch signalling in hair follicles. Although little is known about the mechanism, abnormal notch signalling appears to promote the development of nodules and to lead to inflammation in the skin [273].

In addition, the composition of the intestinal microflora has been suspected to also play a role. The concurrent existence of inflammatory gut and skin diseases has led to the postulation of a gut-skin axis in which gut microbiota are implicated.

Indeed, analysis of bacterial taxa in foecal samples from HS patients supports the possibility of a role for intestinal microbial alterations in this chronic inflammatory skin condition [274]. Possible dysbiosis of the cutaneous microbiome, particularly on the level of the pilosebaceous unit and in lesional skin, is currently under investigation.

Patients with HS usually present with deep-seated painful nodules, abscesses, suppurative sinus tracts or tunnels, bridged scars, and double- and multi-ended comedones (also known as tombstone comedones). Subcutaneous nodules and abscesses can rupture, causing bleeding and purulent discharge, which will ultimately result in dermal contracture and fibrosis. Typically, these lesions are localized in the axillae (Fig. 3.34a), groin, and peri-genital or perianal skin and display a chronic (>3 months) or recurrent (>2 flares/6 months) history [275, 276]. Some patients with HS may have other body sites affected, either primarily or as a contiguous inflammatory process, such as the chest (Fig. 3.34b), inner thighs, buttocks, scalp, and retro-auricular areas.

Even though HS of the beard area may be considered a rare clinical presentation [277], facial HS (Fig. 3.34c) shares clinical features with HS on other body areas, such as nodules, abscesses, ulcerations, and open comedones [278–280]. The cicatricial process that is observed in facial HS evolves with bridged scarring, which is highly specific for HS, making it easier to differentiate from keloidal/hypertrophic scars caused by acne. Although dissecting cellulitis and HS are classified separately, they share many clinical, dermatoscopic, pathogenetic, and histologic aspects, as well as therapeutic options, and may co-exist (Fig. 3.4d–f).

With regard to the pathogenesis of HS, three features are recognized as central to the disease [278] (Fig. 3.35):

- Follicular hyperkeratosis and dilatation
- Follicular rupture and subsequent inflammatory response
- Chronic inflammation with architectural tissue changes

It is believed that the biogenesis of the follicular unit is impaired in HS, eventually leading to pro-inflammatory activation of local keratinocytes. Subsequently, a boosted secretion of antimicrobial peptides and inflammatory cytokines/chemokines, such as IL-1β and IP-10, is also observed, playing a role in the disease process [281]. Once the follicular epithelial is inflamed, progressive alteration and involution of follicle-associated sebaceous glands are observed, leading to anomalous keratinization and subsequent dilatation of the hair follicles. The stimulation of Th-17 pathways also causes changes in resident immune system cells, which result in microbial dysbiosis and alterations of the follicular microenvironment [281]. Autologous antigens that are naturally sequestered from the immune system (follicular immune privilege) in healthy individuals are further exposed due to the rupture of the hair follicle during the inflammation process. As a result, neutrophils and

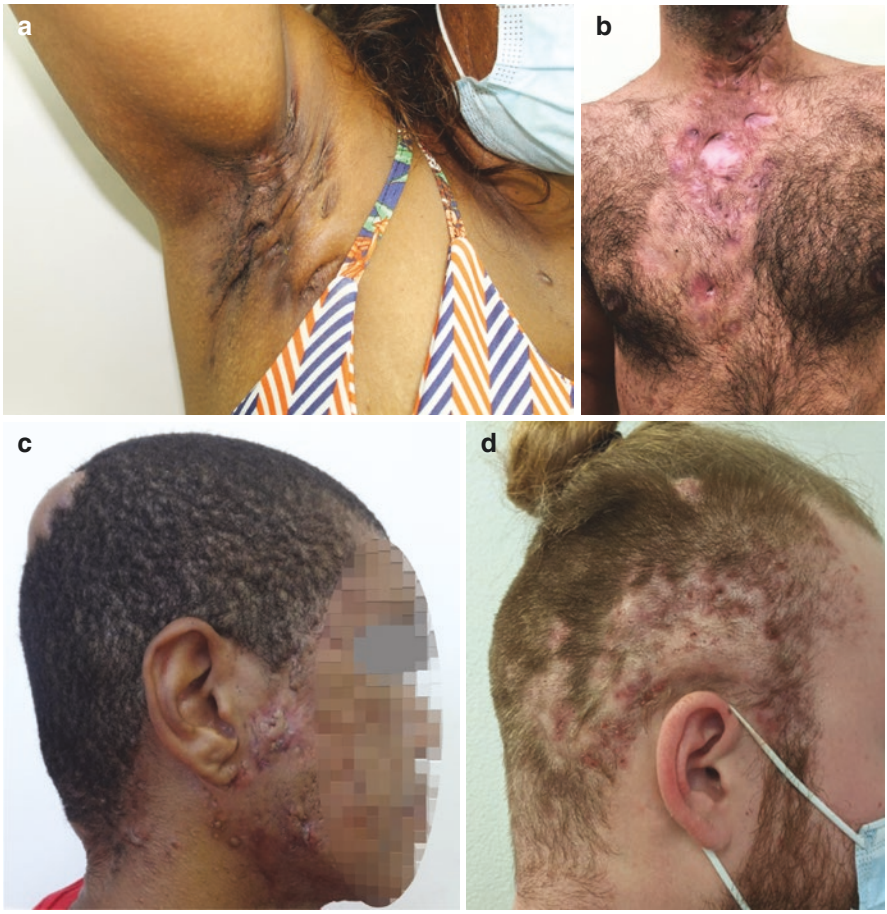


**Fig. 3.35** (**a**–**f**) Hidradenitis suppurativa: (**a**) axillary, (**b**) chest, (**c**) face. (Courtesy of Antonio Pedro Federal Hospital, Federal Fluminense University, Brazil). (**d**–**f**) In association with dissecting cellulitis of the scalp

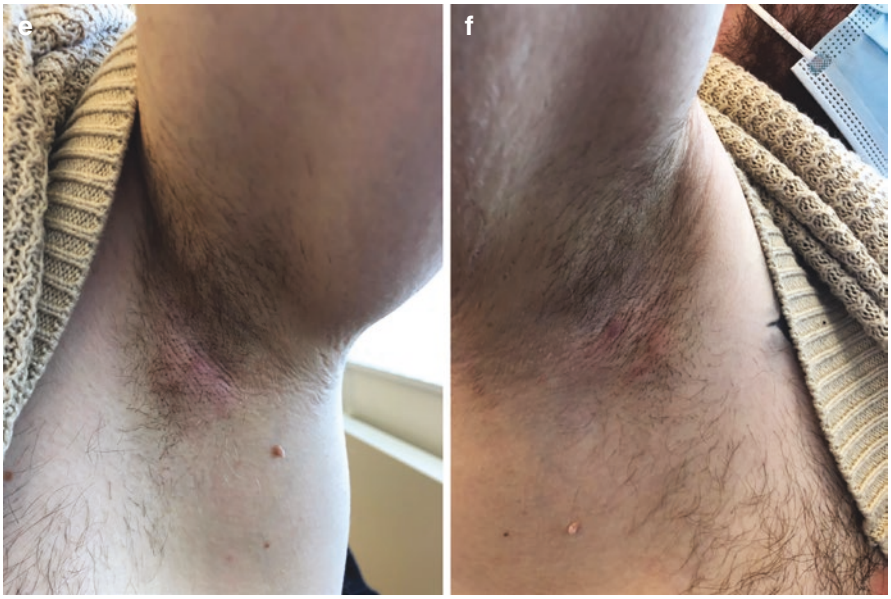


**Fig. 3.35** (continued)

Th-1 and Th-17 pathway cytokines mediate a chronic inflammatory process that eventually affects the hair follicle physiology [281].

Previous studies have usually shown that culturing of HS lesions display no bacteria growth or is predominantly positive for commensal agents, such as *S. epidermidis*. Nonetheless, a recent next-generation 16S sequencing (NGS) study has revealed the existence of a distinct microbiome formed by *Prevotella* spp. and *Porphyromonas* spp., which had so far not been recognized [281].

An interesting observation was made by Jørgensen et al. [282], who have shown the luminal microbiome of HS inside fistulae and tissue tunnels using NGS. The authors observed that *Porphyromonas* spp. and *Prevotella* spp. were the most frequent genera found in the study, and they also defined five microbiome types according to pieces of information retrieved from HS tunnels [281] (Table 3.7):

Based on these observations, it is quite possible that an association of bacteria and HS exists. Further studies are necessary to elucidate whether or not there is a causal effect of such agents in the pathogenesis of HS. Also, even if bacteria do not play a direct role in the disease, chances are that the microenvironment inside HS fistulae facilitates the growth of bacteria, which can ultimately spark inflammation and promote further disease activity.

Another point of interest is that of bacterial biofilms, which have already been identified in lesions of HS. Even though the literature is not clear enough on how this can interfere in the treatment, it is possible that the presence of such bacterial microstructures can, at least partially, explain why so many antibiotic schemes are necessary to fade a disease flare-up [283].

**Table 3.7** Luminal microbiome from fistulae and tunnels in hidradenitis suppurativa

| Microbiome in hidradenitis suppurativa |
|---|
| Type I: *Porphyromonas* spp. |
| Type II: *Corynebacterium* spp. |
| Type III: *Staphylococcus* spp. |
| Type IV*: Prevotella* spp. |
| Type V: *Acinetobacter* spp. |

**Table 3.8** Hurley staging of HS

| |
|---|
| **Stage I**: Abscess formation, single or multiple, without sinus tracts and cicatrization |
| **Stage II**: Recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions |
| **Stage III**: Diffuse or near-diffuse involvement or multiple interconnected tracts and abscesses across the entire area Thus, other classification/staging criteria are necessary to determine the severity of the clinical picture |

Diagnosis of HS is usually made based on clinical grounds [284]. When considering the diagnosis, it is important to define lesions as being typical and also to observe the body sites affected. Besides, recurrence or chronicity defined by the occurrence of two or more episodes of inflammation in 6 months must also be taken into consideration [284, 285]. Based on the modified Dessau definition, three diagnostic criteria should be met:

- Presence of typical lesions
- Typical locations
- Chronicity

Histopathological features include follicular hyperkeratosis, follicular hyperplasia, and follicular occlusion with an associated spongiform infundibulofolliculitis [286]. These changes may be associated with follicular dilatation, follicular rupture, and the formation of keratin-containing cysts, abscesses, sinus tracts, granulomas, fibrosis, and scarring [287].

There is no specific laboratory test for HS.

Staging of HS is another point of practical relevance, since it represents a guide to the appropriate treatment of the disease. In 1989, Hurley proposed a severity classification for HS, which has since been used in clinical practice [288] (Table 3.8).

Imaging studies (ultrasound and nuclear magnetic resonance) can be beneficial for a better characterization of the lesions and/or surgical programming. Ultrasound evaluation can contribute to post-surgery follow-up if recurrence is suspected. Ultrasound imaging has been used to further characterize lesional morphology and depth. For instance, it can demonstrate subclinical fluid collections, increased dermal thickness, and follicular dilatation in early stages of HS and the evolution of sinus tracts in advanced disease. Colour Doppler ultrasound may identity subclinical sinus tracts, aiding in more precise treatment [284].

With regard to treatment of HS, guidelines have emerged since 2015 with the objective of organizing the management of HS in a more effective and comprehensible way; nonetheless, there is considerable discrepancies among the proposed recommendations.

Consistent treatment modalities that are supported by the different guidelines include topical clindamycin, oral tetracyclines, combination of oral clindamycin and rifampicin therapy, adalimumab, and surgical approach.

Irrespective of the severity of the disease, a multidisciplinary approach is recommended, focusing on environmental factors and on the management of chronic wounds and pain.

Dietary adjustments, weight loss, and smoking cessation are compulsory recommendations to be given to all patients [289]. Since the patients' adaptation to a new lifestyle may not be easy, close attention and frequent visits with dermatologists and other specialists are required so that the medical treatment can be adjusted accordingly adjusted [290].

Patients with mild disease who display no abscesses benefit from the use of topical clindamycin 1% gel b.i.d. for 3 months [291]. The vehicle that topical medication is delivered is important (gel preparations are the choice), since HS is typically a disease of hair-bearing areas. For patients who oftentimes face clinical flares with inflammation and suppuration, a systemic tetracycline, such as oral doxycycline or minocycline, is recommended [292]. Intralesional corticosteroid injections can be particularly useful for localized disease, if the drug can be prevented from escaping via the sinuses. A systemic approach based on either oral clindamycin (300 mg b.i.d.) as monotherapy or combination therapy of oral clindamycin (300 mg b.i.d.) and rifampicin (600 mg daily) for 10 weeks represents the recommended therapy for severe cases [293]. It is prudent to remember that in countries where tuberculosis is endemic, rifampicin is avoided as treatment of HS in order to prevent bacterial resistance development. In Brazil, for instance, the combination of oral clindamycin with rifampicin does not represent the treatment of choice, although it comes listed among the possibilities in national guidelines.

For those who fail to respond to the use of oral antibiotics along with topical therapies, a biologic agent may be considered. Scientific evidence supports the use of s.c. adalimumab over others, especially for moderate/severe cases. Adalimumab is prescribed at 160 mg on day 1, 80 mg on day 15, and a single 40 mg injection every week from week 4 onwards or 80 mg every other week [269, 294]. Once an effective result has been reached, adalimumab is continued on a long-term basis for maintenance.

Some patients may benefit from the use of systemic retinoids, such as acitretin, 0.5–0.6 mg/kg/day, or alitretinoin, 10 mg/day, both considered third-line treatments [287, 291].

Oral glucocorticoids (prednisone 10 mg/day) combined or not with intralesional triamcinolone acetonide (5–10 mg/mL) represent a possibility for patients who need a rescue therapy.

Surgery is a reasonable approach that usually leads to local cure [290]. However, it is important to determine whether severe inflammation and suppuration require

anti-inflammatory treatment (induction therapy) before the surgical procedure is performed [286, 291].

Particularly, when the process becomes chronic, wide surgical excision is the procedure of choice, because of the risk of development of spinocellular carcinoma [295] or amyloidosis [296] as long-term complications of HS.

For wounds in the affected area that do not heal by secondary intention, immediate or delayed application of a split-thickness skin graft is an option.

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# Infectious Diseases of the Scalp Following Hair Transplantation

4

Sandeep Sattur, Pedro Colli, and Ralph M. Trüeb

## Contents



Hair transplantation is based on the concept of donor dominance—a relative sparing of follicles of the occipital and occipito-parietal region from miniaturization, which retain their innate properties even when they are moved to the balding areas to improve coverage [1].

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Today, hair transplantation is minimally invasive, refined, and a safe and effective way to address hair loss with natural-looking results (Fig. 4.1a, b). Technical evolution has led to refinement of the procedure, which can now accomplish moving a large number of grafts in a reasonable time to achieve comprehensive coverage. The process of hair transplantation consists of sequential steps, which includes planning, preparation, delivering local anaesthesia, and graft harvesting—either through strip harvest or follicular unit excision/extraction (FUE), holding of grafts in optimal conditions, and implantation of these grafts into the recipient area.

Hair transplantation surgery is categorized as Level I surgery and performed in a Class A facility [2–4]. This basically categorizes a surgery with minimal risk to the patient, independent of anaesthesia, minimally invasive procedures with little or no blood loss, and often done in an office setting, with the operating room principally for anaesthesia and monitoring. These procedures are performed under local, regional, or topical anaesthesia. Per the surgical wound classification created by the Centers for Disease Control and Prevention, hair transplantation falls in the category of SWC-1—Clean wound—an incision in which no inflammation is encountered in a surgical procedure, without a break in sterile technique, and during which the respiratory, alimentary, and genitourinary tracts are not entered [5, 6].

Hair transplant surgery (HTS) is unique among clean skin surgeries as it involves:

- A large number of wounds that are open for a prolonged time
- Transplanted tissue handled for extended periods of time
- Oedematous post-operative field for days after surgery

Most of the HTSs are performed in an office setting though a small percentage are performed in hospital settings. As doctors from a wide variety of specialities perform HTS, the approach is varied, and hence aseptic techniques and antimicrobial prophylaxis are not uniform [7].

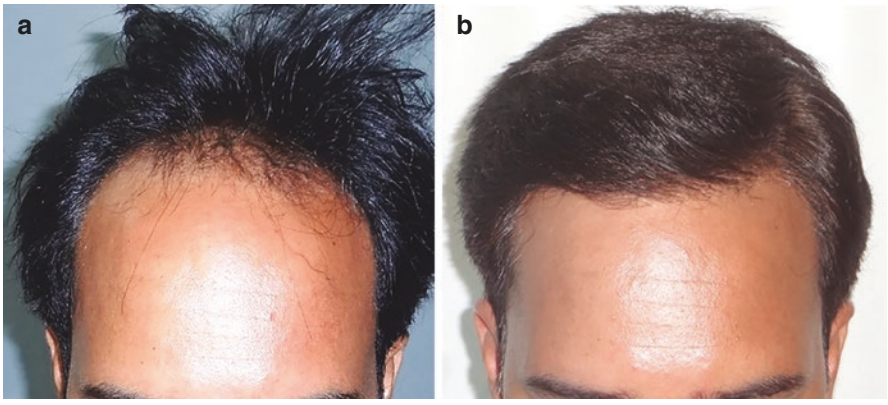


**Fig. 4.1** (**a**, **b**) Autologous hair transplantation (**a**) before, and (**b**) after the procedure

In 1992, the US Centers for Disease Control and Prevention (CDC) revised its definition of 'wound infection', creating the definition 'surgical site infection' (SSI) to prevent confusion between the infection of a surgical incision and the infection of a traumatic wound [8, 9].

**Superficial surgical site infections (SSIs) are defined as:**
1. Infections occurring up to 30 days after surgery
2. Involving only the skin and subcutaneous tissues

**With at least one of the following:**
3. Purulent discharge
4. Culture positive

**And at least one of these signs:**
5. Pain/tenderness
6. Localized swelling
7. Redness/heat

Surgical site infection after hair transplantation is very rare, and literature puts the incidence at less than 1% in patients, and this has been attributed to the robust blood supply of the scalp [10].

Given the vascularity of the scalp, infections after hair transplant are not common. The reasons attributed for infections after surgery range from poor hygiene, break in aseptic protocols, poor surgical techniques, and medical comorbidities like diabetes, immune deficiencies, etc.

To put the matter in perspective, a review of factors which impact the possibility of infection after hair transplantation should be considered.

The factors which influence the probability of infection after hair transplant are:

1. Wound healing after hair transplantation
2. Anatomical factors
3. Microbial factors
4. Host factors
5. Procedure-related factors (surgical technique)
6. Pre-operative and intra-operative sterile techniques

Wound healing after transplantation in general, healing of wounds after injury (surgical or otherwise) comprise of four highly integrated and overlapping phases: haemostasis, inflammation, proliferation, and tissue remodelling or resolution [11]. Hair transplantation involves making hundreds or thousands of scalp wounds to move the hair follicles from one area of the scalp to another.

During hair transplantation, the hair follicle is completely detached from its native location, held for a period outside the body and then implanted in the recipient site created in another part of the scalp. The cascade of events occurring

simultaneously and sequentially with a significant overlap are critical for the survival of the follicle after transplantation [12]. Detaching the hair follicle surgically leads to an anaerobic status with accumulation of waste products. It survives in its transplanted location by virtue of plasmatic imbibition for the first 1–3 days followed by the process of inosculation by local revascularization [12]. The wounds created for harvest donor follicles, either through strip harvest or follicular unit excision (FUE), are considered full-thickness wounds and will go through the integrated and overlapping stages of wound healing. The recipient sites as well as the sutured donor site heal with primary intention, while the healing of donor area after FUE is thought to be with secondary intention [13, 14].

Anatomical factors an understanding of the surgical anatomy of the scalp is the basis on which complication-free scalp surgery is based, and an understanding of the arterial supply is fundamental to the hair restoration process. The scalp skin is thicker than the skin of most areas of the body and has of a rich network of anastomosing arteries (system of anastomoses between branches of the external and internal carotid arteries), veins, and lymphatics in the subcutaneous layer [15, 16]. It is this rich array of anastomoses that covers the complete blood supply to the scalp and is probably the main reason for extremely uncommon incidence of infection post-hair transplantation [16, 17].

## 4.1 Microbial Factors

In general, most SSIs originate from the patient's endogenous flora [9, 18]. The microbial flora constituting bacteria, viruses, and fungi inhabiting a particular region of the skin and adnexal structures is designated as the skin microbiome. The constitution of the microbiome varies according to regions of the body based on many factors including pH, temperature, moisture, and sebum content [19]. The scalp and the hair follicles have a unique microbiome due to abundance of terminal hair follicles and sebaceous glands. Scalps of healthy individuals majorly show presence of *Cutibacterium* spp. (with the vast majority of *C. acnes*) and *Staphylococcus* spp. (with the predominance of *S. epidermidis*), while *Corynebacterium* spp., *Streptococcus* spp., *Acinetobacter* spp., and *Prevotella* spp. comprise the other significantly less numerous species. Deeper recesses of infundibulum also have been shown to harbour gram-positive bacteria. *Malassezia* spp. are predominant, revealing 0.25/1000 incidence rate among hair restoration surgeries as extrapolated from the survey [20]. MRSA infections can originate in the hospital or in the community, and a hair transplant surgeon should have a high level of suspicion when there are two consecutive cases of infection seen in short intervals like days or weeks [18, 20, 21].

Endogenous transmission typically occurs in individuals with poor hygiene or presence of infection of another body sites like respiratory tract infection or skin infection, etc. [18]. Exogenous transmission of the microbes can occur through contact with hands of individuals having infection or those who may be carriers (in the case of MRSA). It is also possible for transmission to occur through contact with

infected or colonized sites of individuals, especially when the integrity of the skin is violated due to cuts or abrasions or due to skin-to-skin contact. Another mode of exogenous transmission could be contaminated instruments, airborne, devices, or critical surfaces in the operating theatre, which can be a result of inadequate skin preparation, lack of adherence to sterile techniques, improper sterilization of surgical instruments and devices, surgical duration, and traffic in the operating room [20–23].

## 4.2 Host Factors

A number of patient-related factors have been shown in multiple studies to influence the risk of developing SSI. These are older age, nutritional status, diabetes mellitus, smoking, obesity, immunocompromised status, existing infection at other body sites, low serum albumin concentration, and ischemia secondary to vascular disease or irradiation [5, 18].

A meta-analysis published in 2016 supported the consideration of diabetes as an independent risk factor for SSIs for multiple surgical procedure types [19]. Similarly smoking too is recognized as an independent risk factor for surgical site infection, and peri-operative cessation of smoking is known to reduce chances of SSIs [20, 21]. Increasing age has been considered as a risk factor for developing SSSIs. A study published in 2005 predicted an increased risk of SSI until age 65 years. The risk of SSI increased by 1.1%/year between ages 17 and 65 years, and thereafter the risk actually starts decreasing [24].

## 4.3 Procedure-Related Factors (Surgical Technique)

Similar to the host factors, procedural or surgical technique-related factors influence the occurrence of the SSIs [5]. The US National Nosocomial Infections Surveillance system (NNIS) risk index was developed in 1986 to provide a scoring system that would be able to predict the risk of SSI in an individual patient [5, 25]. It takes into account the duration of the procedure, presence or absence of contaminated wound, and existence of systemic disease ASA grade 2 or 3 (i.e. mild systemic disease on the American Society of Anesthesiologists (ASA) Physical Status Classification.) [5]. Excessive use of cautery or poor handling of tissues and haematoma formation could be contributory factors [26]. Surgical duration is an independent risk factor for SSIs, and surgical duration >3 h is associated with an odds ratio of 3.34 for SSIs in patients undergoing general surgical procedures [23]. Hair transplantation on an average takes about 6–8 h but in some cases can go on for longer or may be performed in two sessions over 2 days. This is a significant factor which has to be considered when planning the surgery.

Even though majority of infections after surgery are caused by endogenous microbes, a small percentage could be caused by exogenous organisms. The source of these exogenous organisms could be airborne, hand contact from staff members,

and inadequately sterilized instruments [21–23]. It could also be linked to the quality of pre-operative skin preparation and improper scrubbing of hands by the surgical team [6, 19].

The agents used for surgical scrubbing are alcohol, iodine, and chlorhexidine used singly or in combinations. Handwashing is still the best way to prevent transmission of microorganisms. Optimal pre-operative handwashing/scrubbing will depend on the antiseptic agent used; type of scrub method, traditional or dry scrub; and duration of scrubbing. Of the three, the most important factor is the duration, and studies have shown that this should ideally be 2–3 min [23].

The next critical factor is the preparation of the surgical site. Inadequate preparation of the surgical site has been linked to post-operative infections [5, 26]. In hair transplantation, patient usually shampoos his scalp the night prior, which is also normally advocated on the morning of the surgery. Studies have shown using medicated shampoos on the scalp microbiome helps reduce intra-operative emergence of resident skin flora and subsequent contamination of the wound [27–29].

Antimicrobial prophylaxis for HTS is a controversial subject with no consensus on the matter. As HTS is a clean surgery, some believe there is no need for antimicrobial prophylaxis, as studies have not shown any benefit for the same [22]. However, another school of thought feels that, though it is clean skin surgery, it is unique because of its duration and extensive open wounds after surgery and antimicrobial prophylaxis maybe helpful in reducing incidence of infections after HTS [18]. Most commonly, first-generation oral cephalosporins are used and started the night before, with two doses given before surgery, ensuring adequate tissue levels of the antibiotic before the incision is made.

## 4.4 Infections After Autologous Hair Transplantation

Incidence of infections post-hair transplantation has to be viewed in the context of some under reporting. Infections can occur in the recipient area as well as donor area. Most infections seen after hair transplantation would be categorized as superficial SSIs as they will be limited to the skin and usually not extend beyond subcutaneous tissue [5].

### 4.4.1 Infections in the Donor Area

Infections in the donor area after strip harvest technique could present as impetiginous lesions, stitch abscesses, folliculitis, and, in severe cases, wound dehiscence.

Crust formation usually begins with some discharge from the suture line, which solidifies into crusts. Infection is heralded by complaints of painful discomfort and erythema of the suture line. The crusting creates a favourable environment for the microorganisms to grow. Infection in the donor area may present as pustules [7]. These signs are usually accompanied by complaints of painful discomfort. Folliculitis though uncommon in the donor area has been reported [30] (Fig. 4.2).

Stitch abscesses (Fig. 4.3) form due to infection of sutures. But infection may not be the only cause; it could be combination of immunological response to the suture material and infection [30]. The donor area is usually closed in two layers. Absorbable sutures like polyglactin-910 (Vicryl) or poliglecaperone-25 (Monocryl) are used for subcutaneous closure, and monofilament non-absorbable suture materials like polyamide (nylon) or polypropylene (Prolene) are used for donor closure [13, 31, 32]. Stitch abscesses are more common with polyfilament non-absorbable suture materials like silk, and these are not usually used to close donor areas [31]. The abscesses resolve on removal of sutures. The treatment is topical use of mupirocin and systemic antibiotics, usually oral cephalosporins [18]. Sometimes, absorbable suture materials are extruded through stitch abscesses long after the wounds have healed.

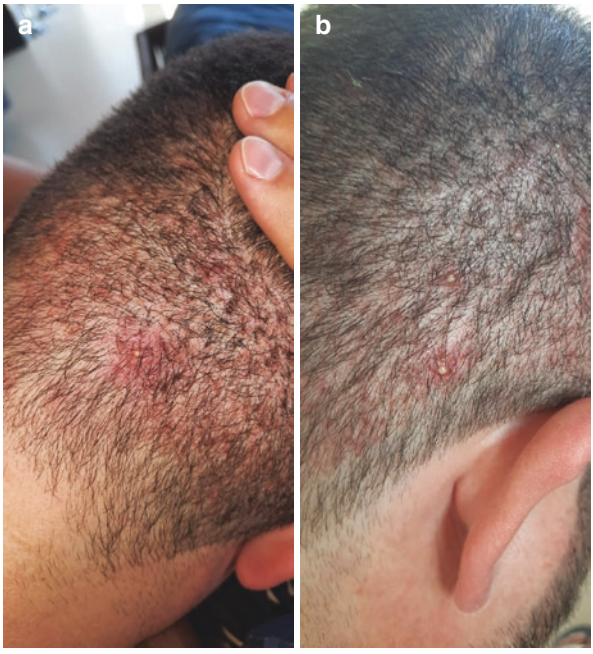


**Fig. 4.2** (**a**, **b**) Donor site folliculitis

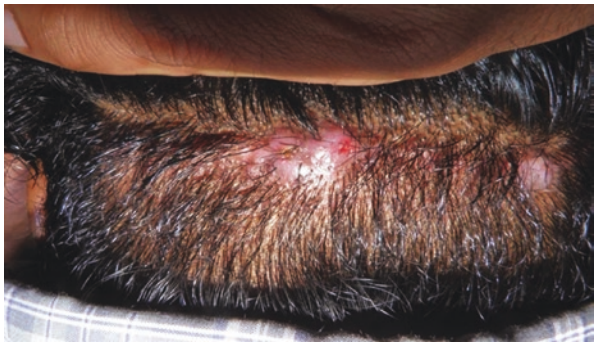

**Fig. 4.3** Stitch abscess after strip harvest for hair transplantation

Infection is thought to occur due to inadequate break in aseptic protocols or haematoma formation (due to suboptimal haemostasis/presence of dead space) and is one of the major predisposing factors for wound dehiscence [33].

Buried grafts, especially while using blunt punches, can lead to chronic folliculitis in the donor area after FUE, which present as painless nodules in the donor area [13, 14].

Rarely infections may assume a deeper manifestation. Staphylococcal osteomyelitis of the skull has been reported post in the case of hair transplant.

### 4.4.2 Infections in the Recipient Area

The most common complication seen in the recipient area is folliculitis, with a reported incidence ranging from 1.1% to 20% [7]. But the caveat here is that folliculitis after hair transplantation has multiple aetiologies, and some of the causes may not have an infective basis [34]. Most of these lesions are self-limiting and do not impact the outcome of the hair transplant [35] (Fig. 4.4a–g). Due to common occurrence of folliculitis after HTS, many hair transplant surgeons consider them as sequela rather than a complication of HTS [35]. Folliculitis can occur in recipient area as well as the donor area, but it is far more common in the recipient area [30, 36].

The onset of folliculitis is seen as early as 2 days post-operatively and as late as 6 months after HTS [34, 35]. The inflammation commonly involves the upper or superficial part of the piliary canal up to the infundibulum or just below it. Therefore, the resolution is usually without scarring and does not affect the result of the HTS [35]. Sometimes, the involvement is deeper, and in such cases, the presentation is in the form of numerous cysts or papules with erythema and pain. These can progress to furunculosis or cellulitis and may heal with scarring, eventually affecting the result of HTS [35, 36]. A study published in 2020 mentioned that younger patients are more prone to develop folliculitis probably due to increased androgen activity leading to increased sebum secretion [34].

An example of post-operative folliculitis is presented here. A 46-year-old male with fairly advanced male pattern hair loss underwent hair transplantation using strip surgery. The post-operative recovery was uneventful. At around 6 months when the hair growth had begun, he presented with a crop of folliculitis scattered at the hairline. Conservative management using warm compresses and topical mupirocin was initiated. The folliculitis subsided in a weeks' time. The healing was scarless. He had full growth after the folliculitis episode.

Numerous theories have been put forward to determine the cause of the folliculitis, and these could be grouped broadly into non-infective and infective causes [34–37]:

Non-infective causes could be an inflammatory response to mechanical or chemical factors:

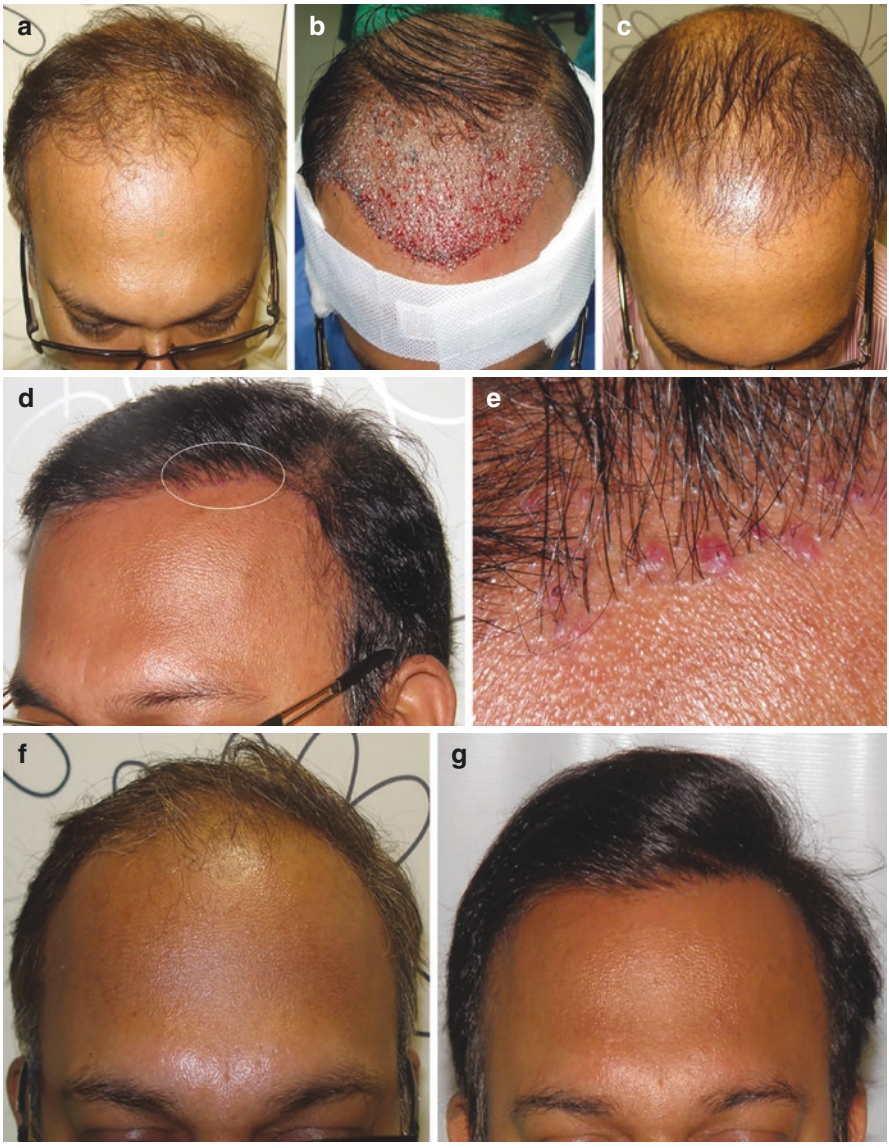


**Fig. 4.4** (**a**–**g**) Recipient site folliculitis: (**a**) before hair transplantation, (**b**) immediate post-operative, (**c**) 3 months post-operative. (**d**) Folliculitis at the hairline after more than 7 months post-operative, (**e**) the new hair growing can be seen in the lesions, (**f**) before, and (**g**) 2 years after hair transplant. Outcome unaffected by folliculitis showing to compromise in the final result

1. Injury caused by hair transection or sebaceous gland (leading to release of sebum)
2. Buried epidermis or piggy backing of grafts
3. A depth mismatch between the graft and the recipient site (grafts being implanted deeper)
4. Foreign body reaction to dermis of the implanted graft or spicules of hair or material of the spatulas on which grafts are dissected
5. Obstruction of follicular orifice by the implanted hair fragment (going into post-operative telogen and unable to shed)
6. High density of implantation
7. New hair growing, which is trapped by epidermal overgrowth at the follicular orifice (this is usually seen)
8. Response to minoxidil therapy initiated after HTS
9. Patients with acne-prone skin (high seborrheic activity) undergoing HTS are more likely to develop folliculitis

Infective causes should be suspected when the folliculitis appears top severe and persistent appearing soon after the HTS. The predisposing factors could be:

1. Poor scalp hygiene with infrequent scalp washing after HTS
2. Exposure to dusty environment post-op
3. Premature shaving or clipping of hair after HTS
4. Cross infection at the hospital
5. Poorly controlled diabetes mellitus [34–36, 38]

The organism commonly found to be the cause of infection is *Staphylococcus aureus*, but in refractory cases, other microbes like *Pseudomonas aeruginosa*, *Enterobacter* spp., *Proteus* spp., or even MRSA could be responsible [34, 37].

On histopathological examination, there is in the superficial folliculitis the inflammatory infiltrate consisting of neutrophils, lymphocytes, and macrophages seen superficially in the follicular canal up to or just below the infundibulum [35]. Due to this superficial involvement, the healing is scarless, but if it progresses to deeper planes, then scarring is inevitable.

General management irrespective of the cause would be to improve scalp hygiene with regular scalp washes, warm compresses, and topical antibiotic such as mupirocin [34]. Most folliculitis lesions resolve uneventfully without the use of oral antibiotics. If the cause is because the shedding of the transplanted hair is obstructed, simply extracting the shaft of hair resolves the folliculitis [34].

If the folliculitis appears in the immediate post-operative period and presents with a significant number of pustules and signs of inflammation (pain and erythema)

that do not respond to the general measures, then an infective aetiology must be considered. Management here would be to first collect a swab for culture and sensitivity from the lesions, and then topical antibiotic should be started. As the commonest pathogen is *Staphylococcus aureus*, oral antibiotics targeting the same should be initiated. Usually, first- or second-generation oral cephalosporins are used. However, if the folliculitis does not resolve, one should suspect MRSA or other species. Other antimicrobials used are of co-trimoxazole (sulfamethoxazole + trimethoprim), minocycline or doxycycline, dicloxacillin, rifampicin, linezolid (for refractory MRSA), etc. for management of folliculitis [20, 34–36].

Prevention includes pre-operative preparation of the scalp with povidone-iodine shampoos the night before and morning of surgery to ensure scalp preparation prior to HTS. Antimicrobial prophylaxis is a debatable issue in HTS. However, many hair transplant surgeons including the author do use antimicrobial prophylaxis [18]. The author has been using second-generation cephalosporin (cefadroxil), starting it the night prior to surgery and on the morning of surgery and continuing it 5 days post-op. Maintaining strict aseptic protocols in the procedure room including proper handwashing helps reduce the incidence of folliculitis [18, 36].

A unique case presentation of folliculitis with abscess formation was shared by a colleague (Dr. Anand Joshi, Mumbai), where the patient developed folliculitis on the 8th day post-op with a painful cyst like swelling on the forehead just below the transplanted hairline (Fig. 4.5a, b). Aspiration revealed pus which cultured MRSA with sensitivity to linezolid and was treated with incision drainage of the abscess followed by oral linezolid. The folliculitis healed uneventfully.

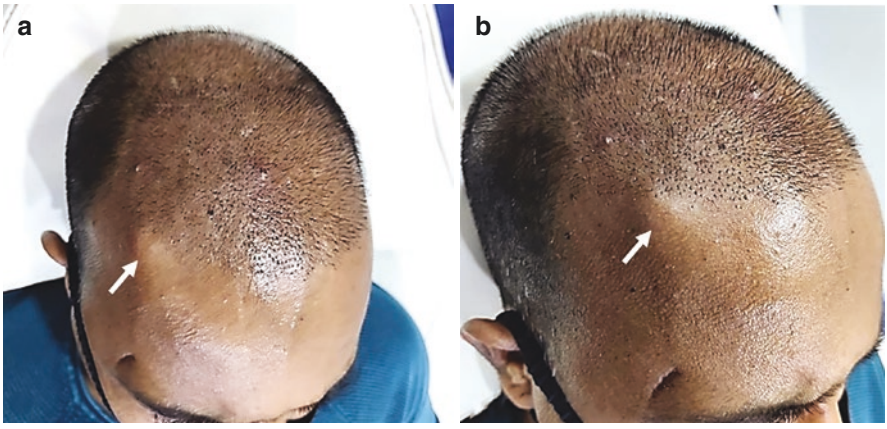


**Fig. 4.5** (**a**, **b**) Folliculitis developing in the second week after hair transplantation with abscess formation (arrow) just anterior to the transplantation hair line. The culture revealed MRSA. Photographs courtesy Dr. Anand Joshi, Plastic and Hair Transplant Surgeon Mumbai, India

### 4.4.3 Folliculitis Decalvans

Otberg et al. originally reported folliculitis decalvans developing after hair restoration surgery in punch grafts [39]. The relationship may have either been causal or fortuitous. Nevertheless, presence of bacterial biofilms in the infra-infundibular part of hair follicles has been identified and proposed to be pathogenic in folliculitis decalvans. A biofilm represents any group of microorganisms in which cells stick to each other within a self-produced matrix of extracellular polymeric substance on living or non-living surfaces. Bacteria living in a biofilm have different properties from free-floating bacteria of the same species, as the dense and protected environment of the film allows them to cooperate and interact in various ways. One benefit of this environment is increased resistance to antibiotics. Biofilms have been found to be involved in a wide variety of microbial infections in the body. Typical examples are catheter infections, formation of dental plaque with gingivitis, coating contact lenses, infections of permanent indwelling devices such as joint prostheses and heart valves, and more recently complications from dermal fillers. No matter the sophistication, biofilms are known to develop on all medical devices and tissue engineering constructs. In the case of folliculitis decalvans, bacterial biofilms form at the interface of the hair shaft. Biofilms are usually found on solid substrates submerged in or exposed to an aqueous solution. Biofilms can contain many different types of microorganism; however, some organisms will form single-species films under certain conditions. In folliculitis decalvans following hair transplantation, it is conceivable that bacteria, usually *S. aureus*, are introduced in the course of the procedure.

### 4.4.4 Deeper Infections After Hair Transplantation Surgery

Report of a patient developing osteomyelitis of the scalp was published by Jones et al. in 1980 [40]. Patient underwent a scalp reduction procedure along with hair transplantation using punch grafting technique. He developed persistent discharge from hair transplant sites. The cause was staphylococcal infection, which was treated with debridement and craniectomies and intravenous antibiotics.

## 4.5 Infections After Artificial/Synthetic Hair Implantation

Synthetic hair implants are considered in alopecia when the patient requests an immediate result with minor surgery and with a poor donor area. However, the procedure has historically been marred by poor-quality fibre and performance, resulting in serious complications. Ultimately, the US Federal Drug Administration (FDA) put a ban on their use in 1983 (Section 895.101 of 21 Code of federal regulations of FDA title 21 vol. 8 revised as of 01 April, 2004) for the following reasons:

**The fibres present risks of illness or injury due to non-biocompatibility of the fibres and non-medical performance of the implant:**

- Recurrent infections
- Rejection and periodic loss of fibres needing frequent replacement
- Frequent allergic reactions leading to severe contact dermatitis or irritant effects
- Fears about possible carcinogenicity
- Cicatricial alopecia
- Granulomatous hypersensitivity
- Cyst formation

**The fibres present fraud due to:**

- Spreading of deceptive information on the efficacy of result
- Inadequate information on risks deriving from implant

Originally, the materials were unsuitable; there was a lack of proper medical protocols and an absence of appropriate patient information on proper aftercare. Moreover, more often, there were unqualified providers, who were not trained physicians. Consequently, patients developed cutaneous complications with the risk of permanent sequelae, such as premature loss of hair, allergic reactions, irritant effects, foreign body granuloma, infection, and scarring [41–46]. One hundred cases of post-operative complications were studied by Lepaw [42] for evaluation of modes of therapy to remedy these problems. The authors found that the best results were obtained by removing the offending material and deferring cosmetic reconstruction at least 3–6 months after the fibres have been removed. They also came to the conclusion that severity of the complications makes the implantation of synthetic hair fibres into the scalp for the treatment of alopecia a dangerous and futile approach with a low-cost benefit and should therefore be abandoned totally (Fig. 4.6a–e).

This technique is not indicated in patients with diabetes mellitus, autoimmune disease, scalp diseases, alopecia that is not stabilized, lack of personal hygiene, or employment in dusty and dirty environment. Furthermore, these implants are not indicated in the temple area, low frontal scalp, or in any scalp area with thin tissue, such as the sideburns.

Colli et al. reported a case of serious inflammation in synthetic hair implants, in which microbiological studies revealed infection with both *Staphylococcus lugdunensis* and *Trichophyton tonsurans* (Fig. 4.7a–f) [47].

*S. lugdunensis* occurs both as a commensal on human skin and as a virulent coagulase-negative *Staphylococcus* that has been recognized to cause skin infections similar to *Staphylococcus aureus* [48]. The presence of bacterial biofilms in the infra-infundibular part of hair follicles has recently been identified and proposed to be pathogenic in folliculitis decalvans, a disease characterized by chronic recurrent inflammation of the hair follicle, in which *S. aureus* has a central role [49, 50]. A biofilm represents any group of microorganisms in which cells stick to each other

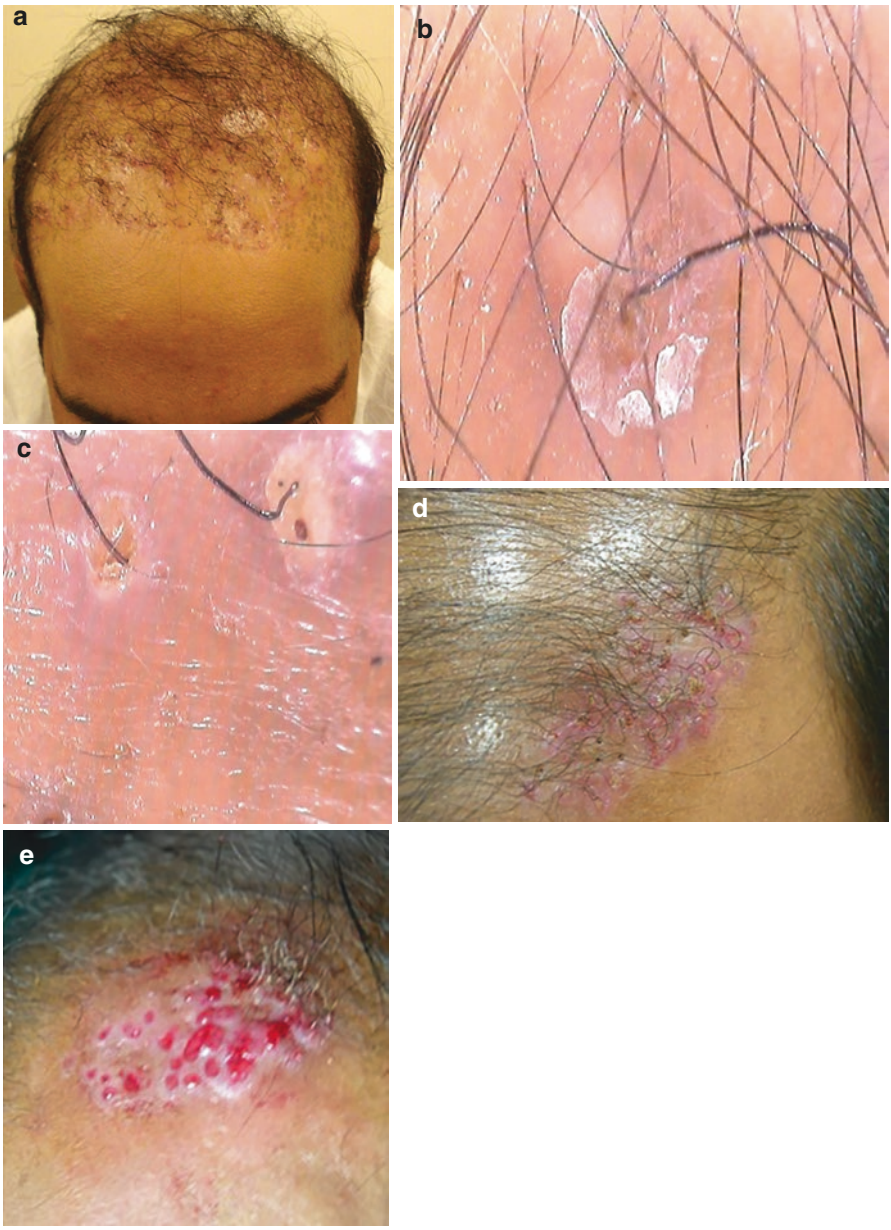


**Fig. 4.6** (**a**–**e**) Infection and inflammation after artificial hair implants: (**a**) multiple discharging sinuses, (**b**, **c**) dermoscopic view of discharging sinuses after artificial air implantation. (**d**) Case of inflammation after a test patch of artificial hair implants, (**e**) after extraction of the artificial hair fibres

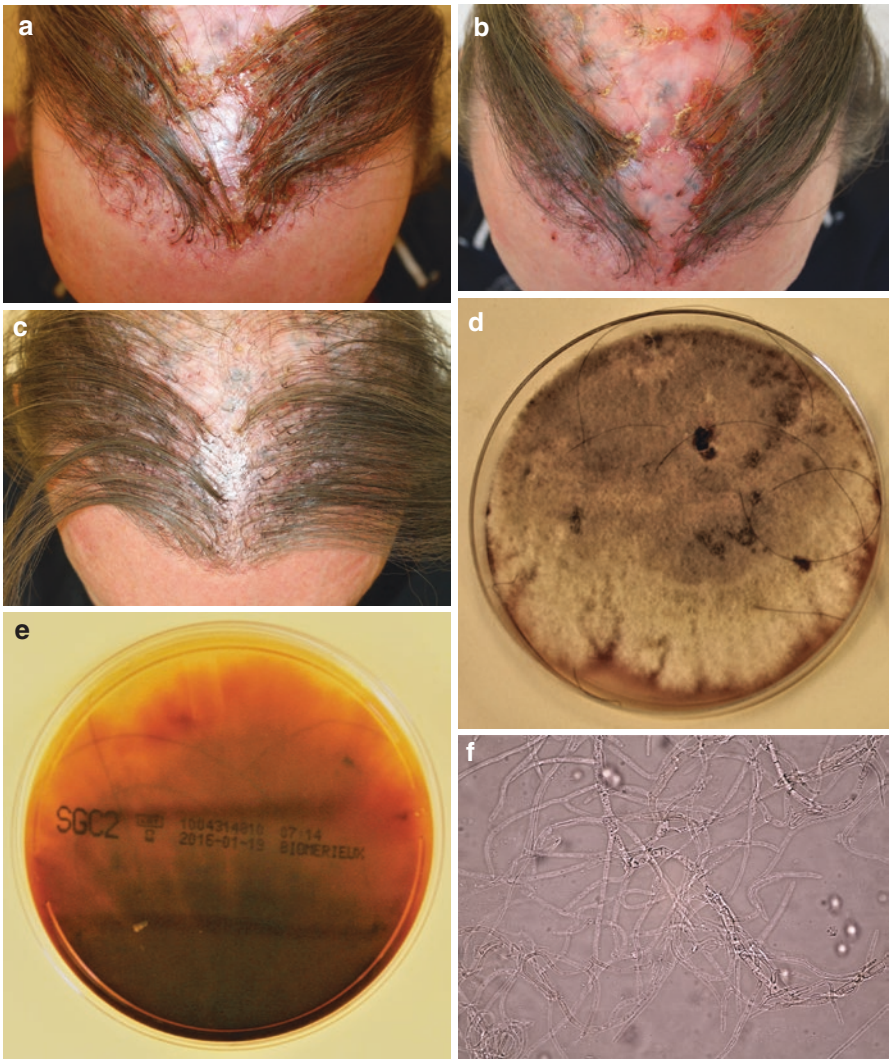


**Fig. 4.7** (**a**–**f**) Frontotemporal fringe of synthetic hair implants associated with atrophy, crusts, and erosions of the scalp (**a**) before systemic antimicrobial treatment, (**b**) after treatment, (**c**) after removal of synthetic hair implants with new implants. (**d**–**f**) *Trichophyton tonsurans*: (**d**) grayish, suede-like surface in culture, (**e**) with reddish brown reverse. (**f**) Microscopic morphology: Septate hyphae with variably shaped microconidia and intercalary chlamydoconidia (from [47])

within a self-produced matrix of extracellular polymeric substance on living or non-living surfaces. Bacteria living in a biofilm have different properties from free-floating bacteria of the same species, as the dense and protected environment of the film allows them to cooperate and interact in various ways. One advantage of this environment for the bacteria is increased resistance to antibiotics. Bacterial biofilms may impair cutaneous wound healing and reduce topical antibacterial efficiency in healing or treating infected skin wounds [51]. No matter the sophistication, biofilms are known to develop on all medical devices and tissue engineering constructs. In the case of folliculitis decalvans, bacterial biofilms form at the interface of the hair shaft. In folliculitis decalvans following hair transplantation or synthetic fibre implants (peri-implantitis), it is conceivable that the respective bacteria, in this case *Staphylococcus lugdunensis*, may have been introduced in the course of the procedure.

*T. tonsurans* is an anthropophilic dermatophyte and a common pathogen in tinea capitis. Tinea capitis may manifest in a seborrheic dermatitis-like pattern, in a black dot ringworm type, or as kerion celsi [52, 53]. However, this pathogen causes an indolent and even asymptomatic disease in the majority of affected adults, whereas more severe inflammatory cases are associated with zoophilic or geophilic species [54]. Apart from microbiological features and virulence of the fungus, inappropriate use of topical corticosteroids may worsen the infectious process since they suppress the local fungus-specific immune response. This complication is becoming more common by the increasing of self-diagnosed diseases and self-prescribed treatments [55], as in the reported case. A question that arises is when and how the fungal pathogen was introduced into the scalp, suggesting again that the hygienic and aftercare standards for synthetic hair implants were not met by the provider in question (a hairstylist) and the patient.

Safer and more effective options are available for hair restoration, with both follicular unit transplantation and follicular unit extraction offering very satisfactory results in most cases, when they are provided by trained hands.

The option of synthetic hair implants may be considered in patients who fail on hair growth-promoting agents and do not have adequate donor hair, and for whom a hair prosthesis is unacceptable. The matter was reflected on by the International Society of Hair Restoration Surgery. After evaluating all aspects on the subject, the society stated that:

> It is the view of the Society that this is a surgical procedure and as such should be confined to active participation of an experienced, licensed medical doctor in a reputable medical clinic or university setting. As with any surgical procedure, complications may occur which should be handled under a physician's care. [56]

Therefore, good post-implant care, periodical professional check-ups, and yearly implant retouches are necessary to maintain best results. Usually, problems result from lack of asepsis during the procedure, lack of patient hygiene, excessive quantity and density of implanted fibres in one session, incorrect choice of implant area, and poor aftercare.

In cases where implant-related problems, such as minor inflammation, cannot be resolved with topical cortisone and local or systemic antibiotic treatment within 15 days, an extended microbiological workup is warranted, and it may be necessary to remove the fibres.

Casañas Quintana et al. reported a case of dystrophic calcinosis of the scalp from artificial hair implants [57, 58]. Clinical examination displayed hard subcutaneous nodules, fragments of synthetic implants (Fig. 4.8a), and shedding of calculi from the scalp (Fig. 4.8b). Histopathology revealed a granulomatous foreign-body type inflammation with fibrosis and focal calcification with trans-epidermal elimination

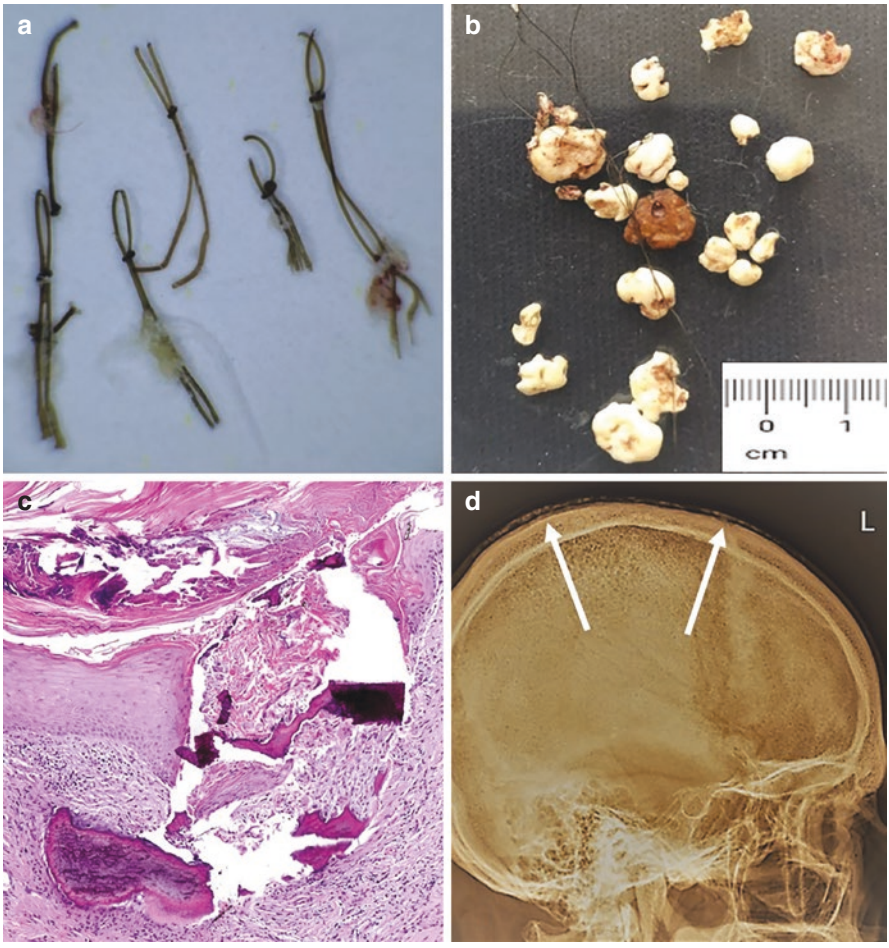


**Fig. 4.8** (**a**–**d**) Dystrophic calcinosis of the scalp from artificial hair implants: (**a**) fragments of synthetic implants, (**b**) and shedding of calculi from the scalp, (**c**) histopathology with a granulomatous foreign-body type inflammation with fibrosis and focal calcification with transepidermal elimination, (**d**) radiological images using the soft beam x-ray technique showed roundish opacities, confirming presence of subcutaneous calcifications (from [57])

(Fig. 4.8c). Radiological images using the soft beam x-ray technique showed roundish opacities, confirming presence of subcutaneous calcifications (Fig. 4.8d). The authors did not identify any pathogen. Dystrophic calcinosis of the skin is an abnormal deposition of calcium as a result of damaged, inflamed, or necrotic tissue, in the absence of abnormality of calcium metabolism, in this case a granulomatous foreign-body reaction. Treatment with corticosteroids, dapsone, doxycycline, and colchicine was unsuccessful, while synthetic hair fibre fragments were extracted without effect. Treatment with 25% topical sodium metabisulfite in petrolatum jelly was prescribed with clearing of the hard subcutaneous nodules (Fig. 4.9a, b). Except for surgical extraction of calculi, so far no standard therapy of dystrophic calcinosis of the skin has generally been accepted. Sodium metabisulfite is an inorganic compound, which oxidizes to form sodium sulphate, a metabolite of sodium thiosulphate with the ability to inhibit calcium stone formation. This case observation demonstrates yet another long-term complication of synthetic hair implants and illuminates a therapeutic option for topical treatment.

In summary, infectious complications after autologous HTS are not common but can occur due to various reasons mentioned earlier. Preventive measures put in place peri-operatively will go a long way in further reducing the incidence of infection after HTS. Starting from patient selection to pre-operative preparation, antimicrobial prophylaxis, adequate preparation of the surgical areas, proper handwashing techniques, and maintaining scalp hygiene post-operatively help in reducing infection after HTS. Maintaining a high index of suspicion in the post-operative period would also help in timely intervention if infection were to occur.

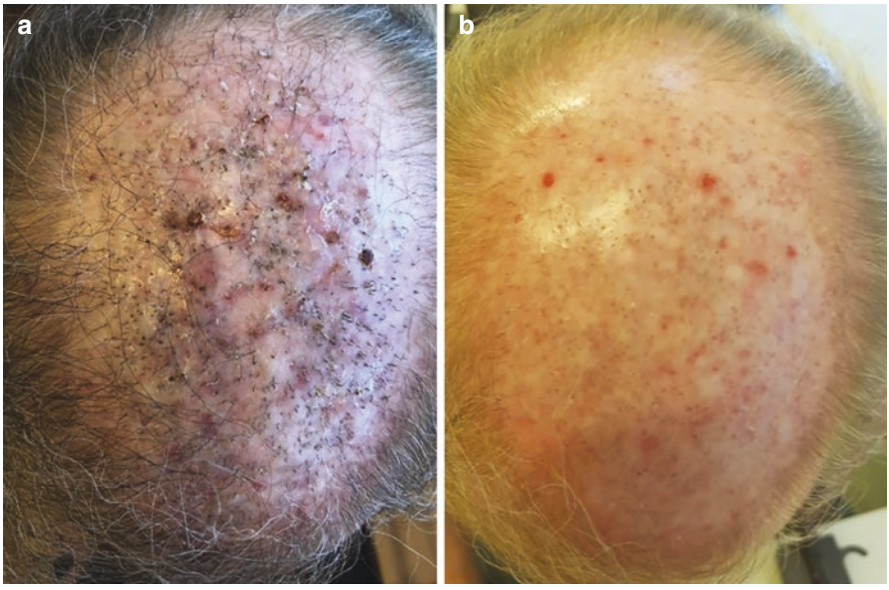


**Fig. 4.9** (**a**, **b**) Successful treatment of (**a**) dystrophic calcinosis of scalp with 25% topical sodium metabisulfite in petrolatum jelly with (**b**) clearing of hard subcutaneous nodules (from [57])

Meanwhile, synthetic implants are associated with a higher complication rate. The etiopathogenetic role of microbial biofilms as a major cause of peri-implantitis is yet to be further elucidated. For the time being, good post-implant care, periodical professional check-ups, and yearly implant retouches are necessary to maintain best results. In cases where minor implant-related problems cannot be resolved with topical cortisone and local or systemic antibiotic treatment within 15 days, an extended microbiological workup is warranted, and it may be necessary to remove the fibres. Dystrophic calcinosis of the scalp may result as late complication from artificial hair implants.

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# Fungal Diseases of the Hair and Scalp

# 5

Ralph M. Trüeb and Maria Fernanda Reis Gavazzoni Dias

## Contents



A fungus is any member of the group of eukaryotic organisms that are classified as a kingdom separately from plants, animals, protozoa, and chromista. A characteristic that places fungi in a different kingdom is chitin in their cell walls. Fungi, like animals, are heterotrophs. They acquire their food by absorbing dissolved molecules, typically by secreting digestive enzymes into their environment. Fungi do not

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photosynthesize. Growth is their means of mobility, except for spores, which may travel through air or water. Fungi are the principal decomposers in ecological systems. The fungus kingdom encompasses an enormous diversity of taxa with varied ecologies, life cycle strategies, and morphologies. Abundant worldwide, most fungi are inconspicuous because of the small size of their structures and their cryptic lifestyles in soil or on dead matter. Fungi include symbionts of plants, animals, or other fungi and also pathogenic parasites.

Fungal infection is transmittable disease caused by fungi. Fungal infections have a worldwide distribution and are common, affecting more than one billion people every year. The different types are traditionally divided according to the part of the body affected: superficial, subcutaneous, and systemic.

Fungi that cause infections include the dermatophytes, yeasts, molds, and dimorphic fungi that can exist in the form of both mold and yeast. Signs and symptoms range widely.

Superficial fungal infections include common tinea of the skin (ringworm), piedra, and yeast infections such as pityriasis versicolor, candida intertrigo, and oral thrush. Subcutaneous types include eumycetoma and chromoblastomycosis, which affect tissues in and beneath the skin. Systemic fungal infections are more serious and include cryptococcosis, histoplasmosis, pneumocystis pneumonia, aspergillosis, and mucormycosis, with pneumonia-like symptoms or meningitis.

Fungal infections are more likely to occur in people with weak immune systems, such as individuals with HIV/AIDS or on corticosteroids, cancer treatments, or antibiotics, people with diabetes, the very young, and the very old.

During the 2003 SARS outbreak, fungal infections were reported in 14.8–33% of people affected, and it was the cause of death in 25–73.7% of people with SARS [1]. During the COVID-19 pandemic, some fungal infections have been associated with COVID-19. The most common serious fungal infections in people with COVID-19 include aspergillosis and invasive candidiasis [2] COVID-19-associated mucormycosis is generally less common but as of 2021 was noted to be significantly more prevalent in India.

Diagnosis of a fungal infection is based on signs and symptoms, microscopy, or culture and sometimes requires a biopsy.

Treatment is generally with antifungal drugs and depends on the specific infection and its extent, in the form of a cream, by mouth, or injection. Some may require surgically removing the infected tissue.

As a matter of fact, the scalp was the site in which Johann Lukas Schoenlein originally reported in 1839 resp. David Gruby in the early 1840s, where human disease could be caused by fungi, specifically *Trichophyton schoenleinii* in favus resp. *Microsproum audouinii* in scalp ringworm.

The scalp may occasionally also be the site of mycetoma and of systemic fungal infections (dermatomycosis).

## 5.1 Dermatophytes

Dermatophytosis, tinea, or ringworm is a superficial fungal infection of the skin with dermatophytes. About 40 types of dermatophytes can cause ringworm. They are typically of the *Trichophyton*, *Microsporum*, or *Epidermophyton* species. Globally, approximately 20% of the population may be infected at any given time.

These fungi afflict various parts of the body. Infections of the groin and inner thighs (tinea inguinalis or jock itch) are more common in males, and infections of the lower legs (tinea cruris) are more frequent in women who shave their legs, while infections of the body (tinea corporis), face (tinea faciei), hands (tinea manuum), feet (tinea pedis or athlete's foot), and nails (tinea unguim or onychomycosis) occur equally in both sexes.

Infection of the beard area in men (tinea barbae or barber's itch) is by definition seen only in males and most commonly among agricultural workers, since transmission is more common from animal-to-human than human-to-human, making it a zoonotic disease. Prior to the introduction of modern-day antisepsis, tinea barbae was also transmitted from person to person by contaminated barber's razors or clippers, hence the term barber's itch. Three clinical types of tinea barbae are recognized:

1. Inflammatory or kerion-like (Fig. 5.1a)
2. Superficial or sycosiform type (*Sycosis parasitaria*) (Fig. 5.1b)
3. Circinate, spreading type (Fig. 5.1c)

Infections of the scalp (tinea capitis or scalp ringworm) are particularly common in children, where they can be either transmitted from animal to human or from human to human. The Latin names are for the clinical disease patterns, and not the agents that cause them.

Risk factors include using public showers, contact sports such as wrestling, excessive sweating, contact with animals, obesity, age, and poor immune function. When ringworm spreads from animals to humans, it is termed zoophilic and if between people, anthropophilic. Fungi thrive in moist, warm areas, such as locker rooms, tanning beds, swimming pools, and skin folds; accordingly, those that cause dermatophytosis may be spread by using exercise machines that have not been disinfected after use or by sharing towels, clothing, footwear, or hairbrushes.

Tinea capitis (scalp ringworm) is a dermatophytosis of the scalp and the associated hair. The different organisms causing tineas capitis may present with several different clinical patterns. Clinically, a noninflammatory and an inflammatory type occurs. The existence of an asymptomatic carrier state in tinea capitis has been repeatedly documented with its important epidemiologic implications, since silent sources are more difficult to detect and eradicate.

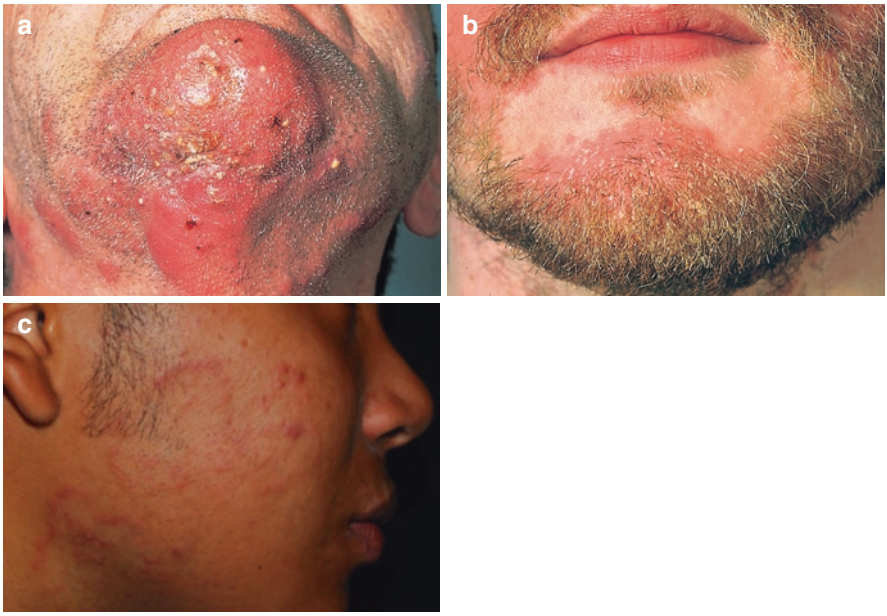


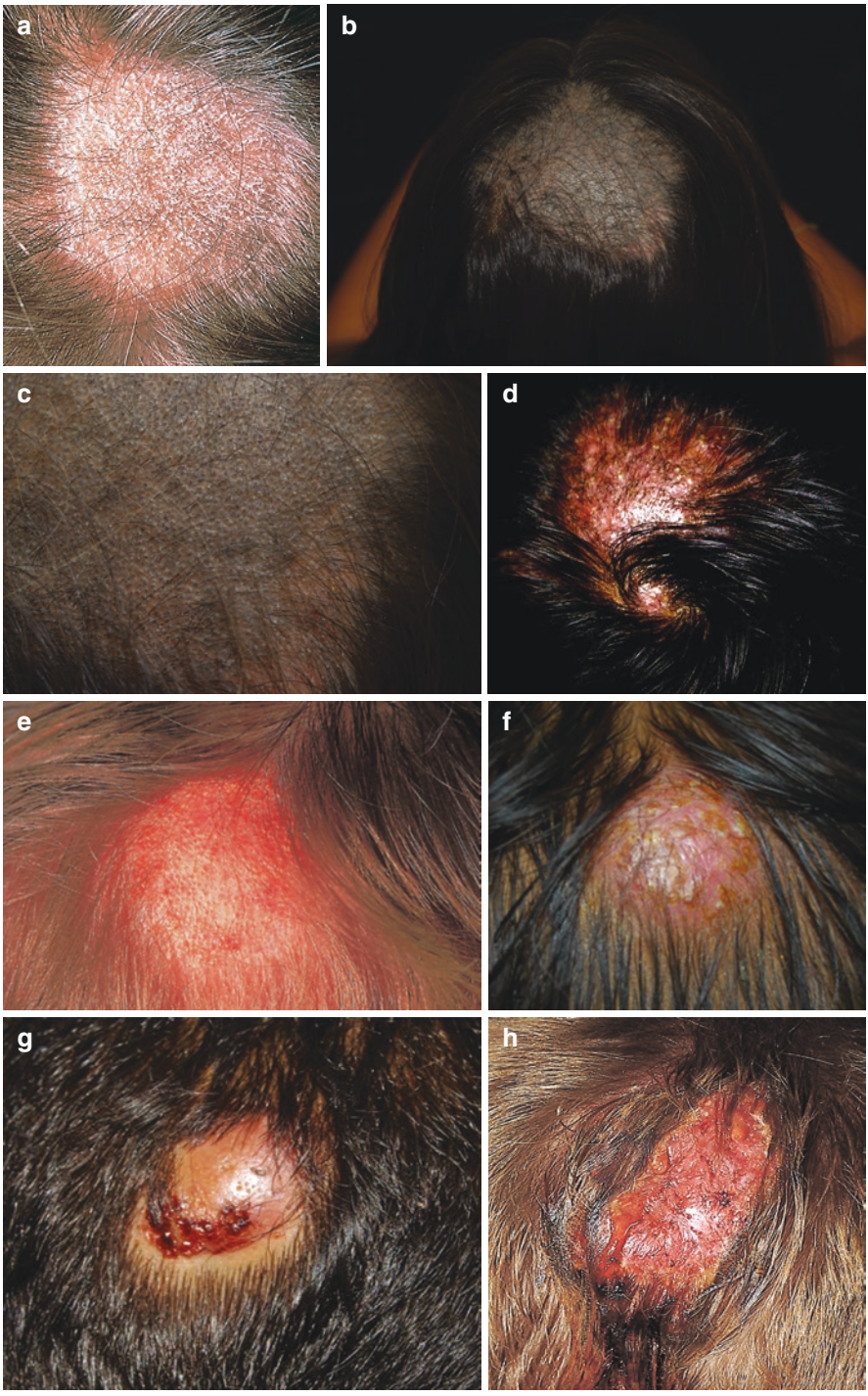

**Fig. 5.1** (**a**–**c**) Tinea barbae (barber's itch): (**a**) inflammatory kerion-like, (**b**) superficial sycosiform, (**c**) circinate spreading type (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil)

The noninflammatory type begins as a small erythematous papule surrounding a hair shaft. Subsequently, the lesion spreads centrifugally, involving the hairs in its path. Typically, there is scaling with minimal inflammation, and the hairs frequently break off just above the level of the scalp, rather than being shed entirely (Fig. 5.2a).

Black dot tinea capitis is due to extremely brittle hair shafts that break at the level of the scalp. The remnants of hair left behind in the infected follicle appear as black dots on clinical examination (Fig. 5.2b, c). There may be diffuse scaling with minimal hair loss and inflammation. When hair loss occurs, the affected areas are characteristically multiple or polygonal in outline with distinct, fingerlike margins. Black dot infections may also be quite inflammatory, ranging from a pustular folliculitis (Fig. 5.2d) to furuncle-like lesions or obvious kerion.

The inflammatory type may either present as superficial inflammatory tinea capitis with a seborrheic dermatitis-like appearance with redness and scaling with or without loss of hairs (Fig. 5.2e) and as such may not be recognized, especially in

**Fig. 5.2** (**a**–**h**) Tinea capitis (scalp ringworm): (**a**) superficial non-inflammatory, (**b**, **c**) black dot alopecia (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), (**d**) with pustular folliculitis (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), (**e**) superficial inflammatory, (**f**) deep inflammatory (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), (**g**, **h**) kerion (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil)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adults, or as deep inflammatory tinea capitis with a spectrum of inflammatory changes ranging from a pustular folliculitis (Fig. 5.2f) to a kerion, which presents as an inflammatory, boggy mass, studded with broken hairs, and oozing purulent material from the follicular orifices (Fig. 5.2g, h).

The inflammatory type of tinea capitis is caused most commonly by zoophilic organisms, such as *Microsporum canis* or geophilic dermatophytes, such as *Microsporum gypseum*. The noninflammatory type is produced most commonly by *Microsporum audouinii* or *Microsporum ferrugineum*. Black dot tinea capitis is most often caused by endothrix organisms, such as *Trichophyton tonsurans* or *Trichophyton violaceus*.

Favus or tinea favosa is a chronic mycotic infection of the scalp, glabrous skin, and/or nails that is characterized by the formation of yellowish crusts within the hair follicle (scutula) (Fig. 5.3a, b) and is most commonly caused by *Trichophyton schoenleinii* (Fig. 5.3c, d). In the early stages of infection, the hyphae invade the hair follicle and gradually distend the follicular opening. On microscopic examination, the favus hair shows hyphae coursing lengthwise of the hair shaft and no arthroconidia. The concentrations of hyphae and keratinous debris take root at the opening of the hair follicle, where they gradually expand to form yellowish, cup-shaped structure that may become 1 cm or more in diameter. The center of such a scutulum is often pierced by a single, lusterless, dry hair.

Favus is typically a chronic infection that begins early in life and commonly extends into adulthood. Up until the advent of modern therapies, favus was widespread worldwide. Prior to Schönlein's recognition of it as a fungal disease, it was frequently confused with leprosy, and European sufferers were sometimes confided to leprosaria. Today, due to this species' high susceptibility to the modern antifungals, it has been eliminated from most parts of the world except rural central Asia and scattered rural areas of Africa associated with conditions of poor hygiene, malnutrition, and squalor. It is mainly a disease connected to demographic poverty and isolation but is so readily treatable that it is among the diseases most likely to be completely eliminated by modern medicine.

The variable clinical presentations are in part due to the fungal organism involved with its specific ecology and type of hair involvement. The organisms associated with clinical types of tinea capitis are summarized in Table 5.1.

Diagnosis of tinea capitis requires a high rate of suspicion. At times, tinea capitis may be difficult to distinguish from other scaling skin diseases, such as psoriasis and seborrheic dermatitis. Pustular lesions on the scalp of children are more commonly associated with fungal infections, while in adults, they are more commonly seen with bacterial infection.

The basis for the diagnosis is a positive microscopic examination (Fig. 5.4a) and mycological culture of epilated hairs for evaluation of colony morphology (Fig. 5.4b) and microscopic morphology (Fig. 5.4c) [3]). Using traditional methods to verify the existence of a fungal infection in children with suspected tinea capitis is a cumbersome process. Scraping scale and pulling hairs for culture or microscopic examination can be time-consuming and uncomfortable for the child. For this purpose, the brush method has been proven a reliable, painless, and more expedient way to

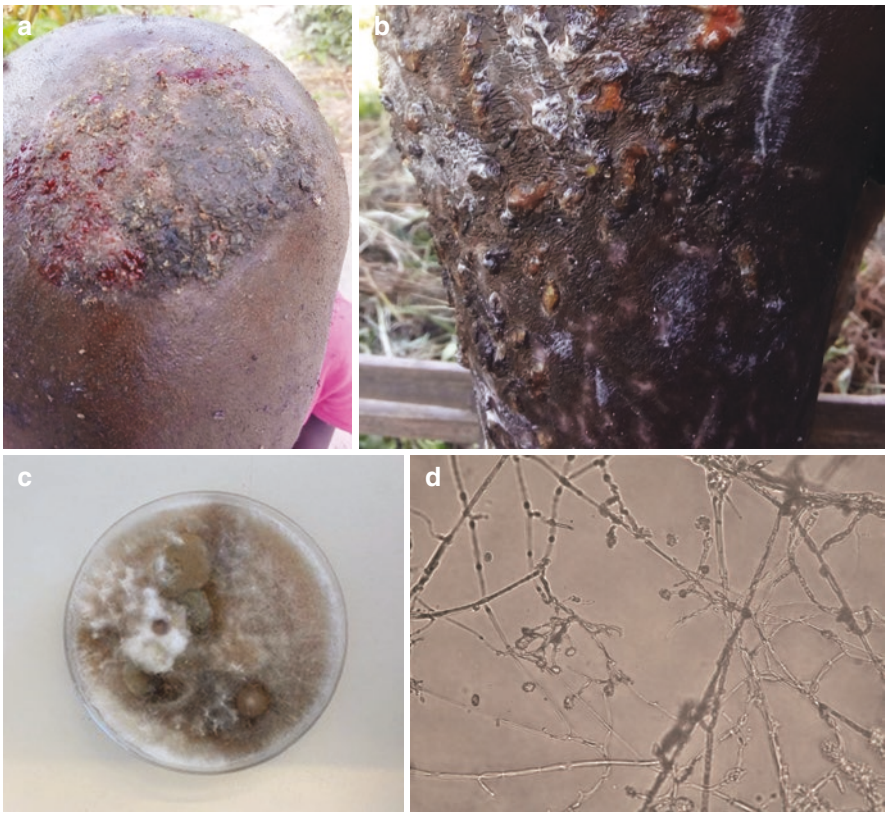



**Fig. 5.3** (**a**–**d**) Tinea favosa (favus): (**a**) of the scalp and (**b**) glabrous skin. Yellowish, circular, cup-shaped crusts (scutula) grouped in patches like a honeycomb. These increase in size and become crusted over so that the characteristic lesion eventually can only be seen round the edge of the scab. (**c**) Colony morphology (*Trichophyton schoenleinii*): whitish, waxy, or slightly downy, with a heaped or folded appearance. (**d**) Microscopic morphology (*Trichophyton schoenleinii*): hyphae are septate, highly irregular, and knobby. The subsurface hyphae usually form characteristic antler-like branching structures (favic chandeliers); they have swollen tips that resemble nail heads

**Table 5.1** Organisms associated with clinical types of tinea capitis

| Inflammatory | Noninflammatory | Black dot | Favus |
|---|---|---|---|
| *M. canis*<br>*M. gypseum*<br>*T. mentagrophytes*<br>*T. tonsurans*<br>*T. verrucosum*<br>*T. schoenleinii*<br>*M. audouinii*<br>*M. nanum* | *M. audouinii*<br>*T. tonsurans*<br>*M. canis*<br>*M. ferrugineum* | *T. tonsurans*<br>*T. violaceum* | *T. schoenleinii*<br>*T. violaceum*<br>*M. gypseum* |

obtain cultures from children with suspected tinea capitis [4]. It can also be used for detection of the carrier status within affected families [5] and in pets, specifically cats [6]. In our experience, the toothbrush sampling technique is most effective for this purpose [7]. Fungal culture samples from the scalp or the haircoat are collected by stroking the respective skin surface with a sterile toothbrush. Specimens are inoculated onto Sabouraud agar and incubated at 25 °C for 21 days. The optimum inoculation technique is to press the toothbrush bristles onto the agar plates to maximize growth of the fungus and minimize introduction of contaminant inoculation [8].

Wood's lamp examination will reveal bright green to yellow-green fluorescence of hairs infected by *M. canis*, *M. audouinii*, *M. rivalieri*, and *M. ferrugineum* and a dull green or blue-white color of hairs infected by T. *schoenleinii* [9].

In individuals with *M. canis* infection, scalp dermoscopy will show characteristic small comma hairs [10] (Fig. 5.4d) or corkscrew hairs (Fig. 5.4e).

Histopathology of scalp biopsy shows fungi sparsely distributed in the stratum corneum and hyphae extending down the hair follicle, placed on the surface of the hair shaft. These can be made visible with either the periodic acid-Schiff (PAS) (Fig. 5.4f) or Grocott's methenamine silver stain (GMS) stain. While the former will only stain living fungal organisms magenta, the latter will stain both living and dead fungal organisms brown to black. These findings may be associated with a neutrophilic (within the hair follicle) or granulomatous (perifollicularly) inflammatory tissue reaction.

Due to the risk of permanent scarring alopecia (Fig. 5.5a–c), treatment of tinea capitis should be initiated promptly and, independent of the type of clinical presentation or age of the patient, should always be systemic for successful management (Fig. 5.6a–c). While griseofulvin has been the original systemic antimycotic agent successfully introduced in 1958 for treatment of fungal infections of the scalp and nails, as well as of the skin when antifungal creams have not worked, and the gold standard for the treatment of tinea capitis, today, it has been replaced with the newer antimycotic agents terbinafine and itraconazole for better compliance reasons (griseofulvin must be ingested with a fatty meal and has high rate of adverse effects, such as nausea, diarrhea, headache, trouble sleeping, and feeling tired, and long treatment duration). Terbinafine given for 2 to 4 weeks is at least as effective as griseofulvin given for 6 to 8 weeks for treatment of *Trichophyton* scalp infections (Fig. 5.7: endotrich infection) However, griseofulvin is more effective than terbinafine for treatment of *Microsporum* scalp infections. In the latter case, oral itraconazole is preferred for a duration of 4 to 6 weeks or sometimes longer (up to 12 weeks), depending on clinical and mycological findings [11] (ectotrich infection).

It is known that *T. schoenleinii* can survive for years on epilated hair. For this reason, cleanliness with removal of hairs or other sources of infection is an important factor in controlling the disease [12]. Treatment of tinea capitis (in children) is summarized in Table 5.2.

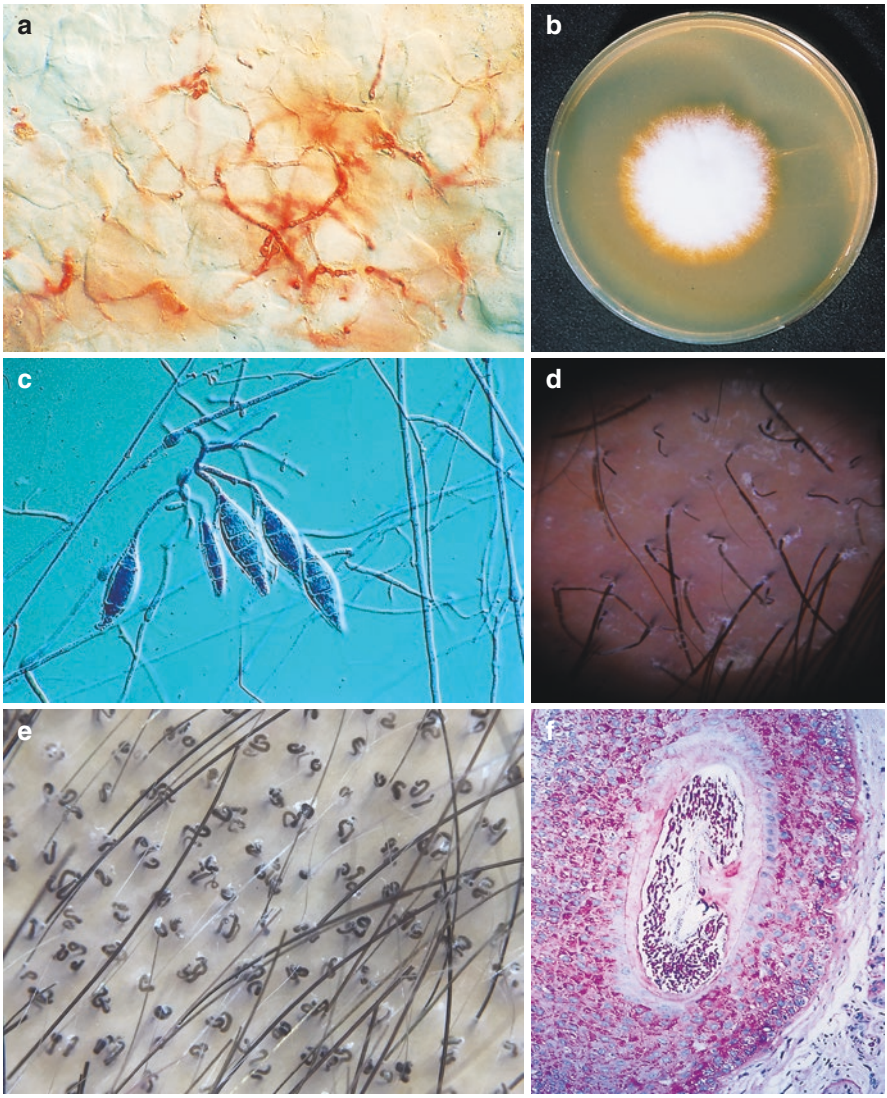



**Fig. 5.4** (**a**–**d**) Diagnostic techniques in mycology: (**a**) direct microscopic examination with visualization of fungal hyphae (Congo red), (**b**) mycological culture (Sabouraud agar), (**c**) with direct visualization of microscopic fungal morphology (lactophenol cotton blue), (**d, e**) dermoscopy of scalp: (**d**) comma hairs (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), and (**e**) corkscrew hairs, (**f**) histopathology with visualization of fungal hyphae in the biopsy (PAS stain)

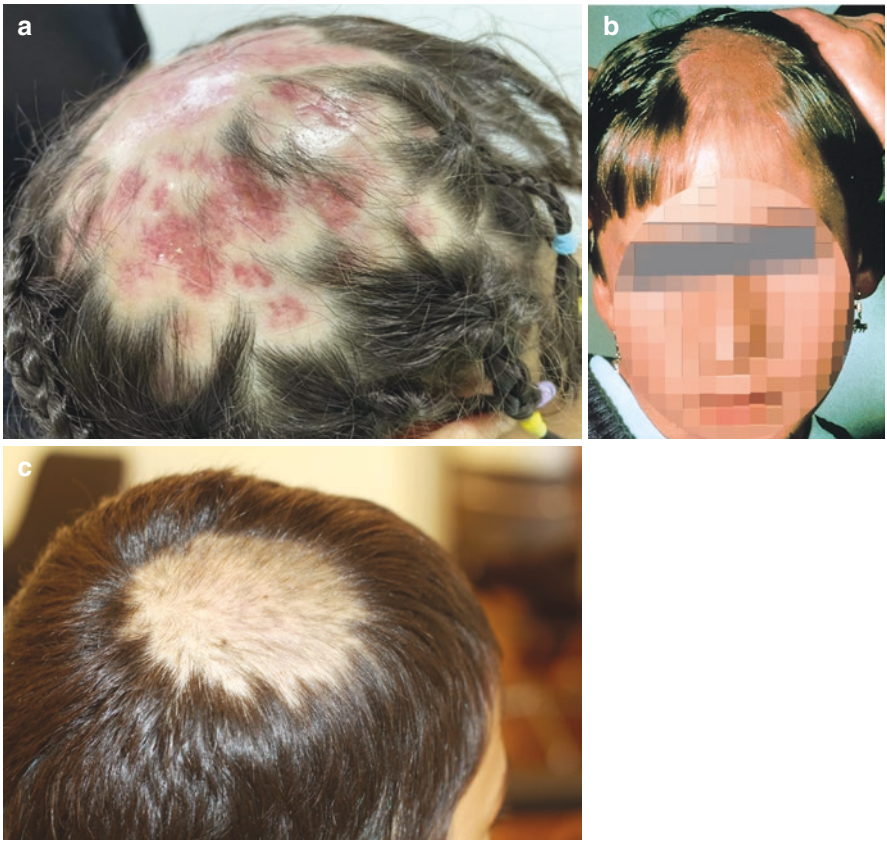



**Fig. 5.5** (**a**–**c**) Tinea capitis management: (**a**) due to potential widespread scarring and (**b**) permanent alopecia, treatment should be prompted early and with a systemic antimycotic agent, independent of patient age, clinical presentation type, or fungus species. However, choice of antimycotic agent and duration of treatment will depend on the fungal specie. (**c**) Partial regrowth of hair

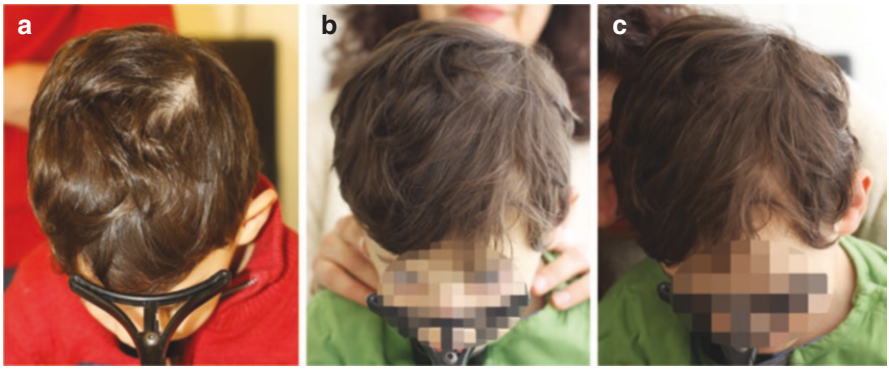



**Fig. 5.6** (**a**–**c**) Example of successful treatment of tinea capitis with total regrowth of hair

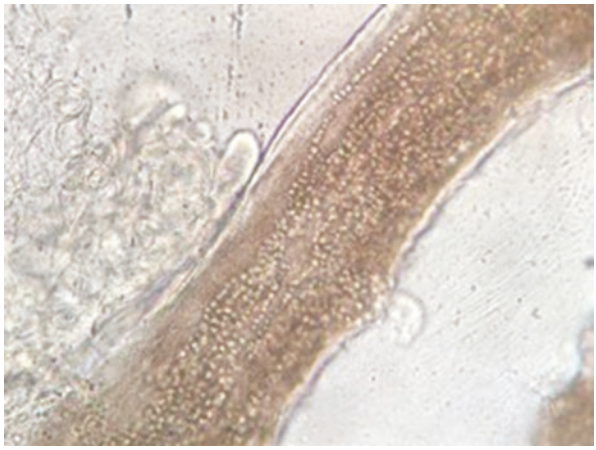


**Fig. 5.7** Endotrich infection. Anthrophilic pathogens, such as *T. tonsurans*, mainly grow endotrich (penetrating into the hair), while zoophilic pathogens, such as *M. canis*, grow ectotrich (around the hair) with large spore cuffs. Therefore, zoophilic pathogens are highly contagious and need a longer treatment time

**Table 5.2** Treatment of tinea capitis (children)

| |
|---|
| • Systemic antimycotic treatment: in the case of endotrich infection with *Trichophyton* spp. with oral terbinafine 6 mg/kg body weight per day for 2–4 weeks; in the case of ectotrich infection with *Microsporum* spp. with oral itraconazole 5 mg/kg body weight per day for 4–6 weeks (or sometimes longer depending on clinical and mycological findings), in combination with |
| • Topical antimycotic treatment, either as shampoo (selenium disulfide, ketoconazole, or povidone iodine) or topical antimycotic agent (ciclopiroxolamine, an imidazole, or terbinafine) |
| • May combine oral prednisone 1 mg/kg body weight per day for 1–2 weeks in case of deep inflammatory tinea (Kerion) |
| • Combine with oral antibiotic, preferably an oral macrolide antibiotic, if secondary pathogenic bacterial infection is present. |
| • Check for carrier status for sanitation of family members or pets, depending on anthropophilic or zoophilic fungal agent resp. detected in mycologic culture |

Dermatophytid reactions (*Trichophyton*, *Microsporum*) are fungus-free disseminated skin lesions resulting from induced sensitization in patients with fungal infections. They are usually accompanied by a reactive delayed trichophytin skin test. Clinically, dermatophytid reactions may take several forms, including follicular papules (Fig. 5.8), erythema nodosum, vesicular id reactions of the hands and feet, erysipelas-like, erythema annulare centrifugum, urticaria, and vasculitis. These reactions tend to occur at the height of the dermatophyte infection, or just after initiation of systemic antifungal therapy. The mechanism responsible for the id reaction is believed to involve an immunologic response to systemically absorbed fungal antigen. Disappearance occurs when the dermatophyte infection is successfully treated. In case of especially widespread or inflammatory id reactions, a short course of concomitant corticosteroid therapy in addition to the antifungal agent may be warranted.

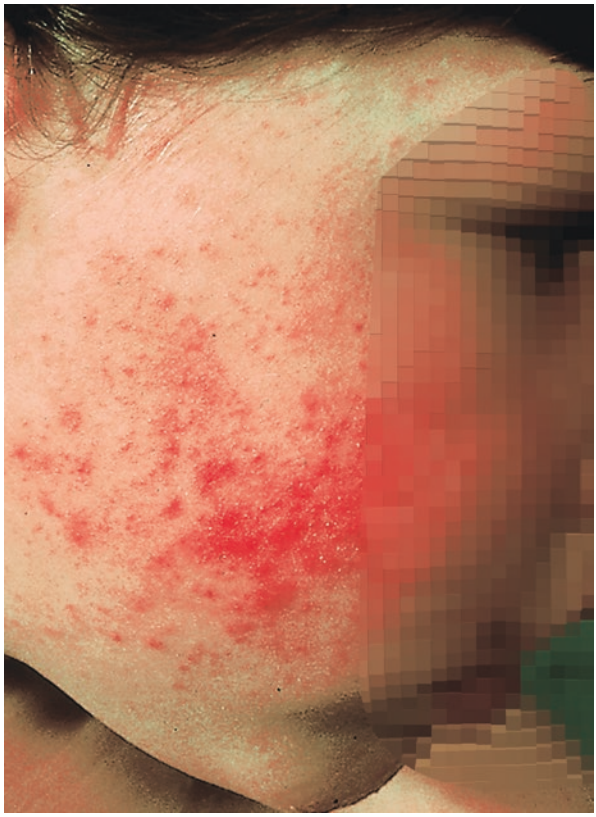


**Fig. 5.8** Papular dermatophytid reaction

## 5.2 Yeasts

Yeasts are eukaryotic, single-celled microorganisms classified as members of the fungus kingdom. The first yeast originated hundreds of millions of years ago, and at least 1500 species are currently recognized. They are estimated to constitute 1% of all described fungal species. Yeasts are unicellular organisms that evolved from multicellular ancestors, with some species having the ability to develop multicellular characteristics by forming strings of connected budding cells known as pseudohyphae or false hyphae.

### 5.2.1 Candida

Candidiasis is a fungal infection due to any type of *Candida*, a yeast. More than 20 types of *Candida* can cause infection with *Candida albicans* being the most common.

*Candida* yeasts are generally present in healthy humans, frequently part of the human body's normal oral and intestinal flora, and particularly on the skin. However,

their growth is normally limited by the human immune system and by competition of other microorganisms, such as bacteria occupying the same locations in the human body. *Candida* requires moisture for growth, notably on the skin.

Signs and symptoms of candidiasis vary depending on the anatomical area affected and the immunity of the individual.

In healthy, immunocompetent individuals, candidiasis is usually a localized infection of the skin, fingernails or toenails, or mucosal membranes, including the oral cavity and pharynx (thrush), esophagus, and the genitalia. Signs and symptoms of candidiasis in the skin include itching, irritation, and chafing or broken skin.

In immunocompromised individuals, *Candida* infections in the esophagus occur more frequently than in healthy individuals and have a higher potential of becoming systemic, causing a much more serious condition, a fungemia called candidemia.

Factors that increase the risk of candidiasis include HIV/AIDS, mononucleosis, cancer treatments, steroids, stress, antibiotic usage, diabetes, and nutrient deficiency. Hormone replacement therapy may also be a predisposing factor. Use of inhaled corticosteroids increases risk of *candidiasis* of the mouth. Inhaled corticosteroids with other risk factors such as antibiotics, oral glucocorticoids, not rinsing mouth after use of inhaled corticosteroids, or high dose of inhaled corticosteroids put people at even higher risk. Treatment with antibiotics can lead to eliminating the yeast's natural competitors for resources in the oral and intestinal flora, thereby increasing the severity of the condition. Almost 15% of people with weakened immune systems develop a systemic illness caused by *Candida* species [13]. Diets high in simple carbohydrates have been found to affect rates of oral candidiasis [14]. Among individuals being treated in intensive care units, the mortality rate is about 30–50% when systemic candidiasis develops [15].

Diagnosis of a *Candida* infection is done either via microscopic examination or culturing.

For identification by light microscopy, a scraping or swab of the affected area is placed on a microscope slide. A single drop of 10% potassium hydroxide (KOH) solution is then added to the specimen. KOH dissolves the skin cells but leaves the *Candida* cells intact, permitting visualization of pseudohyphae and budding yeast cells typical of *Candida* spp.

For the culturing method, a sterile swab is rubbed on the infected skin surface. The swab is then streaked on a culture medium. The culture is incubated at 37 °C for several days, to allow development of yeast or bacterial colonies. Characteristics such as morphology and color of the colonies may allow initial diagnosis of the organism causing disease symptoms (Fig. 5.9a, b).

Candidiasis may be divided into the following types:

**Mucosal candidiasis**
- Oral candidiasis (thrush, oropharyngeal candidiasis)
- Pseudomembranous candidiasis
- Erythematous candidiasis
- Hyperplastic candidiasis
- Denture-related stomatitis—*Candida* is involved in about 90% of cases
- Angular cheilitis—*Candida* is responsible for about 20% of cases, mixed infection of *C. albicans* and *Staphylococcus aureus* for about 60% of cases.
- Median rhomboid glossitis
- Candidal vulvovaginitis
- Candidal balanitis—almost exclusively occurring in uncircumcised males
- Esophageal candidiasis (candidal esophagitis)
- Gastrointestinal candidiasis
- Respiratory candidiasis

**Cutaneous candidiasis**
- Candidal folliculitis
- Candidal intertrigo
- Candidal paronychia
- Perianal candidiasis—may present as pruritus ani
- Candidid
- Chronic mucocutaneous candidiasis (Fig. 5.9b, c)
- Congenital cutaneous candidiasis
- Diaper candidiasis
- Erosio interdigitalis blastomycetica
- Candidal onychomycosis

**Systemic candidiasis**
- Candidemia, a form of fungemia, which may lead to sepsis
- Invasive candidiasis (disseminated candidiasis)—organ infection by *Candida*
- Chronic systemic candidiasis (hepatosplenic candidiasis)—sometimes arises during recovery from neutropenia
- Antibiotic candidiasis (iatrogenic candidiasis)

**Alternative medicine**
- A 2005 publication noted that "a large pseudoscientific cult" [16] has developed around the topic of *Candida*, with claims stating that up to one in three people is affected by yeast-related illness, particularly a condition called "candidiasis hypersensitivity" [17]. Some practitioners of alternative medicine have promoted these purported conditions and sold dietary supplements as supposed cures; a number of them have been prosecuted

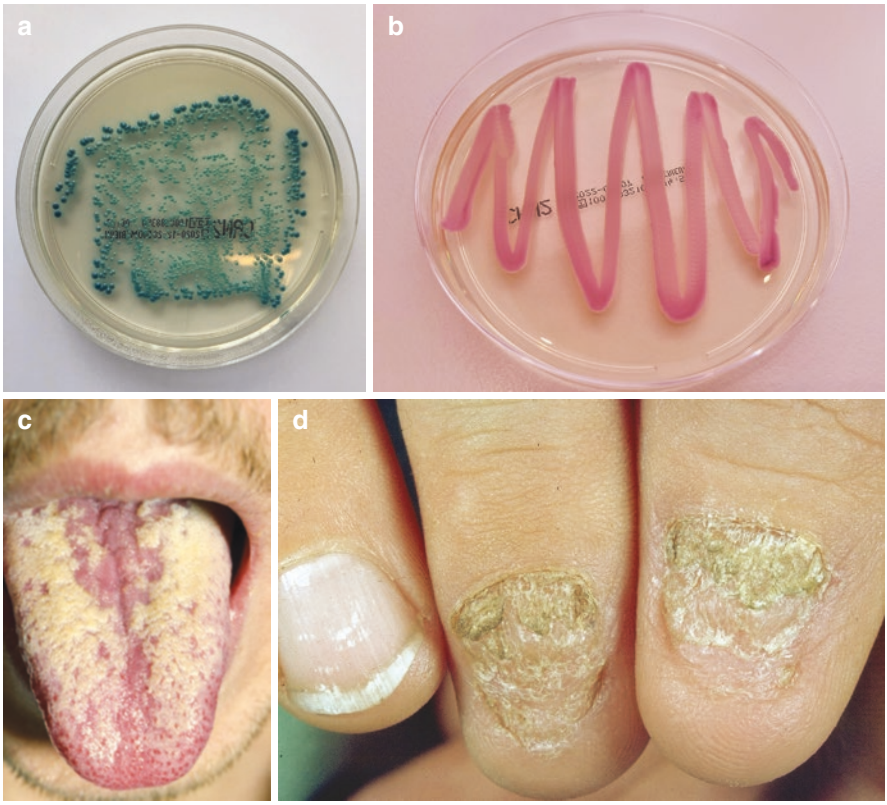



**Fig. 5.9** (**a**–**d**) *Candida* spp.: (**a**) *Candida albicans*. Identification in culture on chromogenic *Candida* agar. *C. albicans* can be identified by the blue color of colonies. The concept of developing chromogenic differential media for *Candida* came from the observation that *C. albicans* produces an enzyme N-acetyl-galactosaminidase, which can break down chromogenic hexosaminidase substrates incorporated in a medium. (**b**) *Candida tropicalis*. Identification in culture on chromogenic *Candida* agar by pink color. (**c**, **d**) Chronic mucocutaneous candidiasis: (**c**) involvement of oral cavity and (**d**) nails. Patients may have associated alopecia totalis

Besides bacteria and dermatophytes, *Candida albicans* may rarely cause folliculitis, particularly in the beard area of adult men. Predisposing factors are seborrhea, diabetes, HIV infection, systemic corticosteroids, immunosuppressive treatment, and previous long-term treatment of skin lesions with topical glucocorticosteroid or antibiotics. Occasionally, oral thrush may be the source of infection. Different clinical types of *Candida* folliculitis have been described:

- Similar to impetigo contagiosa with honey yellow crusts
- Folliculitis simplex with small follicular pustules
- Tinea barbae with small nodules covered with crusts
- Perioral dermatitis-like
- Acne conglobate-like with multiple papular pustular lesions
- Disseminated candidiasis in intravenous heroin abusers with skin lesions confided to the scalp and other hair-bearing areas

Oral fluconazole is found to be very effective in this condition and should be considered as first-line treatment. It is well absorbed after oral intake and is highly lipophilic, preferentially redistributing in the skin. Its action mechanism is the inhibition of the fungal cytochrome P450-dependent enzymes that block the synthesis of ergosterol [18].

Disseminated candidiasis in intravenous heroin abusers with skin lesions confided to the scalp and other hair-bearing areas, such as the beard, seems to represent a distinctive clinical presentation. Originally reported by Collignon and Sorrell in 1983 [19], the condition has been confirmed by several other authors [20–23]. The characteristic clinical picture is widely different from that of classic disseminated candidiasis in immunodeficient patients. Collignon and Sorrell's indicator cases were seven young men who developed similar manifestations of disseminated candidiasis after a single episode of intravenous heroin abuse. Sequential development of lesions of the eye (chorioretinitis), skin (deep-seated scalp nodules and pustulosis), and bone or costal cartilage (vertebrae, costal cartilage, knees, and sacroiliac) was noted within 10 days after injection. Skin lesions were confined to the scalp and other hair-bearing areas. *Candida albicans* was cultured readily from the affected skin. Histological examination of scalp biopsy specimens showed infiltration of hair follicles with chronic inflammatory cells and *C albicans*. Pseudohyphae of *C. albicans* were identified in and around hair shafts. The skin, skeletal, and small eye lesions resolved on systemic treatment with 1 g amphotericin B plus flucytosine. Fortuna et al. report a rare case of scalp infection by *Candida albicans* in an immunocompetent patient and independent of intravenous drug abuse and cautioned dermatologists to not exclude *Candia* infection of the scalp in an immunocompetent patient and perform the respective mycological workup by means of multiple swabs from the affected area. Typically, bacteriological culture is negative. Treatment was successful with oral fluconazole 100 mg bid for 1 month [24].

The autoimmune polyendocrinopathy syndrome with chronic mucocutaneous candidiasis is an autosomal recessive disease caused by mutations in the autoimmune regulator gene and characterized by the clinical triad of chronic mucocutaneous candidiasis (Fig. 5.9c, d), hypoparathyroidism, and adrenal insufficiency.

Additional features may be insulin-dependent diabetes mellitus, chronic atrophic gastritis with pernicious anemia, hypogonadism, alopecia areata, and vitiligo. Onset is in childhood, candidiasis is usually the first symptom, and manifestations continue to appear until the fifth decade, including alopecia. The acquired adult form of chronic mucocutaneous candidiasis may be associated with a thymoma [25].

### 5.2.2 Pityrosporum

*Pityrosporum* or *Malassezia* is a genus of fungi that are naturally found on skin surfaces of many animals and humans.

*Malassezia* was originally identified by the French anatomist and histologist Louis-Charles Malassez (1842–1909) in the late nineteenth century.

French dermatologist Raymond Sabouraud (1864–1938) identified a dandruff-causing organism in 1904 and named it *Pityrosporum malassezia*, in honor of Malassez, but at the species level as opposed to the genus level. When it was determined that the organisms were the same, the term *Malassezia* was judged to possess priority.

Due to progressive changes in their nomenclature, some confusion exists about the naming and classification of *Pityrosporum* yeast species.

In the mid-twentieth century, it was reclassified into *Pityrosporum* (*Malassezia*) *ovale*, which is lipid-dependent and found only on humans. *P. ovale* was later divided into two species, *P. ovale* and *P. orbiculare*, but current sources consider these terms to refer to a single species of fungus, with *M. furfur* the preferred name. *Pityrosporum* (*Malassezia*) *pachydermatis* is found on the skin of most animals. *Malassezia pachydermatis* is a species that is associated with otitis externa in dogs.

As the fungus requires fat to grow [26], it is most common in areas with many sebaceous glands, such as the scalp, face, and upper part of the body.

In the mid-1990s, scientists at the Pasteur Institute in Paris, France, discovered additional species. As of April 2021, Species Fungorum accepts 22 species of *Malassezia*. Work on these yeasts has been complicated because they require specific growth media and grow very slowly in laboratory culture [27]. Identification of *Malassezia* on skin has been aided by the application of molecular or DNA-based techniques.

*Malassezia* is among the many mycobiota undergoing laboratory research to investigate whether it is associated with types of disease. These investigations show that the *Malassezia* species causing most skin disease in humans, including the most common cause of dandruff and seborrheic dermatitis, is *M. globosa*, though *M. restricta* is also involved [28]. The hypopigmentation or hyperpigmentation on the trunk of tinea versicolor (pityriasis versicolor) is also due to infection by this fungus. Allergy tests for these fungi are also available.

Dandruff is a skin condition that mainly affects the scalp, with flaking that is sometimes associated with mild itchiness. The dandruff scale is a cluster of corneocytes, which have retained a large degree of cohesion with one another and detach as such from the surface of the stratum corneum. The size and abundance of scales are heterogeneous from one site to another and over time. Parakeratotic cells often make up part of dandruff (Fig. 5.10a). Their numbers are related to the severity of the clinical manifestations, which may also be influenced by seborrhea (Fig. 5.10b).

The characteristics of the epidermal turnover time, detachment and clusters of corneocytes, and scalp condition in the normal scalp, dry scalp, dandruff, seborrheic dermatitis, and scalp psoriasis are summarized as follows:

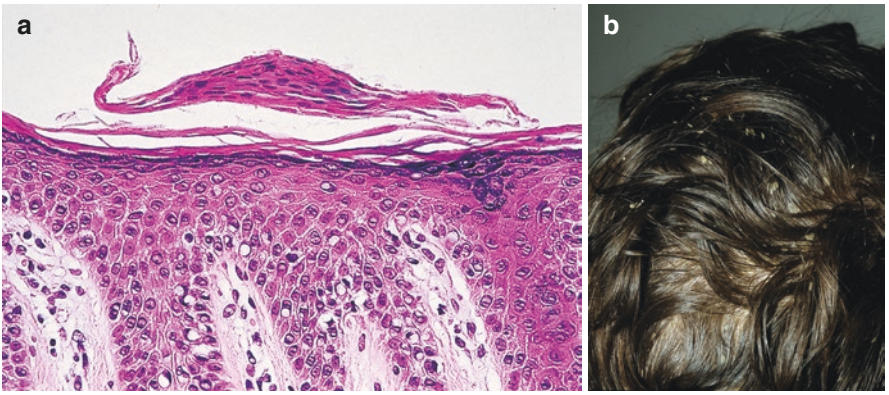



**Fig. 5.10** (**a**–**d**) Dandruff: (**a**) histopathology: cluster of parakeratotic corneocytes, (**b**) seborrhea with dandruff, (**c**) scheme of events underlying the pathogenesis of dandruff, and (**d**) targets for management

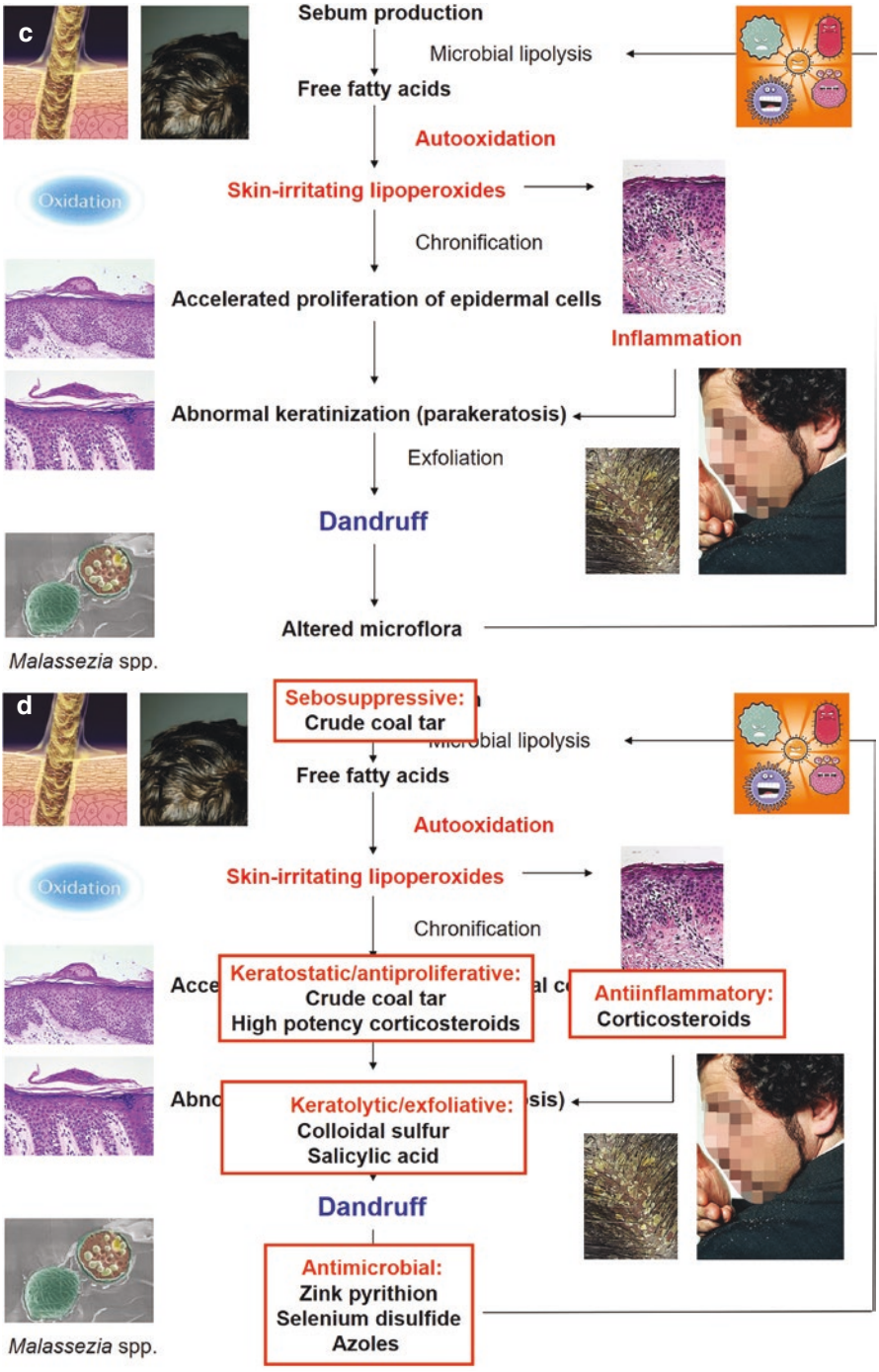
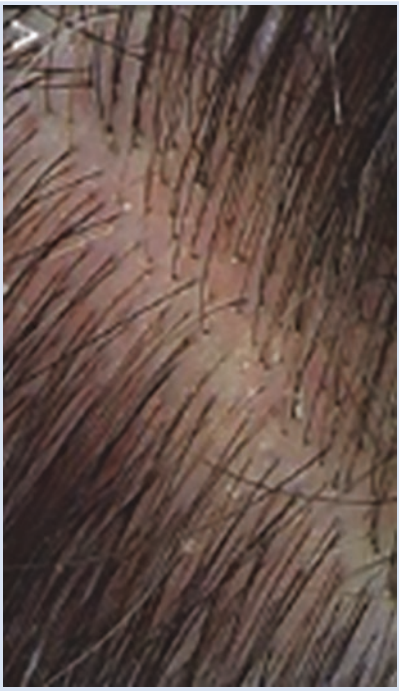
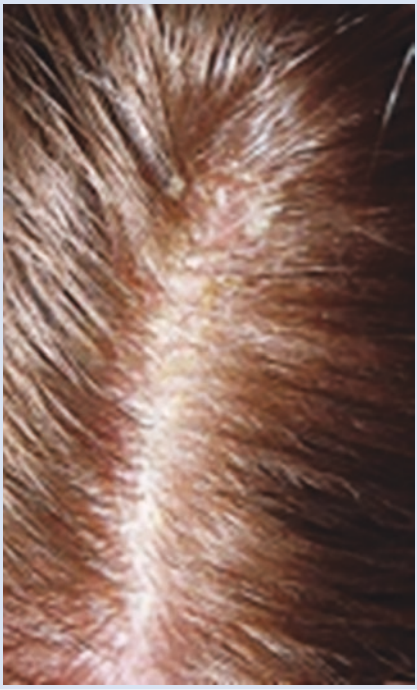
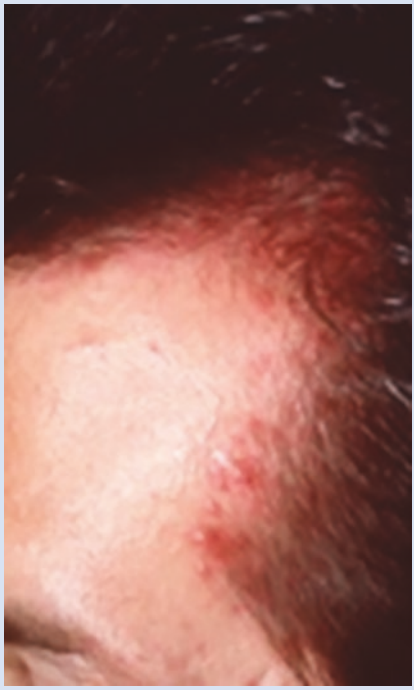


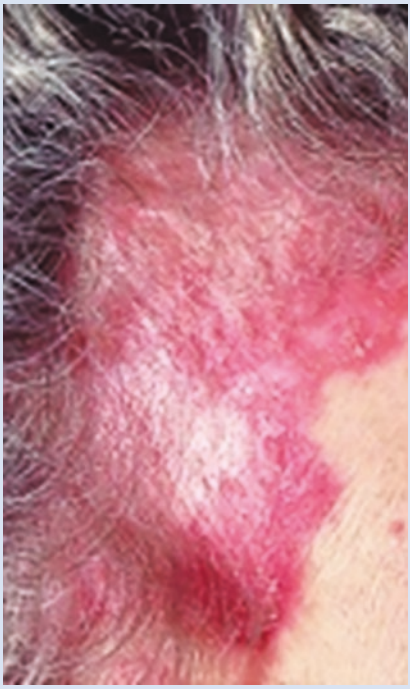

**Fig. 5.10** (continued)

| | |
|---|---|
|  | *Normal scalp*<br>Epidermal turnover time: 28–40 days<br>Corneocytes detach as single cells<br>Scalp condition: inconspicuous |
|  | *Dry scalp*<br>Epidermal turnover time: 28–40 days<br>Corneocytes detach in clusters of 10–25 cells<br>Scalp condition: sebostatic |

*Dandruff*
Epidermal turnover time: 7–21 days
Corneocytes detach in clusters of 100–1000 cells
Scalp condition: seborrheic



*Seborrheic dermatitis*
Epidermal turnover time: 7–21 days
Corneocytes detach in clusters of 100–1000 cells
Scalp condition: seborrheic and erythematous



| *Scalp psoriasis* |
| --- |
| Epidermal turnover time: <7 days |
| Corneocytes detach in clusters of >1000 cells |
| Scalp condition: erythematous and infiltrated, often reaches 1 cm beyond the hairline |

It is now recognized that dandruff in the hair is caused by *Malassezia* yeasts, which break down the sebum fats to produce a new substance, oleic acid, which acts as an irritant in many people. The scheme of events leading to dandruff are summarized in Fig. 5.10c.

Accordingly, management of dandruff aims at targeting the critical steps in its pathogenesis (Fig. 5.10d): sebosuppressive with crude coal tar; keratostatic and antiproliferative with crude coal tar and high-potency glucocorticosteroids; keratolytic and exfoliative with salicylic acid and colloidal sulfur; antimicrobial with selen disulfide, zink pyrithione, ciclopiroxolamin, piroction olamine, ketaconazole, econazole, miconazole, or bifonazole; and anti-inflammatory with low-, medium-, or high-potency glucocorticosteroids depending on the severity.

Seborrheic dermatitis is considered a more severe form of the condition, which includes inflammation of the skin. It represents a chronic recurrent condition characterized by scaling and poorly defined erythematous patches with a predilection for areas rich in sebaceous glands. The scalp is almost invariably affected (Fig. 5.11a); other areas of the skin involved in order of frequency are the face (Fig. 5.11b), chest, and intertriginous areas. Thin arborizing vessels, atypical vessel, and yellowish interfollicular scaling are mainly observed (Fig. 5.11c). Histopathology is characterized in acute lesions by focal, usually mild, spongiosis (Fig. 5.11d), with overlying scale crust containing a few neutrophils (Fig. 5.11e); the crust is often centered on a follicle; the papillary dermis is mildly edematous, blood vessels in superficial vascular plexus are dilated, and there is mild superficial perivascular infiltrate of lymphocytes, histiocytes, and occasional neutrophils, with some

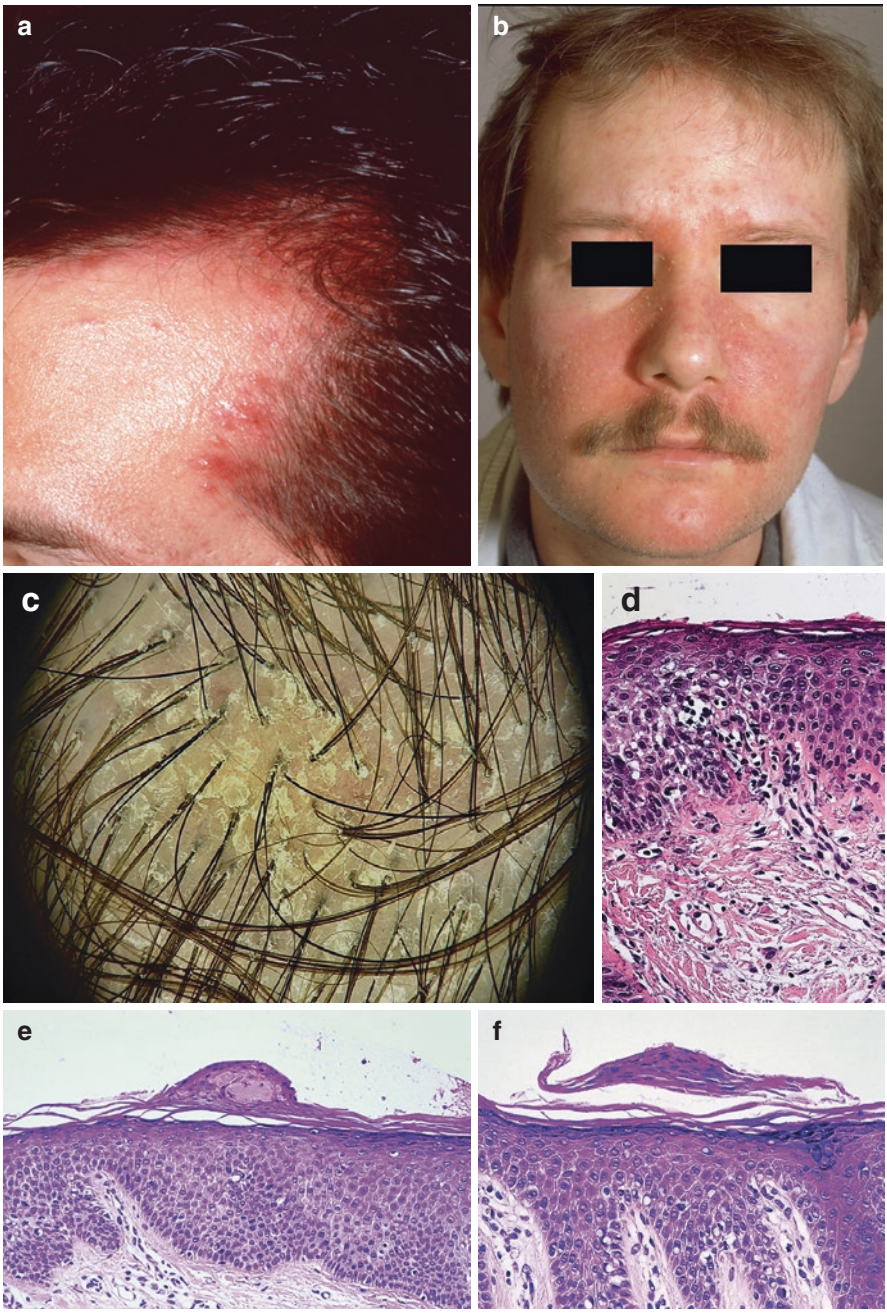



**Fig. 5.11** (**a**–**f**) Seborrheic dermatitis (**a**) of the scalp and (**b**) of the face, (**c**) dermoscopy, and (**d**–**f**) histopathology: (**d**) spongiosis with mild exocytosis, (**e**) overlying scale containing neutrophils, (**f**) psoriasiform hyperplasia

exocytosis of inflammatory cells. In subacute lesions, there is also psoriasiform hyperplasia (Fig. 5.11f), initially slight, with mild spongiosis and the other changes already mentioned; numerous yeast-like organisms can usually be found in the surface keratin. Chronic lesions show more pronounced psoriasiform hyperplasia and only minimal spongiosis; sometimes, the differentiation from psoriasis can be difficult, but the presence of scale crusts in a folliculocentric distribution favors seborrheic dermatitis.

The cause of seborrheic dermatitis is understood to involve fungi of the genus *Malassezia*. The inflammatory process is believed to be mediated by fungal metabolites, specifically free fatty acids released from sebaceous triglycerides.

Accordingly, antifungal agents are the mainstay of treatment of seborrheic dermatitis, with a number of well-performed studies proving superiority of ketoconazole and ciclopirox olamine shampoo over placebo for treatment. With respect to the use of topical corticosteroids either as lotion, cream, or foam, there is a consensus that they are useful in the short term, mainly to control erythema and itching, but no data are available regarding whether the combination of topical antifungal agents with topical corticosteroid results in a greater benefit than single-agent therapy.

A typically successful therapy for seborrheic dermatitis of the scalp would be using a 2% ketoconazole or a 1.5% ciclopirox olamine shampoo every other day during the first 2 weeks and thereafter twice weekly, depending on severity, either as monotherapy or in the more severe cases in combination with systemic itraconazole 200 mg daily during the first 7 days of treatment (and thereafter 200 mg every second week), and topical clobetasol propionate 0.05% foam as needed.

*Malassezia* folliculitis or *Pityrosporum* folliculitis is yet another skin condition caused by *Malassezia* (formerly *Pityrosporum*) yeast. The skin of the upper trunk area including the back, chest, arms, and sometimes the neck is often affected, and this condition is more commonly seen in young to middle-aged adults. Its diagnosis is based on the pruritic papulopustules found in a follicular pattern in these regions (Fig. 5.12a, b) caused by an overgrowth of *Malassezia furfur*, which plugs the follicles. *M. furfur* is lipophilic, requiring fatty acids with carbon chain lengths C11 to C24, like what is present in oily skin to proliferate. The microorganism is part of the normal skin flora but overgrows in certain conditions, particularly in association

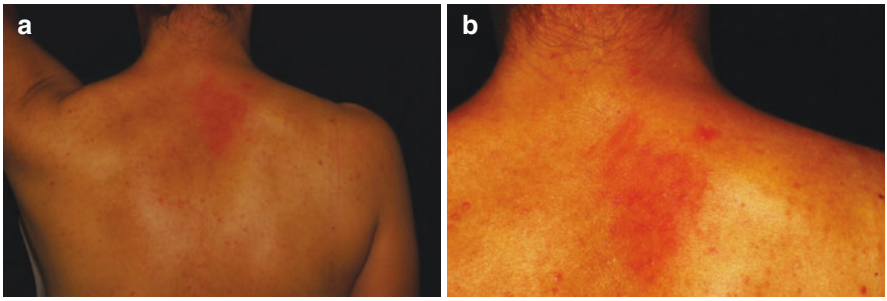



**Fig. 5.12** (**a**, **b**) *Malassezia* folliculitis (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil)

with oily skin, humidity, or other preexisting dermatologic conditions such as seborrheic dermatitis.

Atopic dermatitis, also known as atopic eczema, is a common, again chronic, relapsing, inflammatory skin disorder that may affect the scalp in a significant manner. The pathogenesis of atopic dermatitis is complex and involves genetics, environmental factors, disrupted permeability of the skin, and immunologic mechanisms.

In infantile eczema (Fig. 5.13), much of the body may be affected, while the typical scalp manifestation is cradle cap. As the children get older, the flector aspects of the extremities are most commonly affected. In adults, the hands and feet are often affected, and a subset of patients suffer of head and neck dermatitis.

The diagnosis of atopic dermatitis is based primarily on the clinical presentation, while skin prick tests, serologic testing, and the atopy patch tests may serve as diagnostic tools. Skin prick tests involve the identification of immediate-type allergic reactions (within 15 min) and serologic testing the detection of allergen-specific IgE. The atopy patch test aims at reproducing delayed-type allergic skin reactions (after 24 to 72 h) to immediate-type allergens, in an effort to determine whether a

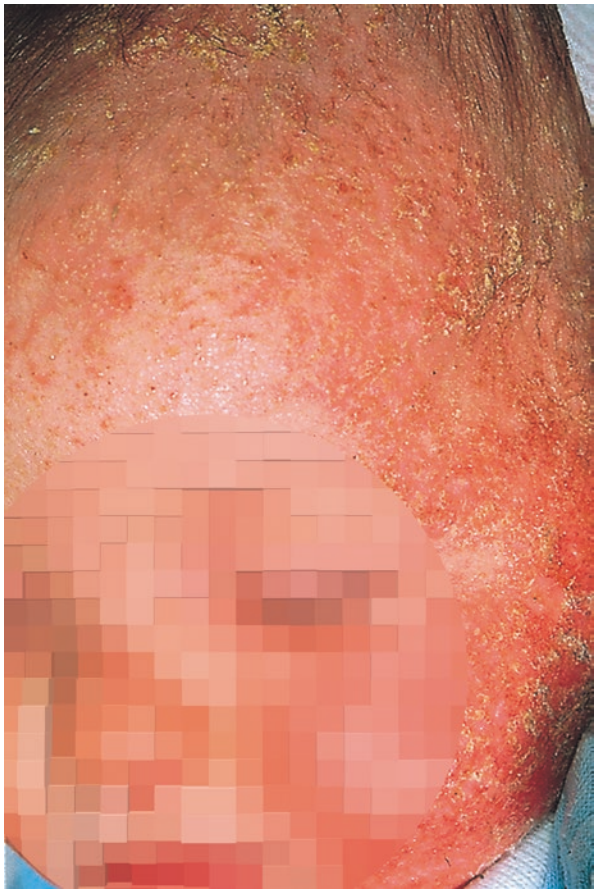


**Fig. 5.13** Infantile eczema

specific IgE-mediated allergen is causing the symptoms of the eczematous skin reaction.

A subset of patients with head and neck dermatitis may have a reaction to resident *Malassezia* flora, fueling their condition [29–32]. This reaction is likely related to both humoral- and cell-mediated immunity. Even in the absence of differences in *Malassezia* spp. colonization, patients with head and neck atopic dermatitis are more likely to have positive skin prick test results [33] and *Malassezia*-specific IgE [34, 35], compared to healthy control subjects and to patients with atopy without head and neck dermatitis. However, no clear relationship with atopy patch testing has been found. *Malassezia* allergy may be suspected in patients with atopic disease and:

- Eczema involving the head and neck region
- Exacerbations during adolescence or early adulthood
- Lesions recalcitrant to conventional therapy
- Positive skin prick tests for *Pityrosporum ovale*
- Malassezia-specific IgE

There is literature to suggest that these patients may benefit from a 1- to 2-month course of daily oral itraconazole (200 mg) followed by long-term weekly treatment in combination with regular use of 2% ketoconazole shampoo and 1% ciclopiroxolamine cream [36–40].

Finally, there is ample evidence from data involving collections and characterization of hair samples from various unhealthy scalp conditions to help establish a link between scalp health and hair growth and quality. Most of the published data are epidemiological in nature comparing hair obtained from individuals with dandruff or seborrheic dermatitis, atopic dermatitis, and psoriasis with that from a control group of healthy scalp individuals [41].

The most common manifestation on hair emerging from an unhealthy scalp is an altered cuticle with evidence of surface pitting, roughness, cuticle rigidity, or breakage. In some cases, the impact is manifested as shine reduction. In addition to the physical changes, there are biochemical alterations observed in hair emerging from an unhealthy scalp, with both protein and lipid components affected, most commonly by oxidative damage.

Moreover, a number of observations have found that premature hair loss may be caused by the poor scalp health associated with either dandruff (Fig. 5.14) or seborrheic dermatitis [42–45], indicating that the effect on the preemergent hair fiber may alter the anchoring force of the fiber within the follicle, as evidenced by an increased proportion both of catagen and telogen and of dysplastic anagen hairs (anagen hairs devoid of hair root sheaths) in the trichogram (hair pluck) [46].

Originally, Piérard et al. [47] hypothesized on a microbial-driven inflammatory reaction abutting on the hair follicles and performed a pilot study with 20 males using 0.25% Octopirox leave-on product and demonstrated that the product improved the semi-quantitative self-assessment of hair loss over a 1.5-year

**Fig. 5.14** Shedding of tufts of hair within clusters of dandruff

treatment period. Subsequently, Piérard-Franchimont et al. [48] conducted a study to compare the effect of 2% ketoconazole shampoo to that of an unmedicated shampoo used in combination with or without 2% minoxidil therapy for male androgenetic alopecia and found that hair density and size and proportion of anagen follicles were improved almost similarly by both ketoconazole and minoxidil regimens, even in the absence of dandruff. The authors concluded that there may be a significant action of ketoconazole upon the course of androgenetic alopecia and that *Malassezia* spp. play a role in the inflammatory reaction.

Following the original investigations of Piérard et al. and Piérard-Franchimont et al., Berger et al. performed a 6-month, randomized, investigator-blinded, parallel-group clinical study to assess the hair growth benefits of a 1% zinc pyrithione-based shampoo in males between the ages of 18 and 49 years exhibiting Hamilton-Norwood type III vertex or type IV baldness. The efficacy of the 1% zinc pyrithione-based shampoo used daily was compared with that of 5% minoxidil topical solution applied twice daily, a placebo shampoo, and a combination of the 1% zinc pyrithione-based shampoo and the 5% minoxidil topical solution. Hair count results showed a

significant net increase in total visible hair counts for the 1% zinc pyrithione shampoo, the 5% minoxidil topical solution, and the combination treatment groups relative to the placebo shampoo after 9 weeks of treatment [49].

## 5.3 Molds

A mold is a fungus that grows in the form of multicellular filaments called hyphae in contrast to the yeast that adopt a single-celled growth habit. Molds are a large and taxonomically diverse number of fungal species in which the growth of hyphae results in discoloration and a fuzzy appearance. The network of these tubular branching hyphae, called a mycelium, is considered a single organism. The hyphae are generally transparent, so the mycelium appears like very fine, fluffy white threads. The dusty texture of many molds is caused by profuse production of asexual spores (conidia) formed by differentiation at the ends of hyphae. The mode of formation and shape of these spores are traditionally used to classify molds. Many of these spores are colored, making the fungus much more obvious to the human eye at this stage in its life cycle.

Molds cause biodegradation of natural materials. Some diseases of animals and humans can be caused by certain molds: disease may result from growth of pathogenic molds within the body, the effects of ingested or inhaled toxic compounds (mycotoxins) produced by molds, or allergic sensitivity to mold spores.

Common genera of molds with relevance to human health and disease include *Alternaria*, *Aspergillus*, *Cladosporium*, *Fusarium*, *Mucor*, *Penicillium*, and *Rhizopus.*

Primary cutaneous mold infections are especially caused by *Aspergillus*, *Fusarium*, *Mucor*, and *Rhizopus* spp. These infections may invade deeper tissues and cause disseminated fungal infections in the neutropenic host.

Mold infections involving the scalp have been reported with *Penicillium*, *Aspergillus*, *Mucor*, and *Rhizopus*.

### 5.3.1 *Penicillium* spp.

*Penicillium* is a genus of ascomycetous fungi that is part of the mycobiome of many species and is of major importance in the natural environment, in food spoilage, and in food and drug products (penicillin).

Species of *Penicillium* are ubiquitous soil fungi preferring cool and moderate climates, commonly present wherever organic material is available. Saprophytic species of *Penicillium* live mainly on organic biodegradable substances. *Penicillium* species are present in air and dust of indoor environments, such as homes and public buildings.

Penicillin, a drug produced by *P. chrysogenum* (formerly *P. notatum*), was accidentally discovered by Alexander Fleming in 1929 and found to inhibit the growth of Gram-positive bacteria. Returning from holiday on September 3, 1928, Fleming began to sort through petri dishes containing colonies of *Staphylococcus*. He noticed

something unusual on one dish. It was dotted with colonies, except for one area where a blob of mold was growing. The zone immediately around the mold, later identified as *Penicillium notatum*, was clear, as if the mold had secreted something that inhibited bacterial growth. Its potential as an antibiotic was realized in the late 1930s, and Howard Florey and Ernst Chain purified and concentrated the compound. The drug's success in saving soldiers in World War II who had been dying from infected wounds resulted in Fleming, Florey, and Chain jointly winning the Nobel Prize in Medicine in 1945 [50].

*Penicillium* is rarely reported as an infectious agent in man. This mold is ubiquitous in nature, and its frequent isolation in cultures is routinely ascribed to contamination. Person and Ossi reported a case of possible *Penicillium* tinea capitis in a 3-year-old boy with a 1-month history of patchy occipitoparietal hair loss with loss of luster in the remaining hair and scattered "black dots" and light brown crusts on the scalp. Results of potassium hydroxide examination of epilated hairs were normal; the brownish crusts showed brown, double-walled spores, some of which were clumped. A culture grown on dermatophyte test medium showed *Penicillium* species [51]. Disseminated disease has been reported in severely immunocompromised patients.

Growth of *Penicillium* spp. in culture is rapid. The colony surface at first is white and then becomes very powdery and bluish green with a white border (Fig. 5.15a). Reverse is usually white but may be red or brown.

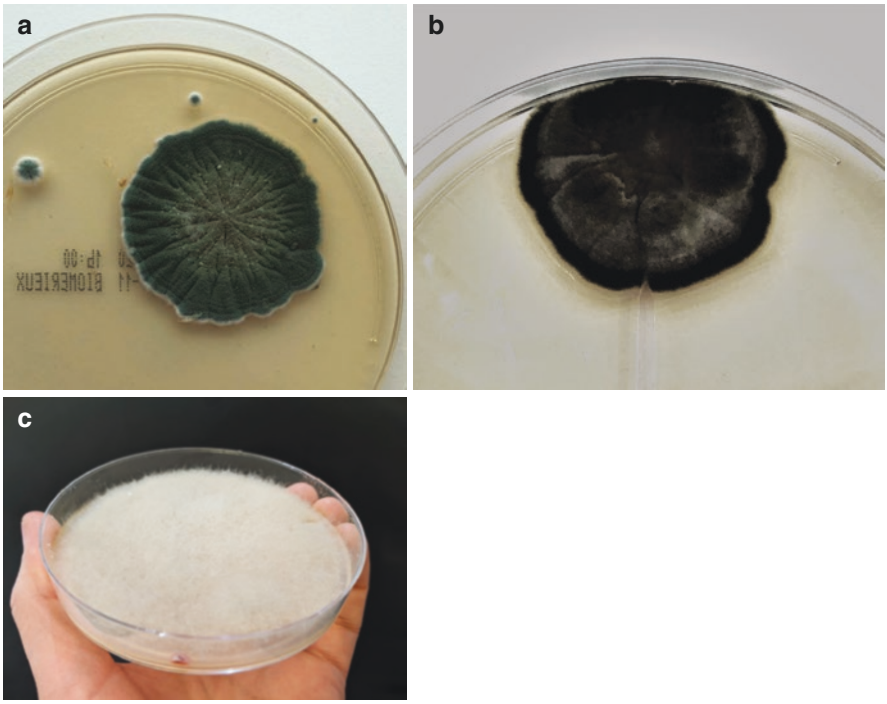



**Fig. 5.15** (**a**–**c**) Molds: (**a**) *Penicillium*, (**b**) *Aspergillus*, (**c**) *Mucor*

Guevara-Suarez et al. obtained a total of 118 isolates thought to belong to the genus *Penicillium* based on morphological features obtained from the Fungus Testing Laboratory at the University of Texas Health Science Center in San Antonio (USA). Antifungal susceptibility testing was performed for nine antifungal drugs. The potent in vitro activity of amphotericin B and terbinafine against *Penicillium* species might offer a good therapeutic option for the treatment of infections caused by these fungi [52].

### 5.3.2 *Aspergillus* spp.

Aspergillosis is a fungal infection of usually the lungs [53] caused by the genus *Aspergillus*, a common mold that is inhaled from ambient air. Most people are thought to inhale thousands of *Aspergillus* spores daily but without effect due to an efficient immune response.

Chronic colonization or infection can cause complications in people with underlying respiratory illnesses, such as asthma [54], cystic fibrosis [55], sarcoidosis [56], tuberculosis, or chronic obstructive pulmonary disease [57]. Most commonly, aspergillosis occurs in the form of chronic pulmonary aspergillosis, aspergilloma, or allergic bronchopulmonary aspergillosis.

Other noninvasive manifestations include fungal sinusitis, otomycosis, keratitis, and onychomycosis. Rarely, it can affect skin.

People who are immunocompromised, such as patients undergoing hematopoietic stem cell transplantation, chemotherapy for leukemia, or AIDS, are at an increased risk for invasive aspergillosis infections. Poorly controlled aspergillosis can disseminate through the blood to cause widespread organ damage. The person may develop kidney failure, liver failure, and breathing difficulties, and death can occur quickly.

Aspergillosis is estimated to affect more than 14 million people worldwide [58] with allergic bronchopulmonary aspergillosis (>4 million), severe asthma with fungal sensitization (>6.5 million), and chronic pulmonary aspergillosis (~3 million), being considerably more prevalent than invasive aspergillosis (>300,000). Other common conditions include *Aspergillus* bronchitis, *Aspergillus* rhinosinusitis (many millions), otitis externa, and *Aspergillus* onychomycosis (10 million).

During the COVID-19 pandemic (2020/2021), COVID-19-associated pulmonary aspergillosis was reported in some people who had been admitted to the hospital and received long-term corticosteroid treatment [59].

Fungal infections from *Aspergillus* spores remain one theory of sickness and untimely death of some early Egyptologists and tomb explorers. Ancient spores which grew on the remains of food offerings and mummies sealed in tombs and chambers may have been blown around and inhaled by the excavators, ultimately linked to the notion of the curse of the pharaohs [60]. Ultimately, the death of Lord Carnarvon (1866–1923), 6 weeks after the opening of Tutankhamun's tomb, resulted in many curse stories in the press, which were fueled further by author Sir Arthur

Conan Doyle's (1859–1930) suggestion that Carnarvon's death had been caused by "elementals" created by Tutankhamun's priests to guard the royal tomb [61].

*Aspergillus* has been reported in kerion-type scalp mycosis [62], in a non-healing scalp wound [63], scalp necrotizing fasciitis with osteomyelitis of the skull [64], and mycetoma of the scalp [65].

Specifically, Chokoeva et al. identified *Aspergillus niger* as a possible etiopathogenic agent in tinea capitis and suggested that pathogenic molds should be considered as a potential source of infection in some geographic regions, which require rationalization of the former therapeutic conception, regarding the molds' higher antimycotic resistance compared to the dermatophytes. Molds-induced tinea capitis should be also considered in clinically resistant and atypical cases, with further investigations of the antifungal susceptibility of the respective alternative pathogens [66].

The diagnosis of aspergillosis is based on medical history, risk factors, symptoms, physical examination, and lab tests. Depending on the location of the suspected infection, imaging such as a chest X-ray or a CT scan of the lungs or other anatomic sites is performed. Tissue biopsies are needed to provide the evidence for *Aspergillus* infection microscopically or in a fungal culture (Fig. 5.15b). On microscopy, *Aspergillus* species are reliably demonstrated by silver stains, e.g., Gridley stain or Gomori methenamine silver [67]. These give the fungal walls a gray-black color. Finally, a respective blood test can help diagnose invasive aspergillosis early in people who are severely immunocompromised.

The current medical treatments for aggressive invasive aspergillosis include voriconazole and liposomal amphotericin B in combination with surgical debridement as indicated [68]. A growing proportion of infections are resistant to the triazoles [69]. *A. fumigatus*, the most commonly infecting species, is intrinsically resistant to fluconazole [70].

### 5.3.3 Mucormycosis

Mucormycosis, also known as black fungus, is a serious opportunistic fungal infection, usually seen in debilitated hosts, 70% having diabetes mellitus with persistently high blood sugar levels or diabetic ketoacidosis, but patients with low white cells due to hematologic malignancy or cancer therapy, immunosuppression, extensive burn patients, and severe malnutrition are also at risk. Only 4% of infections occur without an underlying condition.

The infectious agent belongs to the taxonomic class *Zygomycetes*, family *Mucoraceae*. *Rhizopus* (mucormycosis), *Mucor* (zygomcosis), and *Absidia* genera are involved, in decreasing frequency.

During the COVID-19 pandemic, an association between mucormycosis and COVID-19 has been reported. This association is thought to relate to reduced immune function during the course of the illness and may also be related to glucocorticoid therapy for COVID-19. A rise in cases was particularly noted in India.

Symptoms depend on the anatomical site of infection. It most commonly infects the nose, sinuses, eye, and brain, resulting in a runny nose, one-sided facial swelling and pain, headache, fever, blurred vision, proptosis, and tissue necrosis by fungal invasion into the blood vessels resulting in thrombosis and infarction.

It is spread by spores of the respective molds, most often through inhalation, contaminated food, or contamination of open wounds. These fungi are common in soils; decomposing organic matter, such as rotting fruit and vegetables; and animal manure, but usually do not affect people. It is not transmitted between people. The condition tends to progress rapidly and is fatal in about half of sinus cases and almost all cases of the widespread type.

*Rhizopus* is a genus of common saprophytic fungi on plants and specialized parasites on animals. Some *Rhizopus* species are opportunistic human pathogens that potentially cause fatal disease.

Diagnosis requires identifying the mold in the affected tissue by biopsy and confirming it with a fungal culture and medical imaging to help determine the extent of disease, such as CT scan of the lungs and sinuses.

In culture, *Rhizopus oryzae* is characterized to be a fast-growing fungus where growth under optimal temperatures is fast at 1.6 mm per hour (nearly 0.5 μm per second, enough to be able to directly visualize hyphal elongation in real time under the microscope), covering the surface of the agar. Rapidly growing colonies fade from white to dark during sporulation. The colonies have a dense cottony growth or candy flossy or fairly floss in texture (Fig. 5.15c).

Treatment is generally with amphotericin B and surgical debridement.

Harman et al. reported a rare case of mucormycosis of the scalp: a 54-year-old woman patient presented with a wound in the scalp with purulent discharge. An ulcerated discharging lesion with necrotic hemorrhagic crusts in the left parietal region of the scalp and wheals with fluctuation from this lesion to the left periorbital area was observed. The patient had vision loss in the left eye. Biochemical investigations revealed elevated blood sugar level and urine ketone bodies. In the smears, thick-walled non-septate hyphae were detected, and *Rhizopus* spp. were isolated from culture. Antidiabetic therapy and liposomal amphotericin B were initiated with consecutive improvement of the scalp lesion [71].

Zaman et al. observed a case of pediatric scalp mucormycosis in 9-year-old diabetic girls caused by *Rhizopus oryzae*. She was successfully treated with amphotericin B deoxycholate and wound debridement. At 3 months' follow-up, the patient was stable, although she had lost her vision [72].

Rao et al. reported on deep mycosis of the scalp caused by *Rhizopus oryzae* mimicking kerion in a 5-year-old immunocompetent boy who presented with multiple painful boggy swellings with discharging sinuses on the scalp of 4 months' duration. Purulent discharge from the swelling cultured on Sabouraud's dextrose agar yielded *R. oryzae* species, which was confirmed by molecular analysis by polymerase chain reaction. The child was managed with parenteral liposomal amphotericin B, which helped in clearance of infection [73].

Melsom and Knahgure observed a case of craniofacial *Mucor* infection following assault to the forehead with a spanner. The female diabetic developed periorbital

cellulitis adjacent to the scalp wound, which progressed to a necrotizing fasciitis. This did not respond to treatment. Subsequently the patient developed hemiparesis, with CT imaging showing periorbital and paranasal sinus inflammatory changes, evidence of cavernous sinus invasion, and development of a middle cerebral artery territory infarction. The scalp wound was debrided, and *Mucor* spp. were isolated from the debrided tissue. The patient died shortly afterward despite intravenous amphotericin B. Postmortem examination showed fungal invasion of the right cavernous sinus with *Mucor* spp. and thrombosis of the right internal carotid artery and right cerebral infarction [74].

Invasive fungal infection in burn injury is caused by inoculation of fungal spore from patient skin or respiratory tract or from the caregiver. The risk factors for acquiring fungal infection in burns include age of burns, total burn size, full-thickness burns, inhalational injury, prolonged hospital stay, late surgical excision, open dressing, central venous catheters, antibiotics, steroid treatment, long-term artificial ventilation, fungal wound colonization, hyperglycemic episodes, and other immunosuppressive disorders. Invasive fungal infection with *Absidia corymbifera* is a rare opportunistic infection encountered in patients with burn injury. Moon and Jithendran reported on a case of invasive fungal infection with *A. corymbifera* in an immunocompetent patient who sustained high voltage electrical contact burn of the scalp and presented late after 10 days of injury [75].

In general, burn wound infection is primarily caused by bacteria (70%), followed by fungi (20–25%) and virus (5–10%) [76]. Cutaneous invasive fungal infection is a devastating condition in which delay in diagnosis and treatment may lead to high morbidity and mortality.

## 5.4 Dimorphic Fungi

Dimorphic fungi are organisms that have the ability to switch between two morphologies during their life cycle: yeast and hyphae. They usually have natural habitat in soil where they grow as a mold, and when fungal propagules are inhaled or inoculated by injury in the susceptible mammalian host, they undergo a complex process and convert into pathogenic yeasts, causing deep mycoses that are usually endemic to specific geographical areas. The ability to convert to the yeast form is essential for this class of fungal agents to produce disease. Temperature change is one key stimulus that triggers the phase transition from mold (25°) to yeast (37°) (in medical mycology, the memory aid "Mold in the Cold, Yeast in the Heat" helps students remember that among human pathogens, dimorphism largely reflects temperature) (Fig. 5.16a). This morphological transition is crucial to pathogenicity.

After the AIDS pandemic and with the increase in number of patients undergoing immunosuppressive therapy due to cancer, for organ transplantation, and in autoimmune diseases, the incidence of endemic mycosis has been progressively rising.

Several species of dimorphic fungi are important pathogens in humans, including *Sporothrix schenckii*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*,

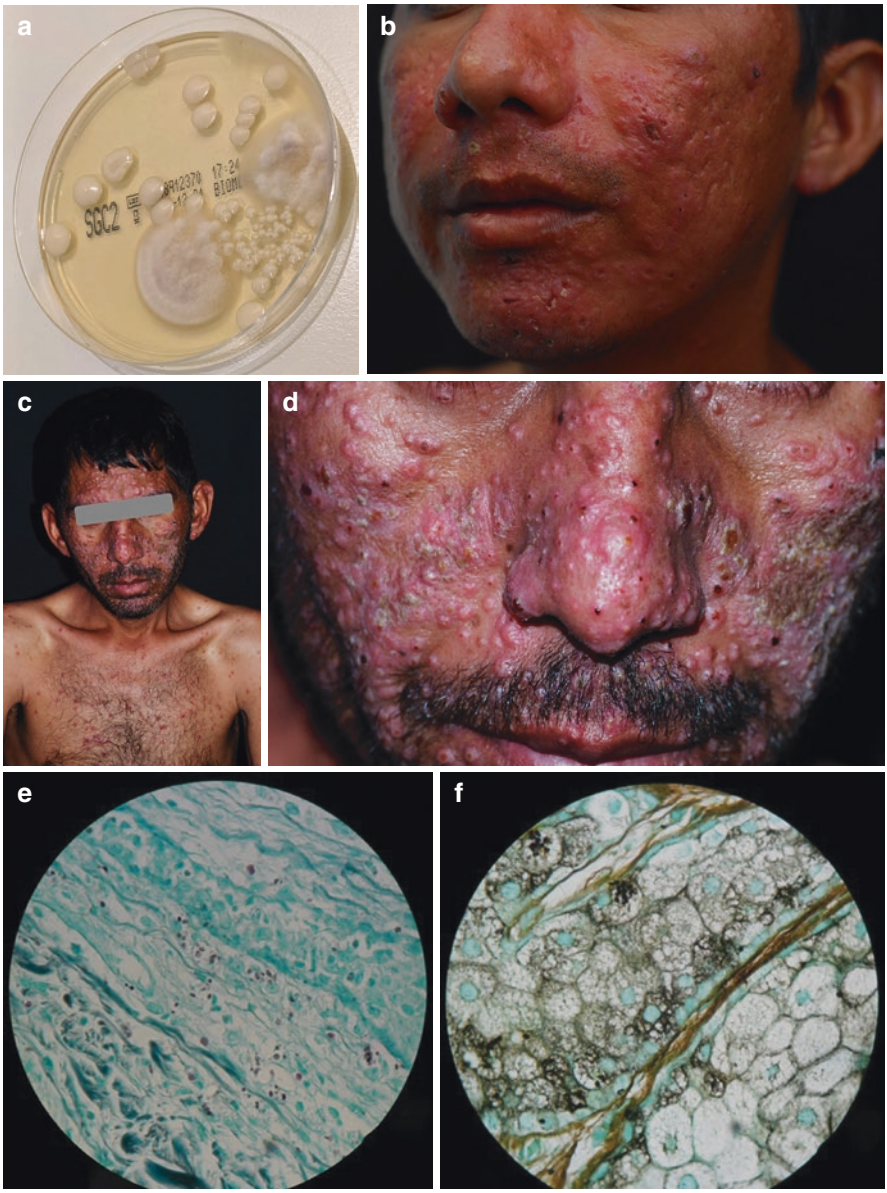



**Fig. 5.16** (**a**–**f**) Dimorphic fungi: (**a**) Two morphologies of *Candida albicans* on Sabouraud medium, mold and yeast. (**b**–**f**) Disseminated histoplasmosis (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil): (**b**) acneiform, (**c**, **d**) molluscum contagiosum-like in a patient with AIDS (courtesy of Prof Sinesio Talhari, Department of Infectious Diseases, Amazonas Foundation of Tropical Medicine, Brazil), (**e**, **f**) methenamine silver stain showing histopathologic changes of histoplasmosis. Note the presence of typical yeast cells, some of which are undergoing replication by budding

*Coccidioides immitis*, *Paracoccidioides brasiliensis*, and *Candida albicans*. Some diseases caused by fungi are:

- Sporotrichosis
- Blastomycosis
- Histoplasmosis
- Coccidioidomycosis
- Paracoccidioidomycosis
- Candidiasis

Of these, scalp involvement has been observed in blastomycosis [77], histoplasmosis [78], coccidioidomycosis [79], paracoccidioidomycosis [80], and candidiasis [24].

Specifically, disseminated candidiasis in intravenous heroin abusers with skin lesions confided to the scalp and other hair-bearing areas, such as the beard, seems to represent a distinctive clinical presentation. Histological examination of scalp biopsy specimens shows infiltration of hair follicles with chronic inflammatory cells and *C. albicans*. Pseudohyphae of *C. albicans* are also identified in and around hair shafts [19].

Although rare, the incidence of scalp involvement is an alert to include dimorphic fungi as a differential diagnosis of lesions on the scalp, particularly in the respective endemic areas.

Blastomycosis is endemic to the eastern United States, especially the Ohio and Mississippi River valleys, the Great Lakes, and the St. Lawrence River. It is also endemic to some parts of Canada, including Quebec, Ontario, and Manitoba.

*H. capsulatum* is found throughout the world. It is endemic in certain areas of the United States, particularly in States bordering the Ohio River valley and the Lower Mississippi River. It is also common in caves in Southern and East Africa. In Canada, the St. Lawrence River Valley is the site of most frequent infections. A review of reported cases in 2018 showed disease presence throughout Southeast Asia. In India, the Gangetic West Bengal is the site of most frequent infections. The humidity and acidity patterns of soil are associated with endemicity. Bird and bat droppings in soil promote the growth of *Histoplasma*. Contact with such soil aerosolizes the microconidia, which can infect humans. It manifests by the presence of fever as the only symptom in most individuals. The disease may present as self-limited pneumonia or as a hematogenous widespread fungal infection with a potentially fatal outcome in elderly individuals and people with compromised T-cell mediated immunity. If symptoms of histoplasmosis infection occur, they start within 3 to 17 days after exposure; the typical time is 12–14 days. Most affected individuals have clinically silent manifestations and show no apparent ill effects. The acute phase of histoplasmosis is characterized by nonspecific respiratory symptoms, often cough or flu-like. Chest X-ray findings are normal in 40–70% of cases. Chronic histoplasmosis cases can resemble tuberculosis. In fact, while *Histoplasma* was

discovered in 1905, only in the 1930s was it discovered to be a widespread infection. Before then, many cases were mistakenly attributed to tuberculosis and patients admitted to tuberculosis sanatoria, where some contracted tuberculosis. Disseminated histoplasmosis affects multiple organ systems and is fatal unless treated. Severe infections can cause hepatosplenomegaly, lymphadenopathy, and adrenal enlargement. Cutaneous manifestations of disseminated disease are diverse and often present as a nondescript rash with systemic complaints. Disseminated histoplasmosis is a relatively common and AIDS-defining illness, occurring in almost 4% of patients living in endemic areas where it may be the first clinical expression of the HIV infection. A broad spectrum of clinical skin lesions associated with *Histoplasma capsulatum* infection have been described in AIDS patients, such as erythematous macules, papules, nodules, and pustules, herpetic, acneiform (Fig. 5.16b), erythema multiforme-like, molluscum contagiosum-like (Fig. 5.16c, d), vasculitic, and exfoliative forms.

Kucharski et al. [81] reported a case of disseminated cutaneous histoplasmosis in a 33-year-old male homosexual patient and intravenous drug user. The patient had been diagnosed with HIV infection 5 years earlier. Although in apparently good health, he had developed erythematous papules and pustules in the skin of the scalp, face, back, thighs, abdomen, palms, and soles. He was placed on antiretroviral therapy, fluconazole, for mucosal candidiasis, trimethoprim/sulfamethoxazole for pneumocystis prophylaxis, and antibiotics for the skin pustules. The skin lesions improved remarkably within 14 days. He was discharged and soon lost to follow-up. After his discharge, skin biopsy and fungal culture results revealed *H. capsulatum*. He was seen again 1 year later. The interim history revealed that he had taken fluconazole 100 mg/day for 1 month and fluconazole 150 mg/week for 7 months. He had not continued antiretroviral therapy, nor taken other antifungal drugs. The clinical evolution of the disease was exceptional in that there was disappearance of all the skin lesions attributed to histoplasmosis with fluconazole, although itraconazole is the drug of choice for histoplasmosis.

Régnier-Rosencher et al. [78] report on an imported case of *Histoplasma capsulatum* var. *duboisii* (*H. duboisii*) infection in a white French woman revealed by cutaneous lesions of the scalp, 18 years after her last stay in West and Central Africa. Asymptomatic bilateral pulmonary infiltrates were discovered on thoracic computed tomography. Skin biopsy allowed the positive diagnosis showing the typical yeast morphology (Fig. 5.16e,f), and culture of biopsy specimens was positive for *H. capsulatum*. In the absence of criteria of severity, the patient was treated for 1 year with oral itraconazole 400 mg/day. The outcome was favorable, and skin and pulmonary lesions resolved slowly. The follow-up is 5 years without relapse after the end of treatment. This case illustrates the possibility of late occurrence of *H. duboisii* infection, many years after exposure, and the major importance of asking any patient for travelling or residency in tropical countries.

Finally, Corti et al. [82] reported on a peculiar presentation of disseminated histoplasmosis in a patient with AIDS, the rupioid lesion. The term rupioid has been used to describe well-demarcated, cone-shaped plaques with thick, dark, lamellate, and adherent crusts on the skin that somewhat resemble oyster or limpet shells.

Rupioid manifestations have been clinically observed in a variety of conditions, including:

- Disseminated histoplasmosis
- Keratotic scabies
- Secondary syphilis
- Rupioid psoriasis
- Photosensitive skin lesions in association with aminoaciduria

Therefore, to diagnose the underlying infectious or inflammatory disease beneath the thick crusts, skin biopsy and a blood test for syphilis are recommended [83].

Coccidioidomycosis is a common cause of community-acquired pneumonia in the endemic areas of the United States. Coccidioidomycosis is endemic to the Western Hemisphere between 40°N and 40°S. The ecological niches are characterized by hot summers and mild winters with an annual rainfall of 10–50 cm. The species are found in alkaline sandy soil, typically 10–30 cm below the surface. In harmony with the mycelium life cycle, incidence increases with periods of dryness after a rainy season. This phenomenon, termed "grow and blow," refers to growth of the fungus in wet weather, producing spores, which are spread by the wind during the succeeding dry weather. In the United States, *C. immitis* is endemic to southern and central California with the highest presence in the San Joaquin Valley. *Coccidioides posadasii* is most prevalent in Arizona, although it can be found in a wider region spanning from Utah, New Mexico, Texas, and Nevada.

Paracoccidioidomycosis, also known as South American blastomycosis, is endemic to Central and South America and is considered a type of neglected tropical disease while causing around 200 deaths per year alone in Brazil.

## 5.5 Piedra

Piedra is a hair disease caused by a fungus, which causes formation of nodules on the hair shaft. Piedra is the Spanish word for stone. Piedra appears as minute stones that attach to the hair shaft and may group to form clusters. Types include white piedra and black piedra.

Since piedra is a superficial fungal infection and is restricted to the stratum corneum, it usually causes no inflammation.

### 5.5.1 White Piedra

White Piedra is a superficial mycosis of the hair caused by several species of fungi in the genus *Trichosporon* and characterized by white-to-tan gelatinous, pearly nodules surrounding the hair shaft (Fig. 5.17a–d). These nodules are typically found in

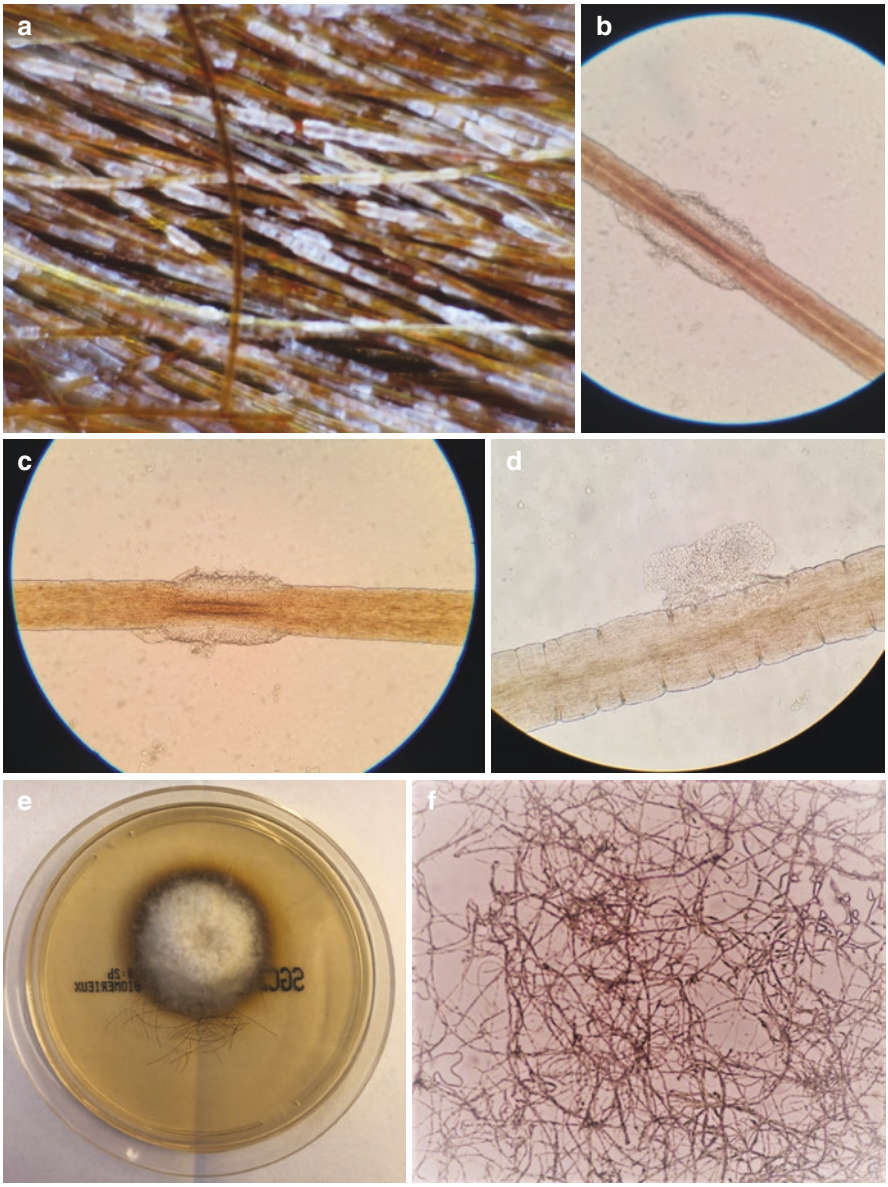



**Fig. 5.17** (**a**–**f**) White piedra (*Trichosporon* spp.): (**a**–**d**) white-to-tan gelatinous, pearly nodules surrounding the hair shaft. (**e**) Colony morphology: yeast-like, at first cream colored, moist, and soft. The surface becomes irregularly wrinkled, rather powdery and crumb-like, and the color often darkens to yellowish gray. (**f**) Microscopic morphology: true hyphae and pseudohyphae with blastoconidia singly or in short chains

facial hair and body hair, for example, in mustaches and beards, on eyelashes and eyebrows, and in armpit and pubic hair. The nodules are about 1 mm or greater in diameter and are fairly easy to remove. However, removal may cause the affected hair shafts to split or break.

*Trichosporon ovoides* is likely the cause of white piedra of the scalp hair, while *Trichosporon inkin* is mainly associated with white piedra of the pubic hair [84]. The obsolete name *Trichosporon beigelii* was formerly applied to all or any of these species.

The spread of white piedra directly from person to person is uncommon. White piedra is more common in the temperate and semitropical climates of South America, Africa, Europe, the Middle East, Southeast Asia, India, Japan, and southeastern United States. After a person is exposed, the fungus needs the right conditions to survive and colonize human hair. Practices that can lead to colonization and result in white piedra infection include:

- Infrequent bathing or poor personal hygiene
- Frequent use of oil applications to the hair
- Irregular combing habits or matted hair
- Covering wet hair with a veil or turban

The most common complication of white piedra is brittle hair. People who are immunosuppressed, have HIV, or are undergoing chemotherapy can have pruritic or necrotic nodules or papules. These can cause intense itching and discomfort.

Much more serious opportunistic infections, collectively called trichosporonosis, have also been reported in immunocompromised individuals [85]. *Trichosporon asahii* is the most common isolate in these cases, followed by *Trichosporon mucoides*. The relative resistance of these organisms to amphotericin B is important to note, and azole-based treatment regimens should be considered the first-line treatment.

The rate of growth of *Trichosporon* spp. in culture is moderately rapid, with maturity in 5–7 days. Colony morphology is yeast-like, at first cream colored, moist, and soft. The surface becomes irregularly wrinkled, rather powdery and crumb-like, and the color often darkens to yellowish gray (Fig. 5.17e). On cornmeal-Tween 80 agar at 25 °C for 72 h, true hyphae and pseudohyphae with blastoconidia singly or in short chains are seen (Fig. 5.17f).

The preferred treatment of white piedra is having the affected area shaved. Medicated shampoos and lotions, such as 1% clotrimazole, 2% miconazole, 2% ketoconazole shampoo or lotion, ciclopirox, or 2% selenium sulfide, may be effective when shaving is not an option for cosmetic, personal, or cultural reasons.

Topical medications do not work for some individuals. In these cases, oral itraconazole 100 mg twice a day after a meal, with a citrus drink for 1 to 2 weeks, can be prescribed to treat persistent white piedra [86].

White piedra of the genitals often recurs, so combining shaving with a short course of a topical antifungal is often necessary for a complete cure.

The fungus may remain in clothing and bedding. A person should throw infected underwear away and disinfect other garments, linen, and towels to help prevent reinfection.

Following good personal hygiene and hair care practices can help prevent future recurrences of white piedra.

### 5.5.2 Black Piedra

Black piedra is a superficial mycosis of the hair caused by *Piedraia hortae*, which is characterized by the formation of black nodules of less than 1 mm size on the hair of the scalp, moustache, or pubic hair (Fig. 5.18a). The nodules are hard and gritty, which produces a metallic sound when the hair is combed. The nodules colonize the hair shaft, which causes progressive weakness of the hair and leads to breakage of the hair in severe cases.

Hairs with black piedra isolated from Brazilian Indians were investigated by studying serial sections with light and transmission electron microscopy. *P. hortae* showed strong keratolytic activity; it was able to destroy both the cuticle and the hair cortex [87].

In histological sections or 10% potassium hydroxide (KOH) mounts, the nodules are observed to be made up of closely packed brown hyphae held in a mass by a viscous or cement-like substance (Fig. 5.18b–c). The cementing extracellular material that holds the nodule together is probably the main factor responsible for preserving the fungus against environmental attack and desiccation. Moreover, this compact organization can also impair successful treatment, which may explain why an untreated black piedra may run a very chronic course.

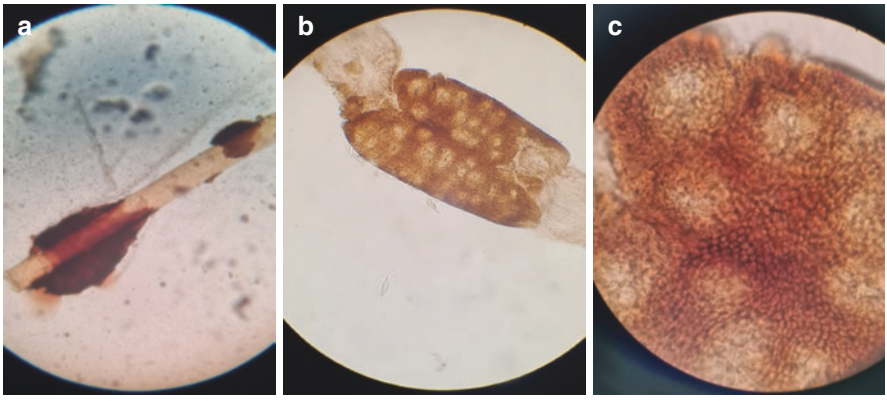



**Fig. 5.18** (**a**–**c**) Black Piedra (*Piedraia hortae*) (courtesy of Elisabeth Maria Heins, Lusiada Foundation, Santos, Brazil)

**Table 5.3** Black piedra. Treatment plan (from [89])

| |
|---|
| • Shaving the head |
| • 2% ketoconazole or 2% miconazole shampoo or 1% to 1.5% ciclopirox shampoo applied once to twice a week for 3 to 4 weeks |
| • Oral terbinafine 250 mg once daily for 6 weeks |
| • Oral itraconazole 100 mg twice a day after a meal, with a citrus drink for 1 to 2 weeks |
| • Counseling on the maintenance of good scalp hygiene, avoidance of sharing combs, etc. |

Black piedra is usually seen in tropical regions. The source of the infection is usually in soils, while poor hygiene, long hair, cultural use of veils, and the application of plant oils to wet hair favor the growth of the infection.

The exact mode of spread of piedra is not clear. The use of an infected comb or sharing of pillows and bedsheets may be the possible factors for transmission. There are also reports of sexual transmission.

In culture on Sabouraud dextrose agar medium at room temperature, *P. hortae* shows a smooth greenish-black colony with a raised and cerebriform center. The reverse side of the colonies is blackish.

Piedra is usually treated with cutting or shaving of the hair, if culturally appropriate and with patient's willful consent, followed by the application of topical antifungal agents, such as 2% ketoconazole or 2% miconazole shampoo applied once a week for 3 weeks. 0.77% ciclopirox lotion or 1% to 1.5% shampoo has also been used successfully. Topical keratolytics such as 1% salicylic acid may also be added in cases nonresponsive to monotherapy with antifungal shampoos.

Oral terbinafine has been used successfully in black piedra resistant to topical treatment. A course of 250 mg of oral terbinafine once daily for 6 weeks was found to be effective [88].

Family members should avoid sharing personal care items with the infected individual.

The treatment plan of black piedra is summarized in Table 5.3.

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# Tropical Diseases

6

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## Contents



By definition, tropical diseases are diseases that are prevalent in or unique to the tropical and subtropical geographic regions of Africa, Asia, and Central and South America [1]. They have long been noted both by explorers, travelers, and physicians. The initial impetus for tropical medicine was to safeguard the health of colonial settlers, notably

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in British India. One obvious reason is that the hot climate present during all the year and the larger volume of rains directly affect the formation of breeding grounds, the larger number and variety of natural reservoirs, and animal diseases that can be transmitted to humans (zoonosis), the largest number of possible insect vectors of diseases. Insects such as mosquitoes and flies are by far the most common disease carrier. These insects may carry a parasite, bacterium, or virus that is infectious to humans and animals. Most often, the disease is transmitted by an insect, which causes transmission of the infectious agent through subcutaneous blood exchange. The diseases are less prevalent in temperate climates, due in part to the occurrence of a cold season, which controls the insect population by forcing hibernation. However, many were present in northern Europe in the seventeenth and eighteenth centuries before modern understanding of disease causation. Socioeconomic factors may be also in operation, since most of the poorest nations of the world are in the tropics. On the other hand, tropical countries like urban Brazil, which have improved their socioeconomic situation and invested in hygiene, public health, and the combat of transmissible diseases, have achieved dramatic results in relation to the elimination or decrease of many endemic tropical diseases in their territory.

Finally, climate change and global warming are possibly causing tropical diseases and vectors to spread to higher altitudes of mountainous regions and to higher latitudes that were previously spared. In addition, human exploration of tropical rainforests, deforestation, rising immigration, and increased international air travel and other tourism to tropical regions have led to an increased incidence of such diseases in the non-tropical countries [2].

Most countries with a tropical climate between 20% and 40% of new consultations at primary care level are motivated by skin problems, although this varies, depending on the underlying prevalence of skin disease and the existence of local variations in the normal pattern and distribution of skin disease. Generally, in hot climates, this picture is dominated by infections, including bacterial skin infections such as pyodermas and cellulitis, mycoses including dermatophytosis, candida, and *Malassezia* infections. The reason for the dominance of skin infections in tropical countries is thought to reflect the prevalence of factors that favor spread and pathogenesis, such as climate and overcrowding, particularly household overcrowding. Other factors which may have affected spread of this infection include the ready availability and use of topical potent corticosteroid combinations and low-quality generic antimicrobials.

Along with the common infections, a group of conditions known collectively as the neglected tropical diseases (NTDs) of the skin, which are the targets for worldwide control or elimination, is also seen in healthcare facilities. These diseases range from the common, such as scabies and cutaneous leishmaniasis, to those that are less frequent, including leprosy, mycetoma, and other deep fungal infections. The initiative to use skin presentations of tropical diseases as a route to diagnosis by front line health workers is both logical and welcome. However, this requires training and monitoring as the work gets underway. Despite also causing scalp conditions, there is as yet little to no surveillance for scalp infection.

Skin infections in the tropics may be associated with significant levels of disability and morbidly. Beyond physical incapacity, skin disease may also be associated with psychological sequelae, particularly depression, and in addition it affects household and societal relationships through discrimination and stigma [3].

## 6.1 Leishmaniasis

Leishmaniasis represents a chronic infectious tropical disease caused by species of *Leishmania*, which are flagellated protozoans that belong to the order Kinetoplastida [4]. *Leishmania* sp. transmission occurs by the bite of infected phlebotomine sand flies of the genera *Phlebotomus* and *Lutzomyia* [5]. The disease has been reported in over 98 countries in America, Europe, Africa, and Asia, though it is mostly seen in tropical and subtropical areas [5]. In America, *L. mexicana* and *L. brasiliensis* are the most commonly involved species in cases of cutaneous leishmaniasis [6].

While the first reports on cutaneous leishmaniasis came from the first century AD, native people from South America, especially Peru, Ecuador, and Bolivia, were probably the ones who first illustrated affected patients with mucosal lesions on New World pottery objects [7, 8]. Despite scientific efforts during the nineteenth century to identify a causative agent for leishmaniasis, it was only in 1885 that Scottish physician David Douglas Cunningham (1843–1914) identified unknown microorganisms within macrophages while studying "Delhi boil" in India. The parasite visualized by Cunningham were species of *Leishmania*, though he did not realize at the time [4, 7].

In 1898, Peter Borovsky, a Russian military surgeon working in Tashkent, Uzbekistan, confirmed the protozoal nature of the organisms obtained from cutaneous biopsy specimens. An even larger spectrum of the disease would be recognized after the identification of parasites from the spleen of a patient from India by Scottish pathologist and British Army medical officer William Boog Leishman (1865–1926), in 1901, pointing to new organ involvement other than the skin [4, 7, 8]. The transmission of parasites by sandflies was finally proved by Brazilian physician and researcher Henrique Aragão (1879–1956) in 1922.

The microscopic characteristics of *Leishmania* were finally revealed in 1900 [8]. Literature descriptions report on the observation of parasites, which had both a nucleus and a rod-shaped structure called the kinetoplast [8]. After more than a 100 years, the identification of the kinetoplast in histopathological studies still provides great value, since it represents an important microscopic feature with diagnostic impact [9].

Genome sequencing of some *Leishmania* species (*L. major*, *L. infantum*, and *L. braziliensis*) has shown very distinguished features of gene expression that could, at least in part, explain their refined abilities to adapt in response to environmental changes [10]. As a result, *Leishmania* species can multiply in human cells in a complex and organized way, which allows frequent parasite morphofunctional transformation that ultimately enables the disease to spread [7, 10].

The vector involved in the transmission of leishmaniases is always a female sand fly [8]. Both insects of the genera *Phlebotomus* and *Lutzomyia* may take part in the process, but the existence of a mammalian reservoir, such as humans, dogs, forest rodents, sloths, and foxes, is essential [7, 8]. Humans are usually accidentally infected after moving to endemic zones, where they get exposed to sand flies [8]. Even though different possibilities of transmission have been reported (e.g., direct contact), it is currently accepted that it occurs almost exclusively following the bite of an infected sand fly [8].

**Table 6.1** Clinical patterns of leishmaniasis and their major features

| Clinical presentations | Characteristics |
|---|---|
| Cutaneous | Lesions occur only in the skin |
| Mucocutaneous | Both skin and mucous membranes are affected. Internal organs are not involved |
| Diffuse cutaneous leishmaniasis | Mucous membranes are usually spared but can rarely be affected. Internal organs are not involved |
| Visceral | Starts with skin lesions and later affects organs of the mononuclear phagocyte system, such as the liver and spleen |

An extracellular form of *Leishmania*, identified as promastigote, is present in the saliva of infected sand flies and are first transmitted to the human tissue during the course of probing the skin [8]. Promastigotes are then phagocytized by macrophages, within which they transform into amastigotes that are more adapted to the intracellular environment. It allows for efficient multiplication in the phagolysosomes, despite the presence of intracellular enzymes [8]. The parasite life cycle is complete when another sand fly bites an infected patient, taking up mature amastigotes, which will transform back to the promastigote form in the insect gut [8].

Patients who are infected by *Leishmania* may exhibit protean clinical manifestations and present both skin and mucosal involvement [4, 11–13]. The incubation period for symptomatic individuals varies from few weeks to several months, and mucosal involvement may only be overt after years from the primary infection [12]. There are four major clinical presentations, as displayed in Table 6.1 (from [7]). The skin is involved in three of them.

At least two factors are known to influence in the type of presentation that the patient with leishmaniasis will have: the parasite virulence and the patients' immune response to the infection [14]. Patients with oligoparasitic disease have noticeable cellular immune response and thus develop milder forms of the disease, presenting localized cutaneous lesions; this is also true for mucosal clinical presentations [14]. On the other hand, individuals with polyparasitic disease are not able to control the infection properly and are prone to develop diffuse infiltrative forms of leishmaniasis. In these patients, macrophages full of *Leishmania* are present, but no granulomatous inflammation is observed [11, 13, 14]. This peculiar immunological spectrum that mostly dictates the clinical manifestations in leishmaniasis is analogous to patients with leprosy [11, 13, 14].

Typical lesions of cutaneous leishmaniasis erupt weeks to months after the patient is bitten by infected vectors, which usually occurs in undressed parts of the body, such as the face, cervical region, and extremities, where the sand flies can easily probe [6, 8]. Cutaneous leishmaniasis can present as:

Localized cutaneous leishmaniasis (LCL) usually shows a solitary, well-circumscribed, pink-colored papule that slowly develops to form a nodule or plaque-like lesion [6, 13] (Fig. 6.1a). The center of the lesion tends to become soft and

- Localized cutaneous leishmaniasis
- Leishmaniasis *recidivans*
- Diffuse cutaneous leishmaniasis

progresses with painless ulceration (Fig. 6.1b, c). Cases with one single lesion are more common, but multiple lesions are also reported (Fig. 6.1d, e), and some patients may show formation of satellites just outside the plaque/ulcer or even lymphatic spread, similar to that seen in sporotrichosis ("sporotrichoid"). It is expected from LCL to spontaneously heal over months to years, depending on the species of *Leishmania* involved [8, 15]. Most regularly, the resolution of the lesions causes

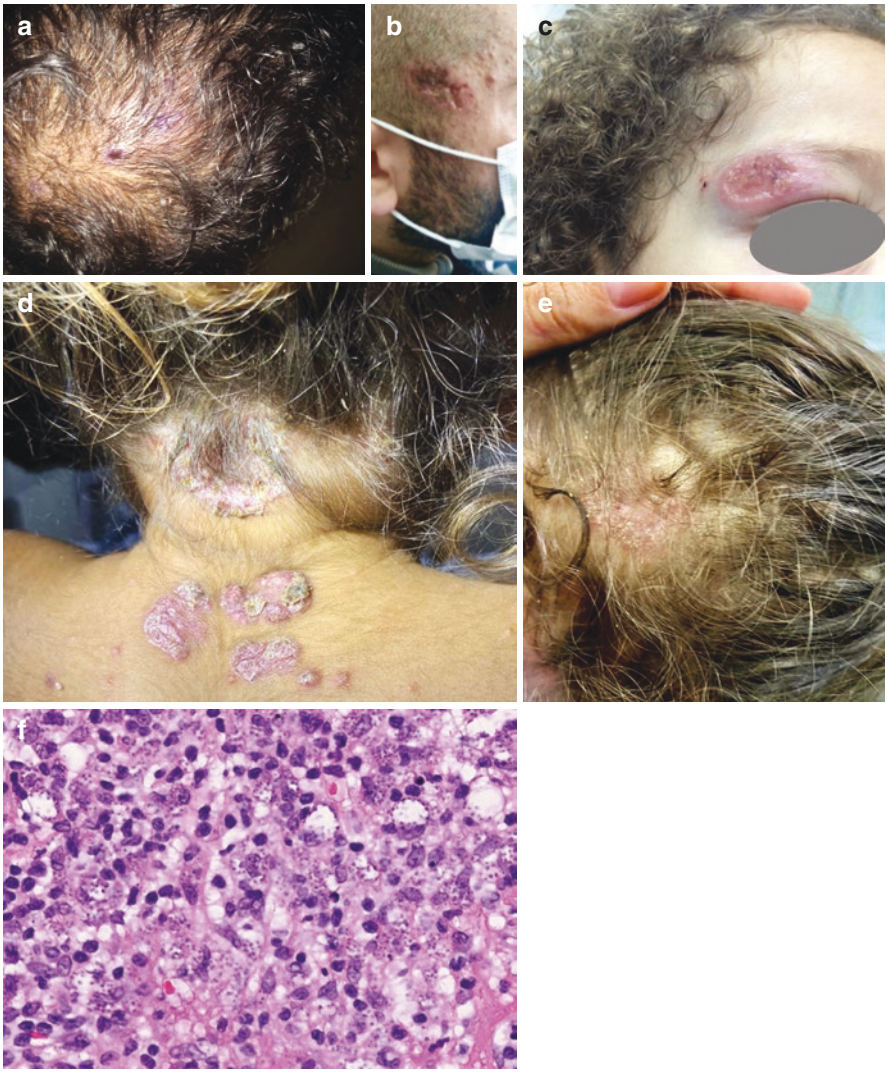


**Fig. 6.1** (**a**–**f**) Localized cutaneous leishmaniasis (**a**) of the scalp, (**b**, **c**) ulcerating lesions, (**d**) multiple lesions including (**e**) the scalp (courtesy of Prof. Remberto Mauricio Vilte, Fluminense Federal University, Brazil). (**f**) Histopathology: the visualization of the kinetoplast is essential for the histologic diagnosis. Courtesy of Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland

cutaneous atrophy, which is manifested by a thin and pale cutaneous appearance over the ulcer site and may have a hyperpigmented halo [15]. Depending on the number of ulcers and the extension of the disease, LCL can be disfiguring. Atypical lesions are also possible in LCL. Ulcers can heal assuming a keloidal appearance in predisposed individuals and verrucous forms; also, zosteriform, psoriasiform, and eczematous lesions have been reported [15]. Similarly, unexpected body areas, such as the scalp and plantar region, can also be targeted [6, 16]. Cárdenas et al. described a case of LCL restricted to the scalp in a 28-year-old male patient from Mexico. The lesion was an asymptomatic plaque that progressed to nodules with central ulceration and yellowish crusting, with raised and well-defined borders [6]. Tironi et al. from Brazil, reported on a case of a plantar ulcer as another possible clinical presentation [16].

Suspecting of scalp leishmaniasis may be challenging, since hairy areas are more difficult to be accessed by sand flies; as of yet, there are only two published papers on scalp LCL [6]. LCL should be considered in the differential diagnosis of patients with unspecific scalp lesions, particularly those who live or have travelled to endemic zones for leishmaniasis [17]. The attending physician should rule out bacterial infection, cutaneous myiasis, pyoderma gangrenosum, cutaneous malignancies, and fungal infections, such as sporotrichosis, blastomycosis, and chromoblastomycosis.

Dermoscopy of LCL is quite unspecific but may be of help as a complimentary part of the physical examination. The first report of dermoscopy from scalp lesions of LCL was published by Cárdenas and colleagues in 2018. On the occasion, the authors observed the presence of erythema (most common feature), yellow tears, hyperkeratosis, central erosion, ulceration, and a white starburst-like pattern [6]. Due to the presence of erythema and yellowish crusting, *kerion celsi* is one of the most important differential diagnoses for scalp LCL [6].

Finally, the usual sparse hair coverage, which is seen on the forearms and distal legs, is not enough to act as a physical barrier that prevents the patient from insect assaults; in fact, leishmaniasis is very frequent in such locations. A noteworthy observation for LCL of the extremities is that it can present itself in a lymphocutaneous distribution that is indistinguishable from lymphocutaneous sporotrichosis; this pattern is usually caused by *Leishmania braziliensis* [18]. In endemic countries, such as Brazil and Colombia, it is therefore always recommended to collect samples for histopathology and culture from ulcerative lesions that show a sporotrichoid aspect so that LCL can be differentiated from cutaneous sporotrichosis and atypical mycobacteriosis [18].

Leishmaniasis *recidivans* occurs when the patient has a strong Th1-cellular immunity axis, which allows for more efficient control of the parasites as granulomatous inflammation develops. *Recidivans* points to new lesions that arise at the margin of the healed primary ulcer and is usually composed of small papules that tend to follow a chronic and relapsing course [19, 20]. *Leishmania tropica* is commonly the causative infective agent.

Reports on leishmaniasis *recidivans* on the scalp lack in the literature, but a case on the face has been published by Masood et al. [20]. Although this clinical presentation is rare, leishmaniasis *recidivans* can be confused with other important

granulomatous conditions, such as leprosy and lupus vulgaris, both clinically and histologically [20].

Diffuse cutaneous leishmaniasis (DCL) is a rare clinical presentation of leishmaniasis that can be caused by several species of *Leishmania*, though it is more frequently seen in patients who are infected by *L. amazonensis* [7, 15]. DCL develops in individuals who have a reduced cell-mediated immunity – they are anergic to *Leishmania* antigen – as also observed in lepromatous leprosy. Patients with DCL may display infiltrative skin lesions that show different clinical features, such as a mix of papular/nodular appearance and even keloidal presentations; nonetheless, ulceration is uncommon as compared to what is observed in LCL [7]. In DCL, the entire body may be involved since there can be a blood spread of amastigotes in macrophages, which can disseminate the parasites to distant skin areas [18]. Mucous involvement is also possible, but not as a primary process; it rather occurs as a contiguous invasion of a given mucous membrane, such as the nasal mucosa in patients who have skin lesions in the vicinity of the nose cavity [15].

The diagnosis of leishmaniasis depends on the direct visualization of the parasites in smears or histopathology (Fig. 6.1f), parasite isolation by in vitro culture, and molecular detection of parasite DNA [21]. Up to now, there is no gold-standard diagnostic test, and since the diagnosis cannot be reached solely based on clinical grounds, it is recommended to combine histopathology, culture, and DNA amplification techniques [6, 7].

The diagnosis of cutaneous leishmaniasis begins with a reasonable clinical hypothesis, considering both epidemiology and the clinical aspect of the lesions. It means that pieces of information such as prior history of trips to endemic areas and where the patient lives should not be ignored [13]. It is also common for patients with leishmaniasis to tell a history of previous unsuccessful treatments with oral antibiotics, since the disease is frequently misdiagnosed as pyoderma by general practitioners [13].

For the ideal specimen collection, the physician must first clean the lesions with soap and water or saline solution so that bacteria from secondary infection do not interfere with the final results [13]. Then, both the base and margins of ulcerative lesions should be brushed with a cytology brush and send to histology, culture, and PCR. Alternatively, the physician may also use a glass slide to touch the ulcer ("touch prep" smears), therefore getting extra diagnostic samples. "Touch prep" smears can be performed too after a skin fragment is taken from a given lesion.

A full-thickness punch biopsy (4 or 5 mm) from the border of a lesion is another easy diagnostic procedure. While some prefer taking two different specimens – one for histopathology and the other for culture – it is possible to split the same skin sample in two, thereby having enough material for both culture and histopathology. In this case, it is of ultimate importance to make sure that the piece of skin that is going to be sent for culture is not immersed in formaldehyde but in saline solution. This is not only vital for the diagnosis of leishmaniasis but also to rule out infections by acid-fast mycobacteria and fungi [13].

When a skin biopsy is correctly performed, *Leishmania* amastigotes can be seen by the experienced eye even in routine histopathological preparations (hematoxylin and eosin staining), though Giemsa staining is typically used to highlight the

kinetoplast, which may be visualized in both tissue samples and touch prep smears [6]. Typically, the parasites are found inside macrophages in the upper dermis and are often surrounded by a mixed inflammatory infiltrate. Since a granulomatous process may develop and other diseases may display the same pattern, the visualization of the kinetoplast is essential for a histologic diagnosis.

The difficulties involving the detection and identification of the parasites in histopathology reinforce the need for culture whenever possible. It is true that amastigotes are highly fastidious organisms, but in adequate media, such as Novy, MacNeal, Nicolle (NNN) media, and in ideal temperatures (26 °C), they can turn back into promastigotes within 2 weeks [13]. These results will also be obtained through if proper caution is taken before the culture preparation itself, since transport of the skin sample in inappropriate media is a frequent cause of false-negative results. Again, culture for acid-fast bacilli and fungi must be performed as well so that potential alternative diagnoses are not missed.

Polymerase chain reaction (PCR) represents the most sensitive (97% to 100%) diagnostic test for cutaneous leishmaniasis and is considered valuable in different scenarios since almost any tissue specimen can be used for this purpose [9, 13, 22]. New lesions that are full of parasites will help more than old ones because PCR sensitivity decreases with time as the number of parasites reduces [6, 7, 13]. In spite of its usefulness, PCR is unavailable in several cities of developing countries where leishmaniasis is still endemic.

In South America, the Montenegro skin test can be used to confirm a given patient's contact with leishmaniasis, but it is only available in very specialized centers and is being gradually less used due to its inability to distinguish between active and resolved infection [19, 22]. To perform the Montenegro test, a phenol-killed preparation of promastigotes is placed into the dermis by needle injection, and the cutaneous response is measured after 48 h; ≥5 mm induration is considered a positive reaction [7, 11, 13].

The diagnostic possibilities for leishmaniasis of the scalp include inflammatory diseases, as well as other infectious processes and several types of neoplasia (Table 6.2). For localized scalp lesions particularly in endemic areas for leishmaniasis, one should consider LCL even if the hair is not shaved.

Since granulomatous conditions of the skin are among the differential diagnosis, diascopy may provide valuable clinical clues regarding the nature of the inflammatory process [23]. Accordingly, cases of lupoid leishmaniasis and leishmaniasis *recidivans* displaying the same apple-jelly appearance seen in sarcoidosis, tuberculosis, and other cutaneous granulomatous diseases have been reported [13, 20, 23,

**Table 6.2** Differential diagnosis of cutaneous leishmaniasis of the scalp

| Acute cutaneous leishmaniasis | Chronic cutaneous leishmaniasis |
|---|---|
| Kerion | Lupus vulgaris |
| Tuberculosis cutis | Sarcoidosis |
| Sarcoidosis | Discoid lupus erythematosus |
| Cutaneous T-cell lymphoma | Keloids |
| Basal and squamous cell carcinomas | Syphilitic gumma |
| Cutaneous metastases | |

**Table 6.3** Features of complicated and uncomplicated cutaneous leishmaniasis

| Complicated disease | Uncomplicated disease |
|---|---|
| Individual lesion ≥5 cm | Lesion size <1 cm |
| Subcutaneous nodules | Immunocompetent host |
| More than 4 lesions with >1 cm | Single or small number of lesions |
| Difficult to treat body location | No mucosal involvement |
| Presence of subcutaneous nodules | |

24]. The apple-jelly aspect distinguishes granulomatous disorders from non-granulomatous diseases that can be similar to the naked eye. For instance, the apple-jelly aspect is not expected from a squamous cell carcinoma of the scalp, though it can occur in cutaneous leishmaniasis.

Dermoscopy, as a complementary tool, can as well add some extra information from scalp lesions of leishmaniasis. Nonetheless, caution is needed since the dermoscopic features on scalp leishmaniasis that have been published are not specific for the disease, and thus they should be well contextualized [13], as is a general rule in dermoscopy. As of yet, the diagnosis of cutaneous leishmaniasis requires a skin biopsy for culture and histopathology.

The treatment of leishmaniasis depends both on the type of *Leishmania* that is involved and the severity of the infection. Even though the treatment itself may vary from country to country, the primary intention of therapy is not to reach a parasitologic cure, since not all patients who undergo treatment demonstrate elimination of the parasites [25]. In this sense, what really matters in practice is the clinical cure, when active cutaneous lesions are no longer detected [21].

As mentioned in the literature, some authors consider that clinical observation alone (no treatment) might be a reasonable approach for immunocompetent patients with uncomplicated lesions (Table 6.3) [21]. This strategy is based on the fact that several cutaneous lesions of cutaneous leishmaniasis eventually resolve clinically without treatment, and thus the patient could be spared from the potentially related undesired therapy effects. Nonetheless, others recommend that an antileishmanial therapy must be promptly started as soon as the diagnosis is given, since it will accelerate the cure of the disease, irrespective of the patients' immune status.

As of yet, there is no universally applicable treatment for cutaneous leishmaniasis [21]. More conservative measures, such as thermotherapy and cryotherapy, are reported in the literature among the therapeutic options for patients with uncomplicated cutaneous leishmaniasis, especially for those who are infected by species of *Leishmania* that are unlikely to cause disseminated disease, such as *L. donovani*, *L.V. braziliensis*, and *L.V. guyanensis*. In daily practice, however, it is not always possible to determine the species of the *Leishmania* involved in the individual case, particularly in the developing countries. In such circumstances, observation alone or the use of isolated local measures may be too risky for the patient. Furthermore, certain hairy body areas can be considered difficult to treat with more conservative measures; for instance, the hairy scalp displays a rich innervation supply, and significant pain is expected from cryotherapy, which could also cause permanent hair loss, resulting in cicatricial alopecia.

It is recommended to carefully examine the patients' nasal and oral mucosa for involvement. In this case, the treatment should be modified regarding both dosing and duration [26, 27]. If a systemic therapy and which one will be prescribed depends on the country the patient is in. In Brazil, for example, LCL is successfully treated with pentavalent antimonials, and most cases show successful results. In the United States, however, pentavalent antimonials are not available as for many other areas of the globe.

Miltefosine, azoles, amphotericin deoxycholate, and liposomal amphotericin are all included in the therapeutic arsenal for the treatment of leishmaniasis. The efficacy of azoles and parenteral liposomal amphotericin B is limited, and the side effects of a long-term treatment should be considered individually [26, 27]. Parenteral agents for the treatment of CL include pentavalent antimonials, amphotericin, and pentamidine, and the use of each drug varies depending on the local availability of the drug and the experience of the attending physician. Most data available in the literature point to parenteral pentavalent antimonials as the first-line systemic treatment for cutaneous and mucocutaneous/mucosal leishmaniasis, whereas liposomal amphotericin B is the treatment of choice for visceral leishmaniasis [21].

Overall, antimonials are the treatment of choice, given their excellent potential to promote regression of cutaneous lesions, and they are especially important for the treatment of patients with the potential of mucosal involvement [28]. There are two parenteral pentavalent antimony agents both considered equally effective in clinical practice, sodium stibogluconate (sodium antimony gluconate, Pentostam) and meglumine antimoniate (N-methyl glucamine antimoniate, Glucantime) [29].

In Brazil, meglumine antimoniate is the most used therapy for cutaneous leishmaniasis, and it can be administered by intramuscular or intravenous routes (single daily dose infused over 30 minutes for 20 days) with doses consisting of 20 mg SbV/kg/day (SbV = pure antimonio). Some experts in Brazil from FioCruz, Manguinhos, Rio de Janeiro, also carry on studies with intralesional therapy in which patients with localized forms of cutaneous leishmaniases can be treated with lower doses of SbV (20 mg SbV/kg/day) with satisfactory results [30, 31].

The reason why researchers have long been dedicating themselves to find the minimal effective dose of antimonials to treat leishmaniasis is because antimonials may cause serious adverse effects, including early elevation of pancreatic enzymes (rarely severe pancreatitis), leukopenia, and QT prolongation [8, 21]. Local pain, myalgia, arthralgia, nausea, fatigue, and headaches are quite common during the treatment, but these represent no source of serious concern [8, 21]. For every patient under treatment with antimonials, electrocardiogram, blood counts, serum concentrations of creatinine, amylase, lipase, and transaminases are required on a weekly basis [8, 21]. The pentavalent antimonial agents are contraindicated in pregnant or breastfeeding women.

## 6.2 South American Blastomycosis/Paracoccidioidomycosis

South American blastomycosis, also known as paracoccidioidomycosis (PCM) is a potentially lethal systemic infectious granulomatous disease caused by dimorphic fungi of the *Paracoccidioidomycosis* complex: *P. brasiliensis* (Pb01), *P. lutzi*, and Pb01-like species [32].

The disease was first reported by a Brazilian physician, father of tropical medicine and medical zoology in Brazil, and a pioneer epidemiologist and researcher in infectious diseases, Adolfo Lutz (1855–1940), in 1908, and is thus also known as Lutz-Splendore-Almeida disease. The term paracoccidioidomycosis was officially acknowledged by the World Health Organization in 1971 [33].

PCM is the most prevalent systemic mycosis of Latin America from 23°N to 23°S. Brazil accounts for 80% of the cases, followed by Venezuela, Colombia, and Argentina [34, 35].

The risk factors for acquisition of the infection are activities related to the handling of contaminated soil. Patients are primarily infected by inhaling fungal cells from the soil, which spread via the bloodstream and the lymphatic system. Penetration of the fungus via broken skin or intestinal mucous membrane is controversial. It is possible that infection may occur by inoculation of the fungus through the habit of picking teeth with small branches, chewing leaves, and using leaves for anal hygiene [33].

The presence of the fungi is related to climatic conditions, like precipitation, air temperature, level of humidity, soil water storage, and altitude. There is evidence that *P. brasiliensis* grows preferentially 2–20 cm below the soil surface. Human rural activities and deforestation remove the surface of the soil, exposing spores and allowing mycelia to be aerosolized [32].

Before pubertal age, PCM affects equally both genders, but after puberty, the male/female ratio is 60% [36]. It is possible that women are protected against PCM by the effect of 17β-estradiol, the main female estrogen, which seems to inhibit conidia-to-yeast transformation, which is required for infection establishment. Further studies inquire that sexual hormones may also act by modulating the host's immune responses. Estrogens favor better cell-mediated immune responses, such as enhanced Th-1 cytokines secretion by T-cells and phagocytes as well as oxide nitric release [37].

The majority of the patients with adult chronic clinical forms come from rural environments with high rates of smoking and alcohol abuse. There are no racial preferences [38].

*Paracoccidioides* spp. can be cultivated as mycelium at 25 °C and as yeasts at 37 °C after 15 to 30 days using agar Sabouraud dextrose. At 37 °C, the fungus presents as oval, spherical, or elliptical yeast-like cells with birefringent wall. Multiple or simple gemmulation is observed in the direct examination of in histopathology. One mother cell can have 10–20 daughter cells attached to it, in a multiple-budding structure called "pilot-wheel." The finding of one mother cell with two attached

daughter cells resembling a Mickey Mouse form is a common feature that facilitates the recognition of the fungus either in the colony examination or in the histopathology [32].

There are the following clinical forms of PCM:

- Acute/subacute juvenile form
- Chronic adult form
- Infection form
- Cicatricial or residual form
- Mixed form

PCM presents with a polymorphism of lesions and can affect any organ with preference for the skin; lymph nodes; lungs; oral, nasal, and gastrointestinal mucous membranes; suprarenal glands; and central nervous system [33].

The *acute/subacute form of PCM* usually affects children, adolescents, and young adults. It is characterized by lymph node enlargement, hepatomegaly, splenomegaly, and bone marrow involvement. Mucosal involvement and lung involvement are infrequent. There is no radiological evidence of lung involvement, but the fungus can be found in bronchoalveolar lavage fluids.

The *chronic adult form of PCM* usually manifests in adults over 30 years of age. The involvement of the lungs is the rule. It is divided in unifocal and multifocal forms. The unifocal form affects only the lungs, and the multifocal form also affects other organs besides the lungs. Preferable sites of infection are the mucous membranes, skin, adrenal glands, and lymphatics. Skin lesions are polymorphic and may present microgranulation, pinpoint hemorrhages, and infiltration. Also, affected mucous membranes can show pinpoint hemorrhages, and this feature is known as moriform stomatitis of Aguiar-Pupo [39].

In the *infection form of PCM*, healthy individuals that had contact with the fungus show no clinical symptoms. Asymptomatic infection is demonstrated by means of paracoccidioidina skin test with 60% positivity in endemic areas, which suggests some individual susceptibility [40]. Gavazzoni Dias et al. compared the expression of HLA class I antigens in healthy individuals and in a group of patients with PCM but failed to find any evidence of individual susceptibility associated with a specific immunological defect related to the HLA system. In this work, all patients with PCM were smokers, suggesting that tabagism may be related to the relapse of the disease in the adult chronic form [40].

The *cicatricial/residual form of PCM* is a result of extreme fibrosis of the lungs and larynx and may cause important restriction on the pulmonary and larynx function. Cicatricial forms are the final sequalae of severe adult chronic disease, leading to emphysema and fibrosis [32].

Patients with severe immune depression usually manifest a *mixed form of PCM* with clinical symptoms of both the acute and the chronic form. There is the involvement of the mononuclear phagocyte system associated with upper aerodigestive tract lesions, mucous membrane, and skin lesions [32].

*P. brasiliensis* exhibits a complex antigenic structure composed by glycoproteins, glycopeptides lipids, and polysaccharides. The fungus virulence appears to be associated with the presence of α-1,3-glucan in the cell wall. The presence of specific serum antibodies against the 43-kDa glycoprotein, the main antigen of the fungus, helps confirm the diagnosis of this infection [41].

The host's immune response to the infection determines the progression of the host-parasite interaction. Depending on the balance between the host, parasite, and environmental factors, the fungi may remain latent for many years or for life. Severe cases are accompanied by some level of immunosuppression, and there is a correlation of depression of cell-mediated immunity and severity of disease [32].

The natural contagion is by aspiration, and with an insufficient immune response (phagocytosis), there is the formation of a primary complex that may spread from the lungs to any other organ of the body via lymphatics and bloodstream [34]. The Th2/Th9 type of immune response is characteristic of the acute clinical form of PCM, and patients produce large amounts of antigen-specific IgA, IgE, and IgG4. In patients with chronic adult forms, the Th1 response is more preserved, except for those with extreme severe forms [41].

Histopathology of skin lesions show well-organized granulomas composed of epithelioid cells, giant cells, yeast cells, leukocytes, and lymphocytes. The fungi are most found inside the abscess [33].

PCM can manifest in the cephalic pole, preferably on the face (Fig. 6.2a), usually with sarcoid-like cutaneous lesions, needing a careful differential diagnosis from chronic discoid lupus erythematous (Fig. 6.2b) and ulcerative sarcoidosis [38]. The majority of cases involving the skin are of the chronic adult form. The presence of important regional lymphadenopathy may help distinguish PCM from other conditions.

The scalp is rarely affected by PCM and may imitate skin tumors or other infectious disease, such as tuberculosis (Fig. 6.2c).

Carrara Camillo et al. [42] reported a case PCM with multiple scalp plaques with central atrophic scarring (Fig. 6.2d). Numerous papules with pinpoint hemorrhages were seen infiltrating the edges of the plaques. Potassium hydroxide mount revealed the fungi cells, and histopathology showed well-formed non-caseating granulomas with multiple budding yeast cells in a wheel-like configuration. The culture was positive for *P. brasiliensis*.

Scalp involvement was also reported by Rocha-Silva et al. [43] in a case of disseminated PCM. The scalp lesions were erythematous infiltrated exulcerated and crusted plaques located in the occipital region combined with yellow-nail syndrome. Internal lesions showed an abdominal mass with lymphadenopathy and an infiltrative pattern affecting gallbladder and intrahepatic bile ducts. The patient was previously suspected of having a malignant neoplasm due to the infiltrative pattern of the disease on imaging. Diagnosis was made by histopathology of the skin, showing micro-abscesses with multinucleated giant cells, combined with detection of the fungus on direct examination of the pus. Also, serology with double radial immunodiffusion for antibodies against Gp43 antigens was positive as well as RT-PCR for *P. brasiliensis* assays.

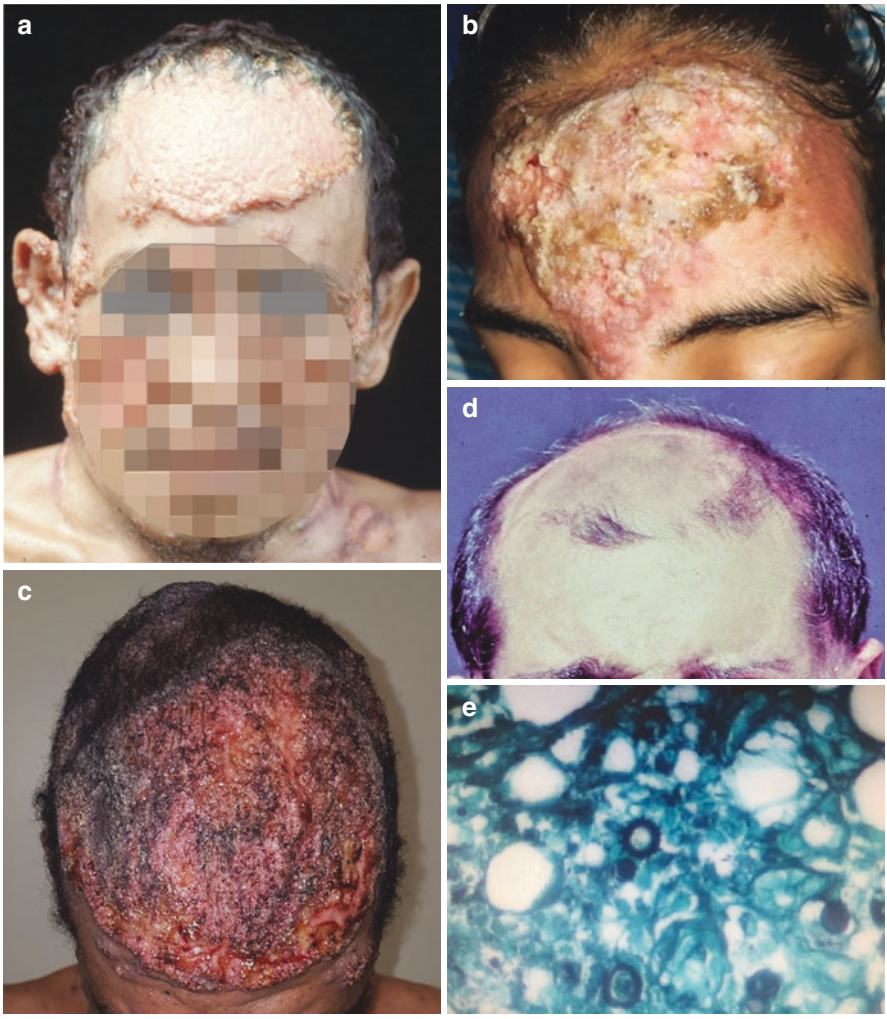


**Fig. 6.2** (**a–e**) Paracoccidioidomycosis: (**a**) chronic adult form with skin involvement in the cephalic pole (courtesy of Prof Sinesio Talhari, Department of Infectious Diseases, Amazonas Foundation of Tropical Medicine, Brazil), (**b**) mimicking chronic discoid lupus erythematosus in the face (courtesy of Prof. Remberto Mauricio Vilte, Fluminense Federal University, Brazil), (**c**) widespread scalp involvement (courtesy of Prof. Dayvison Freitas. Evandro Chagas National Institute of Infectology, Oswaldo Cruz Foundation, Brazil), (**d**) residual scarring (courtesy of Prof Sinesio Talhari, Department of Infectious Diseases, Amazonas Foundation of Tropical Medicine, Brazil), and (**e**) detection of fungal elements with the typical pilot wheel appearance (courtesy of Prof. Remberto Mauricio Vilte, Fluminense Federal University, Brazil)

Deps et al. [44] reported on an 18-year-old woman with a rapid progressive form of PCM affecting the face and scalp without systemic complaints. Skin lesions were hard papules, nodules, and single formations of brown plaques of verrucous shape spreading over the face, ear, and the scalp. The patient also presented with a typical moriform stomatitis of Aguiar-Pupo on the hard palate and oral mucosa in combination with cervical lymph nodes.

Finally, Guerra et al. [45] reported on an elderly female patient with exuberant multiple facial skin lesions associated with cervical and hepatic adenopathy, causing bile duct dilatation, mimicking cholangiocarcinoma. She had a plaque with irregular erythematous verrucous border and central atrophy occupying almost the entire forehead (temporal and parietal areas), resembling cutaneous lupus erythematosus. She also had plaques with a verrucous surface on the eyebrows and the zygomatic area. The presence of the fungus was detected in histopathology of the skin and liver tissues, exhibiting the aspect of the "pilot wheel" (Fig. 6.2e).

Specifically, scalp PCM must be differentiated from squamous cell carcinoma, amelanotic melanoma, scalp metastatic lesions, tuberculosis, syphilis, leishmaniasis, and blastomycosis.

The patient history is important to establish the exposition of the patient to the infectious agent in contaminated areas at any time of life. Direct examination and culture of the affected tissues or harvested material are the gold standard tests for diagnosis. Histopathology, particularly of lesional skin, is also helpful in establishing the diagnosis.

Skin biopsy is important to rule out malignancy, and a tissue culture for detection of the responsible infectious agent. *P. brasiliensis* multiple budding is characteristic and sufficient to establish the proper diagnosis.

Since scalp lesions are accompanied by lung involvement, imaging by tomography for identification is recommended.

Moreover, 13% of PCM chronic adult forms are associated with tuberculosis.

The following laboratory tests and image examinations have also been recommended: total blood cell count, erythrocyte sedimentation rate, liver and renal function tests, protein electrophoresis, chest radiographs and tomography, abdominal ultrasound, and serology. Serology is also used for patient follow-up. Specific tests including double immunodiffusion, counterimmunoelectrophoresis, enzyme-linked immunosorbent assay (ELISA), and immunoblotting methods. Polymerase chain reaction is a promising technique, but it is not always available [33].

The Brazilian guidelines for the management of PCM was published in 2017 and offers a practical guideline for diagnosis and treatment of the disease [46].

*P brasiliensis* complex is normally sensitive to most antifungal drugs. Itraconazole, co-trimoxazole (trimethoprim/sulfametoxazole), and amphothericin B are the predominantly used drugs. *P. brasiliensis* and *P. lutzii* respond equally to treatment. Voriconazole, posaconazole, and isavuconazole are currently being considered as possible new drugs.

The guideline-recommended drugs and dose are specified in Table 6.4.

Itraconazole should not be used in combination with astemizole, H2 blockers, antiacids, cisapride, cyclosporine, barbituric, didanosine, digoxin, fentanyl,

**Table 6.4** Treatment recommendations for PCM

| Drug | Dosage | Duration of treatment |
|---|---|---|
| Itraconazole | 200 mg/daily<br>Children with <30 kg and under 5 years old: 5–10 mg/kg/daily; dose is adjusted without opening the capsule | 9–18 months |
| Co-trimoxazole | Sulfamethoxazole 800 + trimethoprim 160 mg (orally 2–3 times a day)<br>Severe cases: 800 mg/160 mg IV 3 times a day<br>Children: Trimethoprim 8-10 mg/kg + sulfamethoxazole 40–50 mg/kg orally twice a day | 18–24 months |
| Amphotericin B | Deoxycholate (conventional) 0.5–0.7 mg/kg/daily<br>Lipid complex: 3–5 mg/kg once daily | 2–4 weeks, followed by itraconazole or co-trimoxazole treatment |

phenytoin, rifampicin, and terbinafine. Involvement of the central nervous system may require a longer duration of treatment with co-trimoxazole. Fluconazole IV 600–800 mg/daily is a possible option for severe cases. With the involvement of the larynx, trachea, and central nervous system or in AIDS patients, the use of corticosteroids during the first 1–2 weeks of the chosen treatment should be considered [46].

## 6.3 African Trypanosomiasis

African trypanosomiasis, also known as African sleeping sickness or simply sleeping sickness, is an insect-borne parasitic infection of humans caused by the species *Trypanosoma brucei*. Humans are infected by two types, *Trypanosoma brucei gambiense* (TbG) and *Trypanosoma brucei rhodesiense* (TbR). TbG causes over 98% of reported cases. Both are usually transmitted by the bite of an infected tsetse fly and are most common in rural areas.

Initially, the first stage of the disease is characterized by fevers, headaches, itchiness, and joint pains, beginning 1 to 3 weeks after the bite. Weeks to months later, the second stage begins with confusion, poor coordination, numbness, and trouble sleeping. Sleep-wake disturbances are a leading feature of neurological stage and gave the disease its notorious name. Infected individuals experience a disorganized and fragmented sleep-wake cycle. Those affected experience sleep inversion resulting in daytime sleep and somnolence and nighttime periods of wakefulness and insomnia. Additionally, those affected also experience episodes of sudden sleepiness. If the disease is not treated quickly, it can lead to death.

Diagnosis is done by finding the parasite in a blood smear or in the fluid of a lymph node. A lumbar puncture is often needed to tell the difference between first- and second-stage disease.

Prevention of severe disease involves screening the at-risk population with blood tests for TbG. Treatment is easier when the disease is detected early and before neurological symptoms occur. Treatment of the first stage has been with the

medications pentamidine or suramin. Treatment of the second stage has involved eflornithine.

Eflornithine was initially developed for cancer treatment at Merrell Dow Research Institute in the late 1970s but was found to be ineffective in treating malignancies. However, it was discovered to be highly effective in the treatment of African trypanosomiasis and in reducing hair growth. In fact, eflornithine is the only new molecule registered for the treatment of human African trypanosomiasis over the last 50 years. The most commonly used dosage regimen for the treatment of *T. b. gambiense* sleeping sickness consists of 100 mg kg(−1) body weight at intervals of 6 h for 14 days (150 mg kg(−1) body weight in children) of eflornithine given as short infusions. Adverse drug reactions during eflornithine therapy are frequent, and the characteristics are similar to other cytotoxic drugs for the treatment of cancer. Their occurrence and intensity increase with the duration of treatment and the severity of the general condition of the patient. Generally, adverse reactions to eflornithine are reversible after the end of treatment. They include convulsions in 7%; gastrointestinal symptoms like nausea, vomiting, and diarrhea in 10–39%; bone marrow toxicity leading to anemia, leucopenia, and thrombocytopenia in 25–50%; and alopecia in 5–10% [47].

In the 1980s, Gillette was awarded a patent for the discovery that topical application of eflornithine HCl cream inhibits hair growth. In the 1990s, Gillette conducted dose-ranging studies with eflornithine in hirsute women who demonstrated that the drug slows the rate of facial hair growth. Gillette then filed a patent for the formulation of eflornithine cream. In July 2000, the US Food and Drug Administration (FDA) granted a New Drug Application for Vaniqa. The following year, the European Commission issued its marketing authorization.

The drug was registered for the treatment of *T. b. gambiense* sleeping sickness on November 28, 1990. However, in 1995, Aventis (now Sanofi-Aventis) stopped producing the drug, whose main market was African countries, because it did not make a profit. In 2001, Aventis and the WHO formed a 5-year partnership, during which over 200,000 bottles of eflornithine were produced by Aventis, to be given to the WHO and distributed by the association Médecins sans Frontières (also known as Doctors Without Borders) in countries where sleeping sickness is endemic. According to Médecins sans Frontières, this only happened after "years of international pressure" and coinciding with the period when media attention was generated because of the launch of another eflornithine-based product (Vaniqa, for the prevention of facial hair in women), while its life-saving formulation (for sleeping sickness) was not being produced. From 2001 (when production was restarted) through 2006, 14 million diagnoses were made. This greatly contributed to stemming the spread of sleeping sickness and to saving nearly 110,000 lives.

## 6.4 Endemic Treponematoses

The three endemic or non-venereal treponematoses – yaws (frambesia), pinta (carate), and endemic syphilis (Bejel) – have some characteristic features in common: they are all caused by spirochaetes (*T. pallidum* subspecies *pertenue*,

*Treponema carateum*, and *Treponema pallidum* subspecies *endemicum*, respectively), and all occur in regions with hot climate and predominantly in rural communities. The transmission of the diseases is non-venereal and occurs by direct contact. Children and adolescents are most often affected. Yaws (frambesia) is the most prevalent of the endemic treponematoses and occurs in humid equatorial countries. Transmission requires direct skin contact and is favored by skin trauma. Pinta, which is more limited in geographical distribution, occurs among the natives of Mexico, Central America, and South America and is not very contagious. Transmission probably requires contact with broken skin. Bejel (endemic syphilis) occurs mainly in hot, dry regions of the eastern Mediterranean and Saharan West Africa. Transmission results from mouth-to-mouth contact or sharing eating and drinking utensils.

The lesions are located extragenitally. The diseases are chronic and occur in several stages. As in syphilis, the typical course is an initial mucocutaneous lesion followed by diffuse secondary lesions, a latent period, and late destructive disease. Unlike *T. pallidum* subspecies *pallidum*, the other human treponemal subspecies are not transmitted via blood or transplacentally. Therefore, there are no congenital manifestations.

Eaten alopecia is occasionally seen. Diffuse alopecia has also been reported.

Diagnosis is clinical and epidemiologic. Both non-treponemal and treponemal serologic tests for syphilis (the Venereal Disease Research Laboratory [VDRL], rapid plasma reagin [RPR], and fluorescent treponemal antibody absorption tests [FTA-ABS]) are positive; thus, differentiation from venereal syphilis is clinical. Early lesions are often darkfield positive for spirochetes and are indistinguishable from *T. pallidum* subspecies *pallidum*.

Treatment is with penicillin. Active disease is treated with 1 dose of penicillin benzathine 1.2 million units IM. Children <45 kg should receive 600,000 units IM. A single dose of azithromycin 30 mg/kg orally (maximum 2 g) or doxycycline 100 mg orally twice a day for 14 days is an alternative for penicillin-allergic adults. Active disease is treated with 1 dose of penicillin benzathine 1.2 million units IM. Children <45 kg should receive 600,000 units IM. A single dose of azithromycin 30 mg/kg orally (maximum 2 g) or doxycycline 100 mg orally twice a day for 14 days is an alternative for penicillin-allergic adults.

Public health control includes active case finding and treatment of family and close contacts with penicillin benzathine or doxycycline to prevent infection from developing.

All human treponematoses, including syphilis, share remarkable similarities in pathogenesis and clinical manifestations, consistent with the high genetic and antigenic relatedness of their etiological agents. They have a chronic relapsing course and have prominent cutaneous manifestations. They are at present indistinguishable by morphological, immunological, or serological methods. Treponemal diseases are distinguished on the basis of epidemiological characteristics and clinical characteristics. No treponeme of this group, except for that of the rabbit, is known other than in man, but the human treponemes probably arose long ago from an animal infection. The long period of infectiousness of pinta suggests that it may have been the

earliest of human treponematoses and have been spread throughout the world by about 15,000 BC, being subsequently isolated in the Americas when the Bering Strait was flooded. About 10,000 BC, in the Afro-Asian landmass, environmental conditions might have favored treponeme mutants leading to yaws. From these, about 7000 BC, endemic syphilis perhaps developed, to give rise to venereal syphilis about 3000 BC in southwest Asia as big cities developed there. The venereal form of treponematosis, caused by the spirochete *Treponema pallidum*, eventually plagued every major city in the pre-antibiotic era.

"Civilization means syphilization" was an idea touted by Austrian psychiatrist and author of the foundational work, *Psychopathia Sexualis* (1886), Richard von Krafft-Ebing (1840–1902), in that the effects of modern life make men more susceptible to syphilis and other diseases. Krafft-Ebing considered procreation the purpose of sexual desire and that any form of recreational sex was a perversion of the sex drive. According to Krafft-Ebing, particularly homosexuals suffered a degree of sexual perversion, because homosexual practices could not result in procreation. With reference to the Hebrew Bible, the cities of Sodom and Gomorrah have been used historically and in modern discourse as metaphors for homosexuality, based upon exegesis of the Biblical text interpreting divine judgment upon Sodom and Gomorrah as punishment for the sin of homosexual sex. Toward the end of the fifteenth century AD, a further mutation may have resulted in a more severe venereal syphilis in Europe, which, with European exploration and geographical expansion, was subsequently carried throughout the then treponemally uncommitted world. These suggestions find some tentative support in climatic changes, which might have influenced the selection of those treponemes, which still survive in humid or arid climates. Ultimately, venereal transmission would presumably remove the treponeme from the direct influence of climate [48].

A drastic decline in the prevalence of the non-venereal treponematosis was eventually brought about by the implementation of mass treatment campaigns with penicillin under the technical guidance of WHO and with material support from UNICEF in the 1950s and 1960s. However, these diseases have as not yet been eliminated and are currently thought to affect at least 2.5 million persons. Moreover, several cases of imported yaws and endemic syphilis have recently been observed in Europe, and with the escalating US military presence in many remote areas of the world and ever-increasing worldwide travel, the diagnosis of the non-venereal treponematoses must be considered in the appropriate clinical and historical setting.

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# Viral Diseases of the Hair and Scalp

# 7

Ralph M. Trüeb and Hudson Dutra Rezende

## Contents



A virus is a submicroscopic infectious agent hat replicates exclusively within the living cells of an organism. Most virus species are too small to be visualized with an optical microscope and are one-hundredth the size of most bacteria. The first images of viruses were obtained upon the invention of electron microscopy in 1931 by the German engineers Ernst Ruska and Max Knoll. In fact, in 1886, John B. Buist visualized one of the largest, vaccinia virus, by optical microscopy after staining it. Vaccinia was not known to be a virus at that time. Since Dmitri Ivanovsky's 1892 article describing a nonbacterial pathogen infecting tobacco plants and the discovery of the tobacco mosaic virus by Martinus Beijerinck in 1898, more than 9000 virus species have been described in detail of the millions of types of viruses in the

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environment [1]. Viruses are the most abundant type of biological entity and found in almost every ecosystem of the earth.

The origins of viruses in the evolutionary history of life are unclear: some may have evolved from plasmids, pieces of DNA that can traffic between cells, while others may have evolved from bacteria. In evolution, viruses are an important means of horizontal gene transfer, which increases genetic diversity.

When infected, a host cell is often forced to rapidly produce thousands of copies of the original virus. When not inside an infected cell or in the process of infecting a cell, viruses exist in the form of independent particles, or virions, consisting of:

1. DNA or RNA that encodes the structure of the proteins by which the virus acts
2. A protein coat, the capsid, which surrounds and protects the genetic material
3. In some cases an outside envelope of lipids

A viral disease occurs when an organism's body is invaded by pathogenic viruses and infectious virus particles (virions) attach to and enter susceptible cells [2].

Basic structural characteristics, such as genome type, virion shape, and replication site, generally share the same features among virus species within the same family. Human-infecting virus families offer rules that may assist physicians (Table 7.1). However, the clinical characteristics of viral disease may differ substantially among species within the same family (Table 7.2).

As a general rule, DNA viruses replicate within the cell nucleus, while RNA viruses replicate within the cytoplasm. Exceptions to this rule include poxviruses that replicate within the cytoplasm and orthomyxoviruses and hepatitis D virus (RNA viruses) that replicate within the nucleus.

Some species of virus envelop themselves in a modified form of one of the cell membranes, either the outer membrane surrounding an infected host cell or internal membranes such as a nuclear membrane or endoplasmic reticulum, thus gaining an outer lipid bilayer known as a viral envelope. This membrane is studded with proteins coded for by the viral genome and host genome; the lipid membrane itself and any carbohydrates present originate entirely from the host. Influenza virus, HIV, and the severe acute respiratory syndrome coronavirus 2 [3] use this strategy. Most enveloped viruses are dependent on the envelope for their infectivity.

This chapter focusses on the viral infections that affect the scalp and hair through either direct inoculation or local spread from an internal focus. The manifestations of systemic disease, specifically HIV, dengue hemorrhagic fever, chikungunya, Zika, and COVID-19 are covered in the respective chapter.

**Table 7.1** Clinically important virus families and species with virus characteristics

| Family | Baltimore group | Envelopment | Important species |
|---|---|---|---|
| Adenoviridae | I (dsDNA) | No | Adenovirus |
| Herpesviridae | I (dsDNA) | Yes | Herpes simplex, type 1, herpes simplex, type 2, varicella-zoster virus, Epstein-Barr virus, human cytomegalovirus, human herpesvirus, type 8 |
| Papillomaviridae | I (dsDNA) | No | Human papillomavirus |
| Polyomaviridae | I (dsDNA) | No | BK virus, JC virus |
| Poxviridae | I (dsDNA) | Yes | Smallpox |
| Parvoviridae | I (ssDNA) | No | Parvovirus B19 |
| Reoviridae | III (dsRNA) | No | *Rotavirus*, *Orbivirus*, *Coltivirus*, *Banna virus* |
| Astroviridae | IV (positive sense ssRNA) | No | Human astrovirus |
| Caliciviridae | IV (positive sense ssRNA) | No | Norwalk virus |
| Coronaviridae | IV (positive sense ssRNA) | Yes | Human coronavirus 229E, human coronavirus NL63, human coronavirus OC43, human coronavirus HKU1, Middle East respiratory syndrome-related coronavirus, severe acute respiratory syndrome coronavirus [4], severe acute respiratory syndrome coronavirus 2 |
| Flaviviridae | IV (positive sense ssRNA) | Yes | Hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, tick-borne encephalitis virus, Zika virus |
| Hepeviridae | IV (positive sense ssRNA) | No | Hepatitis E virus |
| Matonaviridae | IV (positive sense ssRNA) | Yes | Rubella virus |
| Picornaviridae | IV (positive sense ssRNA) | No | Coxsackievirus, hepatitis A virus, poliovirus, rhinovirus |
| Arenaviridae | V (negative sense ssRNA) | Yes | Lassa virus |
| Bunyaviridae | V (negative sense ssRNA) | Yes | Crimean-Congo hemorrhagic fever virus, hantaan virus |
| Filoviridae | V (negative sense ssRNA) | Yes | Ebola virus, Marburg virus |
| Orthomyxoviridae | V (negative sense ssRNA) | Yes | Influenza virus |
| Paramyxoviridae | V (negative sense ssRNA) | Yes | Measles virus, mumps virus, Parainfluenza virus |
| Pneumoviridae | V (negative sense ssRNA) | Yes | Respiratory syncytial virus |
| Rhabdoviridae | V (negative sense ssRNA) | Yes | Rabies virus |
| Unassigned | V (negative sense ssRNA) | Yes | Hepatitis D |
| Retroviridae | VI (ssRNA-reverse transcriptase) | Yes | HIV |
| Hepadnaviridae | VII (ssRNA-reverse transcriptase) | Yes | Hepatitis B virus |

**Table 7.2** Clinically important virus species, families, with clinical diseases

| Type | Family | Diseases |
|---|---|---|
| Adenovirus | Adenoviridae | Gastroenteritis<br>Keratoconjunctivitis<br>Pharyngitis<br>Pharyngoconjunctival fever |
| Coxsackievirus | Picornaviridae | Hand, foot, and mouth disease<br>Pleurodynia<br>Aseptic meningitis<br>Pericarditis<br>Myocarditis |
| Hepatitis A virus | | Acute hepatitis |
| Poliovirus | | Poliomyelitis |
| Cytomegalovirus | Herpesviridae | Infectious mononucleosis<br>Cytomegalic inclusion disease<br>Premature birth<br>Liver, lung, and spleen diseases in the newborn<br>Small size at birth<br>Small head size<br>Congenital seizures in the newborn |
| Epstein-Barr virus | | Infectious mononucleosis<br>Burkitt's lymphoma<br>Hodgkin's lymphoma<br>Nasopharyngeal carcinoma |
| Herpes simplex virus, type 1 | | Herpes labialis (cold sores)<br>Gingivostomatitis aphthosa in children<br>Tonsillitis and pharyngitis in adults<br>Keratoconjunctivitis |
| Herpes simplex virus, type 2 | | Skin vesicles, mucosal ulcers, oral and/or genital<br>Can be latent<br>Aseptic meningitis |
| Varicella-zoster virus | | Chickenpox<br>Herpes zoster (shingles)<br>Congenital varicella syndrome |
| Human herpesvirus, type 8 | | Kaposi sarcoma<br>Multicentric Castleman disease<br>Primary effusion lymphoma |
| Hepatitis B virus | Hepadnaviridae | Acute hepatitis<br>Chronic hepatitis<br>Hepatic cirrhosis<br>Hepatocellular carcinoma |
| Hepatitis C virus | Flaviviridae | Acute hepatitis<br>Chronic hepatitis<br>Hepatic cirrhosis<br>Hepatocellular carcinoma |
| HIV | Retroviridae | AIDS |

**Table 7.2** (continued)

| Type | Family | Diseases |
|---|---|---|
| Human coronavirus 229E (HCoV-229E) | Coronaviridae | Common cold<br>Pneumonia<br>Bronchiolitis |
| Human coronavirus NL63 (HCoV-NL63) | | Common cold<br>Rhinitis<br>Bronchitis<br>Bronchiolitis<br>Pneumonia<br>Croup |
| Human coronavirus OC43 (HCoV-OC43) | | Common cold<br>Pneumonia |
| Human coronavirus HKU1 (HCoV-HKU1) | | Common cold<br>Pneumonia<br>Bronchiolitis |
| Middle East respiratory syndrome-related coronavirus (MERS-CoV) | | Middle East respiratory syndrome (MERS) |
| Severe acute respiratory syndrome coronavirus (SARS-CoV) | | Severe acute respiratory syndrome (SARS) |
| Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) | | Coronavirus disease 2019 (COVID-19) |
| Human papillomavirus | Papillomaviridae | Common, flat, plantar and anogenital warts, laryngeal papillomas, epidermodysplasia verruciformis<br>Malignancies for some species (cervical carcinoma, squamous cell carcinomas) |
| Influenza virus | Orthomyxoviridae | Influenza<br>Reye syndrome |
| Measles virus | Paramyxoviridae | Measles<br>Postinfectious encephalomyelitis |
| Mumps virus | | Mumps |
| Parainfluenza virus | | Croup<br>Pneumonia<br>Bronchiolitis<br>Common cold |
| Rabies virus | Rhabdoviridae | Rabies |
| Respiratory syncytial virus | Pneumoviridae | Bronchiolitis<br>Pneumonia<br>Influenza-like syndrome<br>Severe bronchiolitis with pneumonia |
| Rubella virus | Togaviridae | Congenital rubella syndrome<br>German measles |

## 7.1 Varicella/Zoster

Although herpetic infections of the skin are very common, herpes folliculitis has relatively been infrequently reported in the literature. Herpes folliculitis is a rare manifestation of herpes virus infection, and it is often misdiagnosed. The clinical presentation of herpes folliculitis often lacks vesicles or pustules. Histopathological features are often devoid of ballooning, multinucleated giant cells, and keratinocytes with steel grey nuclei. The most consistent findings are a lymphocytic folliculitis and perifolliculitis with necrotic keratinocytes within the follicular epithelium [4] (Fig. 7.1a, b).

In 1972, Izumi et al. originally reported two cases of herpes simplex folliculitis, which they called herpetic sycosis. These cases were characterized by a rapid development of mostly grouped vesicular lesions over the beard area with diagnostic, umbilicated, satellite vesiculofollicular lesions at the periphery. Biopsy specimens showed herpetic cytopathic changes involving the infundibulum of the hair follicle and the surrounding epidermis. The diagnosis was confirmed by recovery of herpes simplex viruses (HSV) on tissue culture [5].

Muraki et al. demonstrated a high frequency of follicular involvement (histologically and immunohistochemically) in early herpes zoster skin lesions compared with the epidermis and suggested that varicella-zoster (VZV) spreads to the area of skin innervated by large myelinated sensory nerves which ends around the isthmus of the hair follicles and sebaceous glands [6].

It has been suggested that herpetic folliculitis is more common in infections with varicella-zoster (VZV) than in those with herpes simplex viruses (HSV-1 and HSV-2).

Varicella (chickenpox) and herpes zoster (shingles) are distinct clinical entities caused by a single member of the herpesvirus family, the varicella-zoster virus (VZV). VZV is closely related to the herpes simplex viruses (HSV), sharing much genome homology. Commonality with HSV-1 and HSV-2 indicates a common ancestor; five genes out of about 70 do not have corresponding HSV genes. The known envelope glycoproteins (gB, gC, gE, gH, gI, gK, gL) correspond with those in HSV; however, there is no equivalent of HSV gD. VZV also fails to produce the LAT (latency-associated transcripts) that play an important role in establishing HSV latency [7]. The genome was first sequenced in 1986 [8]. It is a linear duplex DNA molecule; a laboratory strain has 124,884 base pairs. Relation with other human herpes viruses is less strong, but many homologues and conserved gene blocks are still found.

VZV causes chickenpox commonly affecting children and young adults and shingles in adults but rarely in children. The particular clinical presentations of these two diseases are due to differences in the host and in the circumstances of infections, not to differences in the etiologic agent. VZV infections are species-specific to humans.

Primary VZV infection results in chickenpox (varicella). VZV enters through the respiratory system with an incubation period of 10–21 days, averaging at 14 days. Targeting the skin and peripheral nerve, the period of illness is from 3 to 4 days.

1–2 days before the rash appears is when this virus is the most contagious. The disease is characterized by a pruritic generalized rash consisting of vesicles that fill with pus, rupture, and scab before healing. A distinctive feature of chickenpox is the simultaneous presence of lesions in all stages of development (Fig. 7.1c). Lesions most commonly occur on the face (Fig. 7.1d), in the mouth, on the lower back, on

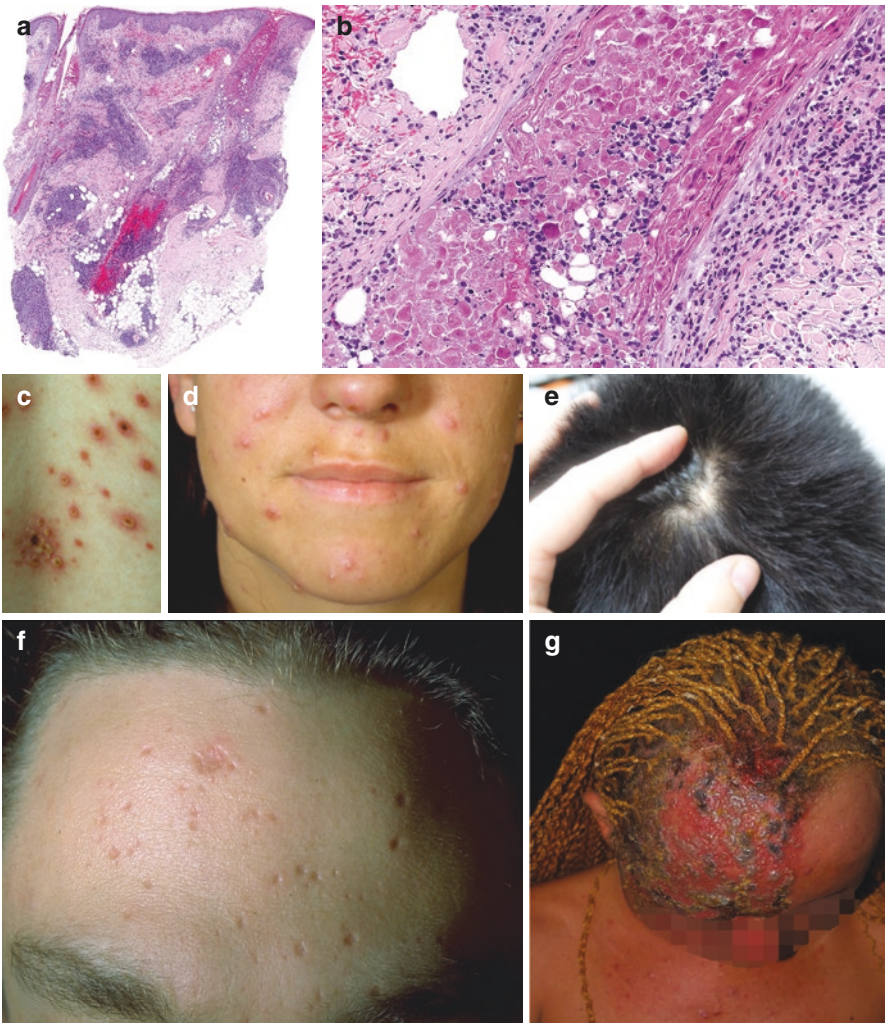


**Fig. 7.1** (**a**–**k**) Varicella-zoster: (**a**, **b**) Histopathology. Necrotizing folliculitis due to VZV. Courtesy Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland. (**c**–**f**) Varicella (chickenpox): (**c**) simultaneous presence of lesions in all stages of development, (**d**) facial rash, (**e**) scalp involvement, secondary alopecia, (**f**) post-exanthematous shallow depressions. (**g**–**j**) Herpes zoster (shingles): (**g**) blistering lesions in dermatomal distribution corresponding to Trigeminus 1, (**h**) detail, courtesy Prof. Fábio Francesconi, Federal University of Amazonas, Brazil, (**i**) crusted lesions, and (**j**) residual lesions, and to (**k**) Trigeminus 3

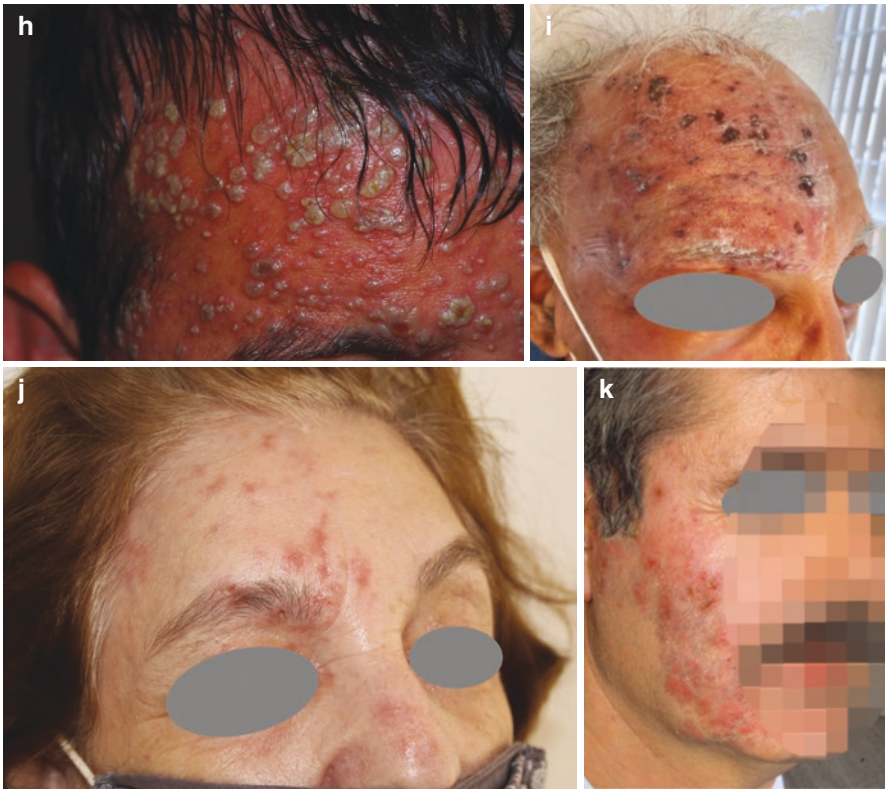


**Fig. 7.1** (continued)

the chest, on the shoulders, and on the scalp (Fig. 7.1e). Crusts fall off spontaneously in 1–3 weeks, leaving shallow pink depressions that gradually disappear (Fig. 7.1f). Scarring is unusual, unless the lesions are picked by the patients or superinfected with bacteria. In fact, the most common complication is secondary bacterial infection of skin lesions usually by staphylococci or streptococci. Fever and constitutional symptoms are more prominent and prolonged in adults, as well as complications. Primary varicella pneumonia is the major complication in adults. Even when clinical symptoms of chickenpox have resolved, VZV remains dormant in the nervous system of the infected person (virus latency), in the trigeminal and dorsal root ganglia [9].

In about a third of cases, VZV reactivates later in life, producing shingles or herpes zoster [10]. The individual lifetime risk of developing herpes zoster is thought to be between 20% and 30%, or approximately one in four people. However, for individuals aged 85 and over, this risk increases to one in two people [11]. Shingles lesions and the associated pain, often described as burning, tend to occur on the skin that is innervated by one or two adjacent sensory nerves, almost always on one side of the body only. The skin lesions usually

subside over the course of several weeks, while the pain often persists longer. In 10–15% of cases, the pain persists more than 3 months, as postherpetic neuralgia.

In the Ramsay Hunt syndrome, VZV affects the geniculate ganglion giving lesions that follow specific branches of the facial nerve. Symptoms may include painful blisters on the tongue and ear along with one sided facial weakness and hearing loss.

Herpes zoster typically breaks out with a dermatomal distribution, while the dermatomes Trigeminus (Trig) 1 (forehead) (Fig. 7.1g–j), Trig 2 (temple), Trig 3 (supra-auricular) (Fig. 7.1k), C2 (occipital), and C3 (nuchal) are located within the scalp.

Herpes zoster is often more painful and challenging to manage on the scalp than elsewhere, because the scalp is very sensitive, and any pressure, scratching, or brushing the hair may cause blisters to burst and bleed. In addition to the painful blisters, shingles of the scalp may also cause headaches, weakness and hearing loss on one side of the face, and vertigo (Ramsay-Hunt syndrome [12]). It can also lead to cicatricial alopecia when the condition destroys follicular cells critical for hair growth. Once these are destroyed, hair loss may be permanent [13].

Other complications associated with VZV reactivation include VZV vasculopathy, encephalitis, myelopathy, and several ocular disorders including herpes zoster ophthalmicus, acute retinal necrosis, and progressive outer retinal necrosis.

In addition to the aforementioned complications, there has been an increasing interest in giant cell arteritis and VZV [14]. Giant cell arteritis or temporal arteritis is a disease commonly occurring in those over 50 years of age. It is an inflammatory process usually involving the temporary arteries and can result in headache, scalp tenderness, jaw claudication, fever, polymyalgia rheumatica, and loss of vision due to anterior ischemic optic neuropathy. Based on the detection of VZV antigens in a large proportion of temporal artery biopsies from patients with giant cell arteritis, VZV infection has been hypothesized to play a role in giant cell arteritis [15, 16]. However, this association between VZV and giant cell arteritis has also been challenged by other reports failing to detect VZV antigens or viral DNA by immunostaining or molecular assays such as polymerase chain reaction (PCR) in temporal artery biopsies from GCA specimens [17–23].

Nevertheless, scalp ulceration from arteritis temporalis (Fig. 7.2a, b) remains a differential diagnosis of hemorrhagic necrotizing herpes zoster of the scalp in the elderly and immunocompromised.

Moreover, trigeminal nerve injury from herpes zoster may result in paresthesia, prompting patients to reflexively scratch the affected area and cause self-induced ulcerations [24].

Trigeminal trophic syndrome has also been reported to present as pityriasis amiantacea [25] and giant lichenification of the scalp associated with scratching in chronic pruritus from scalp dysesthesia secondary to herpes zoster [26].

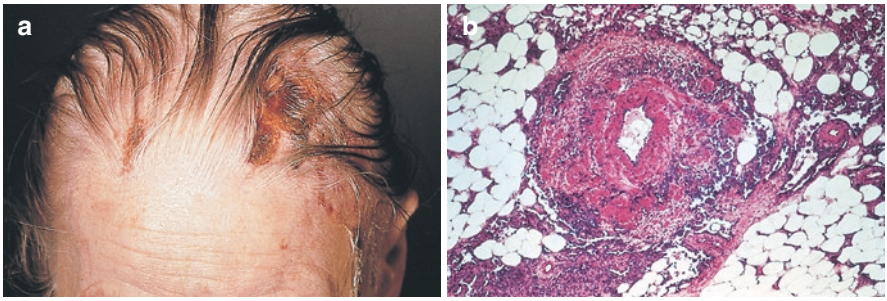


**Fig. 7.2** (**a**, **b**) Temporal arteritis: (**a**) scalp ulceration, (**b**) histopathology: medium sized arteritis

Also, erosive pustular dermatosis of the scalp [27] and pyoderma gangrenosum of the scalp as a pathergic response to herpes zoster infection [28] have been reported.

Wolf's isotopic response is an uncommon phenomenon that refers to the occurrence of a new skin condition at the location of a previously healed dermatosis. In the 58 cases originally reported by Wolf et al., the most common earlier disease was herpes zoster [29]. Examples reported at the site of healed herpes zoster include postherpetic poliosis [30], postherpetic granuloma annulare-like reaction [31], bacterial furunculosis [32], impetigo [33], morphea "en coup de sabre" [34], cutaneous angiosarcoma [35], and squamous cell carcinoma [36].

Treatment of varicella mainly consists of easing the symptoms. It is important to maintain good hygiene and daily cleaning of skin with warm water to avoid secondary bacterial infection. Scratching may also increase the risk of secondary infection. Therefore, cutting the nails short or wearing gloves may prevent scratching and minimize the risk of secondary infections. Although there have been no formal clinical studies evaluating the effectiveness of topical application of calamine lotion (a topical barrier preparation containing zinc oxide and one of the most commonly used interventions), it has an excellent safety profile. Paracetamol (acetaminophen) but not aspirin may be used to reduce fever. Aspirin use by someone with chickenpox may cause serious, sometimes fatal, disease of the liver and brain, Reye syndrome, and is particularly contraindicated in children younger than 16 years. If aciclovir or valaciclovir by mouth is started within 24–48 h of rash onset, it decreases symptoms by 1 day but has no effect on complication rates. People at risk of developing severe complications who have had significant exposure to the virus may be given intramuscular varicella-zoster immune globulin.

Treatment of herpes zoster aims at limiting the severity and duration of pain, shortens the duration of a shingles episode, and reduces complications, specifically postherpetic neuralgia.

Individuals with mild to moderate pain can be treated with 4× daily 1–2× 500 mg paracetamol (acetaminophen) and 30 mg codein and 75 mg amitriptyline at night. Topical calamine lotion used on the blisters may be soothing. Once the lesions have crusted over, capsaicin cream or topical lidocaine may be used to reduce pain from postherpetic neuralgia [37].

Antiviral treatment may reduce the severity and duration of disease; however, it must be initiated with the first 72 h of the appearance of the rash. Of these, aciclovir has formerly been the standard treatment, but valaciclovir demonstrates superior efficacy due to enhanced gastrointestinal bioavailability and good safety and tolerability. Standard dosage is 3 × 1000 mg valaciclovir for 7 days.

Antiviral treatment does not prevent postherpetic neuralgia [38]. Also, corticosteroids do not appear to decrease the risk of long-term pain [39]. Gabapentin in dosages between 900 and 3,600 mg/day or pregabalin in dosages between 300 and 600 mg/day may be used in refractory cases of postherpetic neuralgia, alongside opioid analgesics, such as tramadol (max. 400 mg daily).

Shingles vaccines (Zostavax, Shingrix) reduce the risk of shingles by 50–90%, depending on the vaccine used [40]. It also decreases rates of postherpetic neuralgia and, if shingles occurs, its severity.

## 7.2 Herpes Simplex

Herpes simplex is a viral infection caused by the herpes simplex virus (HSV). There are two types of herpes simplex virus, type 1 (HSV-1) and type 2 (HSV-2). Infections are categorized based on the part of the body infected. HSV-1 more commonly causes infections around the mouth, while HSV-2 more commonly causes genital infections. They are transmitted by direct contact with body fluids or lesions of an infected individual. Genital herpes is classified as a sexually transmitted infection. It may be spread to an infant during childbirth. The first episode is often more severe and may be associated with fever, muscle pains, swollen lymph nodes, and headaches. After infection, the viruses are transported along sensory nerves to the nerve cell bodies, where they reside lifelong. Over time, episodes of active disease decrease in frequency and severity. Causes of recurrence may include decreased immune function, stress, and sunlight exposure.

Herpetic sycosis is a recurrent or initial herpes simplex infection affecting primarily the hair follicles. Herpetic folliculitis of the beard represents a rare manifestation of HSV infection (Fig. 7.3a) [41].

Fulminant herpetic sycosis is a rare but well-known manifestation of herpes simplex virus infection occurring in the context of viral recurrence in immunocompromised patients and is characterized by papulovesicular lesions of the beard accompanied by fever, painful cervical lymphadenopathy, and odynophagia unresponsive to antibiotics [42]. The diagnosis is established by means of direct immunofluorescence, PCR, and/or culture for HSV. Treatment is administration of intravenous acyclovir 5 mg/kg body weight every 8 h for 7 days.

Pimecrolimus is an immunomodulating agent of the calcineurin inhibitor class that acts as immunosuppressant when used in the treatment of atopic dermatitis and other inflammatory skin diseases, such as seborrheic dermatitis, cutaneous lupus erythematosus, vitiligo, and psoriasis, as alternative to topical corticosteroids. An important difference in the safety profile of this drug compared with topical corticosteroids is the lack of potential side effects which are often observed upon

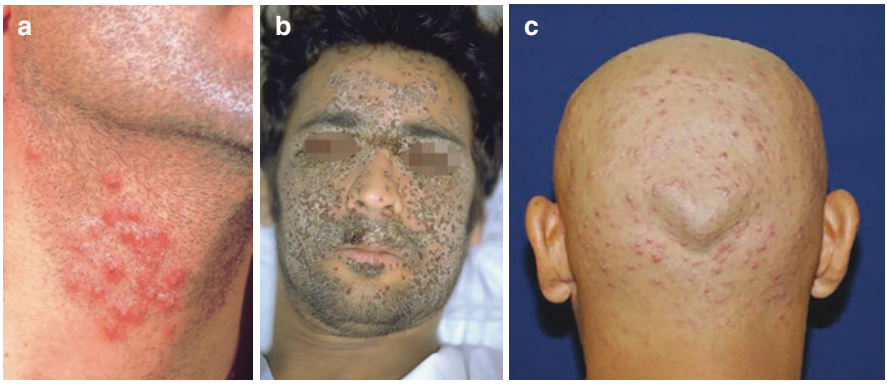


**Fig. 7.3** (**a**–**c**) Herpes simplex infection: (**a**) herpetic sycosis, (**b**) eczema herpeticatum, (**c**) scalp involvement in disseminated herpes simplex, courtesy Prof. Fábio Francesconi, Federal University of Amazonas, Brazil

prolonged use of topical corticosteroids, such as skin atrophy, steroid-induced rosacea or perioral dermatitis. On sensitive areas such as face, intertriginous regions, and scalp, pimecrolimus is preferred over topical corticosteroids. However, placebo-controlled studies and clinical practice suggest that pimecrolimus is associated with an increased incidence of herpes simplex infections [43], particularly in the face and beard area.

Kaposi varicelliform eruption is the name given to a distinct cutaneous eruption caused by HSV that infects a preexisting dermatosis, most commonly atopic dermatitis, and, for this reason, is often referred to as eczema herpeticum (Fig. 7.3b).

Foti et al. reported a case of relapsing folliculitis of the scalp, where HSV nested polymerase chain reaction (nPCR) assays made on swabs and histological sections from the scalp lesions demonstrated the presence of herpes simplex virus type 2 (HSV-2). Virological cultures were negative. Skin swabs of healthy areas yielded negative results for HSV-2 infection. The folliculitis showed a marked and quick improvement after therapy with famciclovir suggesting a possible etiologic role of HSV-2 in the scalp folliculitis [44].

Figure 7.3c shows scalp involvement in disseminated HSV infection.

Neonatal herpes simplex is a HSV infection in an infant. It is a rare but serious condition, usually caused by vertical transmission of HSV-1 or HSV-2 from the mother to the newborn. Neonatal HSV infection has been reported in association with fetal monitor scalp electrodes, presenting as grouped vesicles of HSV at the site of the electrode implantations [45].

No method eradicates HSV from the body, but antiviral medications can reduce the frequency, duration, and severity of outbreaks. Several antiviral drugs are

effective for treating herpes, including aciclovir, valaciclovir, famciclovir, and penciclovir. Analgesics such as ibuprofen and paracetamol (acetaminophen) can reduce pain and fever. Topical anesthetic treatments such as prilocaine, lidocaine, benzocaine, and tetracaine can also relieve itching and pain.

Reductions in morbidity and mortality from neonatal herpes simplex are due to the early use of antiviral treatments such as vidarabine and aciclovir given intravenously to the infant. Pregnant women with active genital herpes lesions at the time of labor are recommended to be delivered by caesarean section. Women whose herpes is not active can be managed with aciclovir.

## 7.3 Cytomegalovirus

Cytomegalovirus (CMV) is yet another genus of viruses in the order Herpesvirales, in the family Herpesviridae. It is also called human betaherpesvirus 5. Several species of CMV have been identified and classified for different mammals. The most studied is Human cytomegalovirus (HCMV). Cytomegalovirus was first observed by German pathologist Hugo Ribbert (1855–1920) in 1881 when he noticed enlarged cells with enlarged nuclei present in the cells of an infant. In fact, the so-called owl's eye appearance of inclusion bodies found on histopathology is highly specific for cytomegalovirus infection (Fig. 7.4). In 1957, American virologist and Nobel Prize laureate Thomas Huckle Weller (1915–2008) [46] isolated the virus, known thereafter as cytomegalovirus [47].

Although they may be found throughout the body, HCMV infections are frequently associated with the salivary glands. HCMV infection is typically unnoticed in healthy people but can be life-threatening for the immunocompromised, such as HIV-infected persons, organ transplant recipients, or newborn infants. After infection, HCMV remains latent within the body throughout life and can be reactivated at any time.

HCMV is found in all geographic locations and all socioeconomic groups and infects between 60% and 70% of adults in developed countries and almost 100% in developing countries. Of all herpes viruses, HCMV harbors the most genes dedicated to evading innate and adaptive host immunity and represents a lifelong burden of antigenic T-cell surveillance and immune dysfunction. HCMV is also the virus most frequently transmitted to a developing fetus. HCMV infection is more widespread in developing countries and in communities with lower socioeconomic status and represents the most significant viral cause of birth defects in industrialized countries. CMV is most commonly transmitted through kissing and sexual intercourse. It can also be transferred from an infected mother to her unborn child.

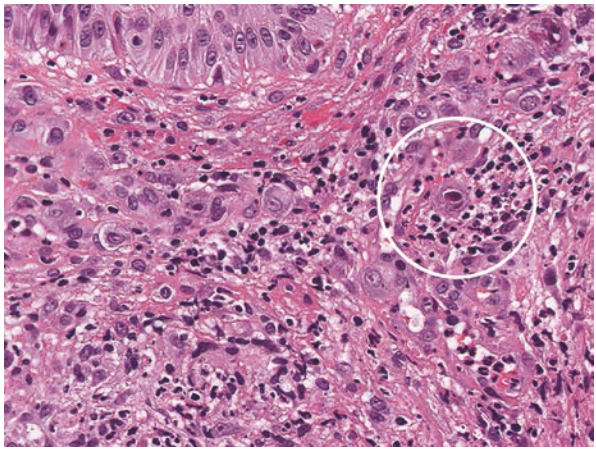

**Fig. 7.4** CMV infection intranuclear inclusions: owl eye cells (circle), courtesy Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland

Infection requires close, intimate contact with a person secreting the virus in their saliva, urine, or other bodily fluids. CMV can be transmitted sexually and via breast milk and also occurs through receiving transplanted organs or blood transfusions.

CMV infection has a classic triad of symptoms: fever, peaking in the late afternoon or early evening; pharyngitis, usually exudative; and symmetrical adenopathy (CMV mononucleosis).

CMV infection or reactivation in people whose immune systems are compromised causes illness and increases the risk of death. Specific disease entities recognized in those individuals are:

- CMV hepatitis
- CMV retinitis
- CMV colitis
- CMV pneumonitis
- CMV esophagitis
- Polyradiculopathy, transverse myelitis, and subacute encephalitis
- Cutaneous CMV infection

Skin involvement with CMV can indicate a disseminated infection and is associated with a mortality of 85% within 6 months in the immunocompromised host [48]. As such, vigilance and suspicion for CMV infection are important, especially when treatment directed against VZV and HSV does not improve the skin lesions.

Involvement of the scalp skin with CMV presenting as ulcers has been reported in an infant with HIV infection [49] and in a patient with metastasized lung cancer [50].

The outcome of CMV infection in an immunocompromised patient can be fatal, but when proper therapy is given, the outcome is often positive. Treatment is with the antivirals valganciclovir or ganciclovir, either intravenous or oral, but the infection must first be correctly diagnosed, which can be challenging when cutaneous CMV infection does not have consistent characteristics or is hidden under coexisting conditions. Diagnosis is largely done through skin biopsy upon recognition of the typical dense inclusion bodies, as well as through immunohistochemistry and PCR [51].

The question of whether latent CMV infection has any negative effects on people who are otherwise healthy has been questioned. As of 2016, the answer remained elusive, but discussions had focused on whether latent CMV might increase the risk of some cardiovascular diseases and cancers [52].

Alopecia areata (AA) is among the most highly prevalent human autoimmune diseases, leading to potentially disfiguring hair loss due to the collapse of immune privilege of the hair follicle with subsequent autoimmune attack. Jackow et al. identified a concordance rate of AA of 55% for monozygotic twins and 0% for fraternal twins. The investigators concluded that a 55% concordance rate in identical twins and AA occurring in families support a genetic component as well as possible environmental triggers that as yet remain unknown [53].

Using molecular biology techniques, DNA sequences of CMV have been reported in paraffin sections of AA lesions. Reactivation of the CMV infection has been postulated as one of the pathogenic mechanisms in AA [54]. Other studies, using different techniques however have demonstrated no correlation between CMV and AA, neither in humans [53, 55–57] nor in C3H/HeJ mice [58].

However, Piras and Aceti reported an AIDS patient developing CMV disease after the occurrence of AA and based on their observation suggested that AA in AIDS patients should be taken into account as an early clinical marker of possible CMV reactivation [59].

Finally, Petukhova et al. undertook a genome-wide association study in a sample of 1054 cases of AA and 3278 controls and identified 139 single-nucleotide polymorphisms that are significantly associated with AA ($P <$ or $= 5 \times 10(-7)$). They showed an association with genomic regions containing several genes controlling the activation and proliferation of regulatory T cells (T(reg) cells), cytotoxic T lymphocyte-associated antigen 4 (CTLA4), interleukin (IL)-2/IL-21, IL-2 receptor A (IL-2RA; CD25), and Eos (also known as Ikaros family zinc finger 4; IKZF4), as well as the human leukocyte antigen (HLA) region. They also found association evidence for regions containing genes expressed in the hair follicle itself (PRDX5 and STX17). A region of strong association resided within the ULBP (cytomegalovirus UL16-binding protein) gene cluster on chromosome 6q25.1, encoding activating ligands of the natural killer cell receptor NKG2D that have not previously been implicated in an autoimmune disease. By probing the role of ULBP3 in disease pathogenesis, the authors also showed that its expression in lesional scalp from

patients with AA is markedly upregulated in the hair follicle dermal sheath during active disease. This study provides evidence for the involvement of both innate and acquired immunity in the pathogenesis of AA [60].

## 7.4 Human Papilloma Virus and Merkel Cell Polyoma Virus

Human papillomavirus (HPV) infection is caused by a DNA virus from the Papillomaviridae family. Many HPV infections cause no symptoms, and 90% resolve spontaneously within 2 years. However, in some cases, an HPV infection persists and results in either warts or precancerous lesions [61]. These lesions, depending on the HPV involved and the anatomical site affected, increase the risk of cancer of the cervix, vulva, vagina, penis, anus, mouth, tonsils, or throat. Specifically, lingering infection with high-risk HPV types, such as types 16, 18, 31, and 45, in some infected individuals, whose immune systems may fail to control HPV, favors the development of cancer [62].

Squamous cell carcinoma of the scalp [63, 64] and verrucous carcinoma of the scalp [65] have been reported in association with cutaneous human papillomavirus DNA as well. Cofactors such as cigarette smoke [66, 67], and UV radiation on the skin can also enhance the risk of such HPV-related cancers [68].

HPV is understood to cause cancer by integrating its genome into nuclear DNA. Some of the early genes expressed by HPV, such as E6 and E7, act as oncogenes that promote tumor growth and malignant transformation [69]. HPV genome integration can also cause carcinogenesis by promoting genomic instability associated with alterations in DNA copy number [70]. E6 produces a protein that binds to and inactivates p53 that normally acts to prevent cell growth and promotes cell death in the presence of DNA damage. p53 also upregulates the p21 protein, which blocks the formation of the cyclin D/Cdk4 complex, thereby preventing the phosphorylation of retinoblastoma protein (RB) and, in turn, halting cell cycle progression by preventing the activation of E2F. In short, p53 is a tumor-suppressor protein that arrests the cell cycle and prevents cell growth and survival when DNA damage occurs. Thus, inactivation of p53 by E6 can promote unregulated cell division, cell growth, and cell survival, characteristics of cancer. Studies have also shown a link between a wide range of HPV types and squamous cell carcinoma of the skin. In such cases, in vitro studies suggest that the E6 protein of the HPV virus may inhibit apoptosis induced by ultraviolet light [68].

HPV infection is limited to the basal cells of stratified epithelium, the only tissue in which they replicate, whereby the virion associates with putative receptors such as alpha integrins, laminins, and annexin A2 [71] leading to entry of the virions into basal epithelial cells through clathrin-mediated endocytosis and/or caveolin-mediated endocytosis depending on the type of HPV [72]. The virus cannot bind to live tissue. Instead, it infects epithelial tissues through micro-abrasions or other epithelial trauma that exposes segments of the basement membrane, as would occur during sexual intercourse or after minor skin abrasions. At this point, the viral genome is transported to the nucleus by unknown mechanisms and establishes itself

at a copy number of 10–200 viral genomes per cell. The infectious process is slow, taking 12–24 h for initiation of transcription. A sophisticated transcriptional cascade then occurs as the host keratinocyte begins to divide and become increasingly differentiated in the upper layers of the epithelium. Finally, the HPV lesions are thought to arise from the proliferation of infected basal keratinocytes. The HPV life cycle strictly follows the differentiation program of the host keratinocyte. HPV infections have not been shown to be cytolytic. Rather, viral particles are released as a result of degeneration of desquamating cells. HPV can survive for many months and at low temperatures without a host.

While sexual transmission is one of the major routes of infection by contact with the genitals, anus, or mouth of an infected sexual partner [73] and studies have also shown HPV transmission between hands and genitals of the same person and sexual partners [74], sharing of possibly contaminated objects, for example, razors, may transmit HPV.

Specifically, scalp verrucae (Fig. 7.5a) are common, and the causative HPV is ubiquitous in the environment. HPV is extremely stable due to its non-enveloped structure, resistance to heat, desiccation, and ability to viably persist for at least 7 days [75]. It can survive on a variety of surfaces, and it is resistant to common disinfectants, remaining infectious despite application of quaternary ammonium compounds, 70% and 95% ethanol, 95% isopropanol, 3.4% glutaraldehyde, 0.55% ortho-phthalaldehyde, phenol, and 0.25% peracetic acid-silver. Only 0.525% hypochlorite (1:10 bleach dilution) and 1.2% peracetic acid-silver-based disinfectants have been shown to reduce infectivity by more than 99.99% [76]. Therefore, HPV is not killed by common hand sanitizers and disinfectants, so increasing the possibility of the virus being transferred via fomites [76]. Histopathology is characterized by an acanthopapilloma (Fig. 7.5b) with koilocytes in the granular layer, condensated nuclei, and enlarged keratohyalin granules (Fig. 7.5c, d). Immunohistochemistry targeting the HPV L1 capsid antigen detects replicating HPV (Fig. 7.5e, f). The method allows no typing, and has a low sensitivity.

Susong et al. noted a significant number of patients who developed numerous scalp verruca following recalled scalp trauma due to short haircuts received on a military base. Scalp verrucae are a particular risk to the military, where males receive frequent haircuts in succession that require firm pressure to ensure uniform length. An epidemiologic investigation was conducted on three local barbershops evaluating their adherence to sanitary practices. The cleaned clippers and guards were sampled with next-generation DNA and RNA whole-genome amplification. Several published databases were referenced, including the NCBI reference sequences (RefSeq), the NCBI Taxonomy Database, and sequences from GenBank. The nonhuman sequences were searched using NCBI's Basic Local Alignment Search Tool (BLAST) software. Finally, the local public health department conducted random no-notice inspections every 6 months and found that the barbers properly performed disinfection using approved commercial solutions between every customer. Despite this, genetic material correlating with HPV types 5, 10, 49, and 92 was recovered. In addition, Merkel cell polyomavirus was also isolated. The impact of this inadequacy of cleaning solutions transcends the development of mere

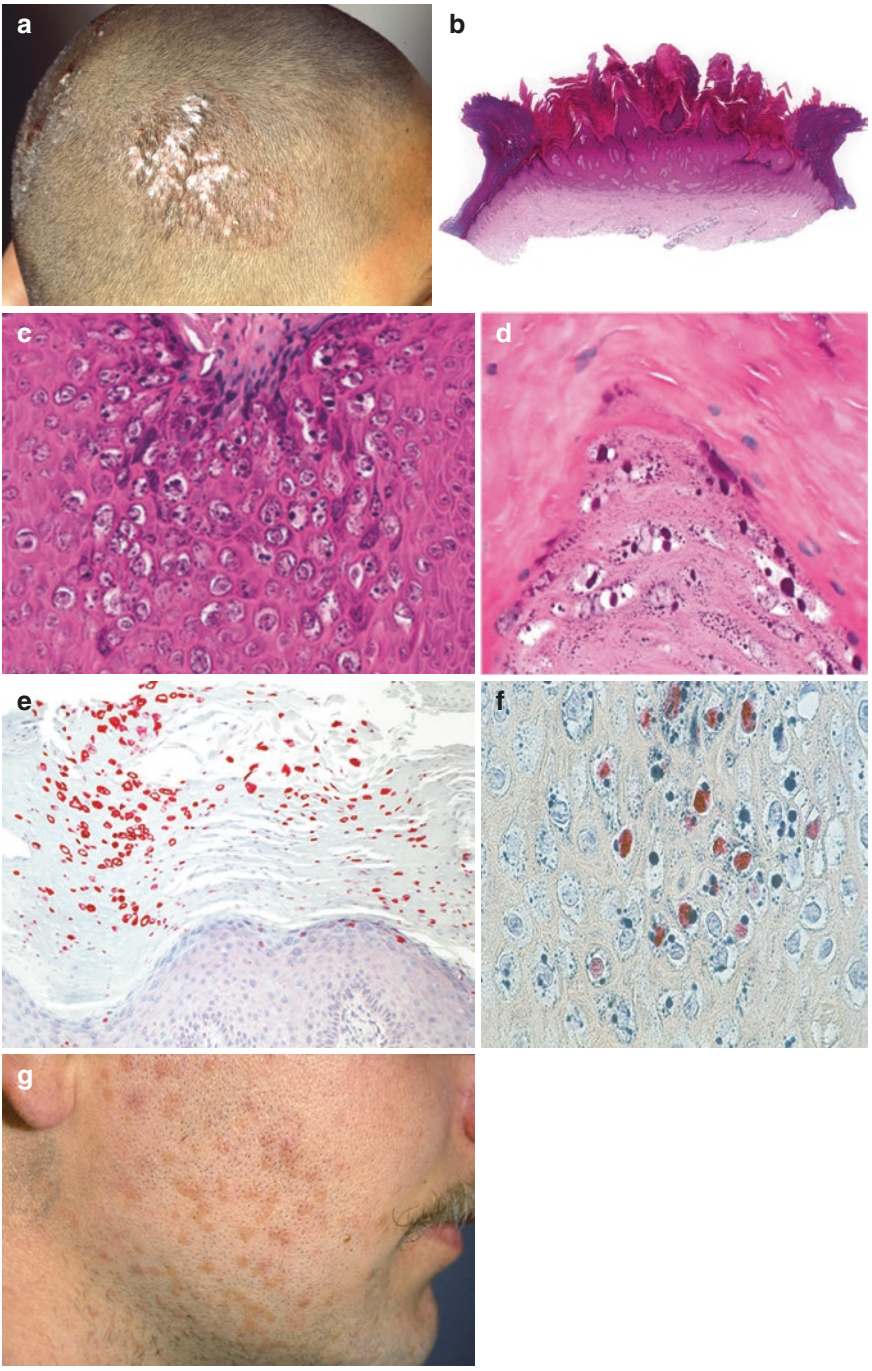


**Fig. 7.5** (**a**–**g**) Verrucae: (**a**) scalp verruca, (**b**–**d**) histopathology: acanthopapilloma with koilocytes, condensated nuclei, and enlarged keratohyalin granules, (**e**, **f**) immune histochemical detection of replicating HPV, courtesy Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland, (**g**) verrucae planae of the face

cutaneous verrucae. HPV has been implicated as an oncovirus in the development of cutaneous squamous cell carcinoma and been detected in squamous cell carcinomas of the scalp, and at least one of the viruses (HPV 5) in this study was shown to be associated with increased risk for squamous cell carcinoma, while Merkel cell polyomavirus is implicated as an oncogene in Merkel cell carcinoma and was isolated from the clippers in significant quantity as well [77]. The authors concluded that it is imperative that future research is conducted to develop safe solutions that adequately disinfect multiple use devices like barbershop clippers to reduce this public health risk.

Flat warts, technically known as verruca plana, are reddish-brown or flesh-colored, slightly raised, flat-surfaced, well-demarcated papule of 2–5 mm in diameter, which can occur in large numbers, most common on the hands, wrists, knees, face (Fig. 7.5g), and neck, specifically in the beard area, where they can be spread by autoinoculation through shaving.

HPV DNA has been detected in plucked hairs from eyebrows, scalp, arms, and/or legs of both renal transplant recipients and a considerable number of healthy volunteers [78]. HPV DNA in plucked hairs was only detected using a nested PCR approach strongly suggesting very low copy numbers of the viral DNA. The exact localization of HPV-DNA remains to be determined by in situ hybridization techniques. Because epidermis can be reconstructed from plucked hairs, plucked hairs contain proliferative keratinocytes, i.e., stem cells, that may act as a reservoir for HPV. HPV could, however, also be present in desquamated cells of the skin which adhere to the plucked hairs. The finding of HPV DNA in scale from the scalp underlines this possibility. The authors argued that subclinical HPV infection of stem cells may lead to a disturbance of the normal proliferation and differentiation of the daughter cells of the stem cells during skin renewal, while an individual's immune response against HPV may play an important role. Accordingly, all renal transplant recipients tested had HPV DNA in their plucked hair, and all renal transplant recipients develop extensive warts, particularly on sun-exposed skin, where the immune response is additionally suppressed by ultraviolet irradiation.

Merkel cell carcinoma is a rare and aggressive skin cancer occurring predominantly in people over 60 years old, Caucasians, and males. Factors involved in the development of Merkel cell carcinoma include the Merkel cell polyomavirus, a weakened immune system, and exposure to ultraviolet radiation [79].

Merkel cell carcinoma usually presents as a flesh-colored, red, or blue firm nodule (up to 2 cm diameter) or mass (>2 cm diameter) that may enlarge rapidly. The tumors can present as painless, tender, or itchy. Although Merkel cell carcinoma may arise almost anywhere on the body, it is most commonly found in sun-exposed areas of the skin. Merkel cell cancers tend to invade locally, infiltrating the underlying subcutaneous fat, fascia, and muscle and typically metastasize early in their natural history.

On histopathology (Fig. 7.6a–d), the tumor cells are small blue cells with basophilic nuclei and minimal cytoplasm. Mitoses are frequent and the apoptosis index is high. Three histologic subtypes have been recognized (Fig. 7.6b): small-cell variant, histologically indistinguishable from bronchial small-cell carcinoma (Fig. 7.6c);

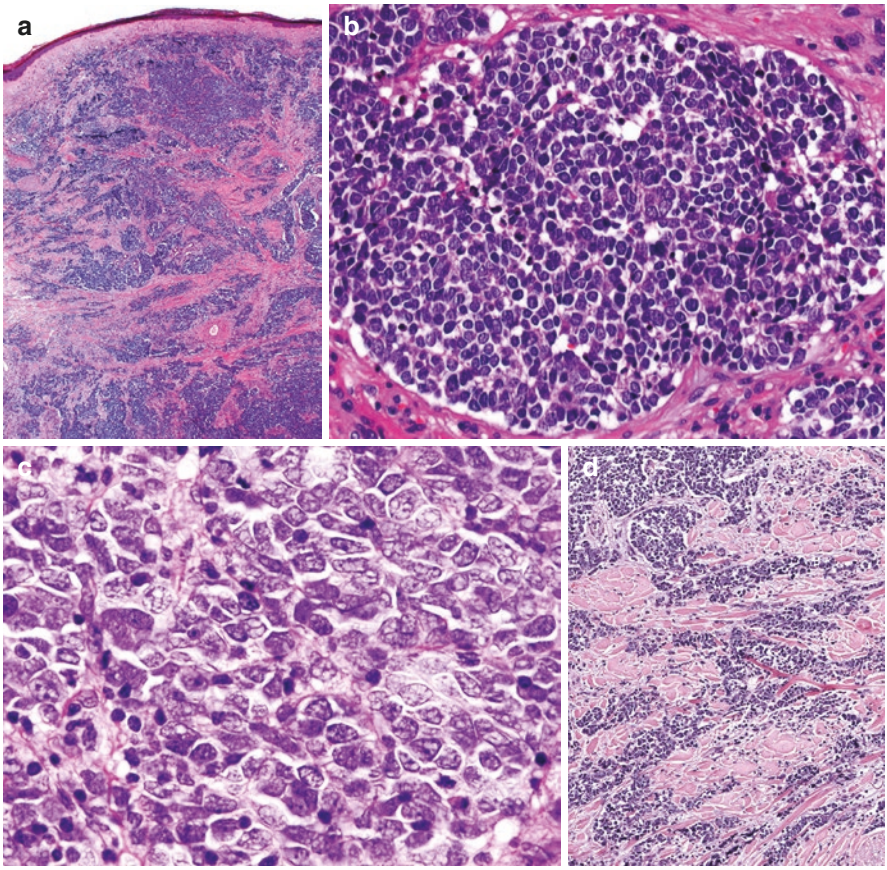


**Fig. 7.6** (**a**–**d**) Merkel cell carcinoma: (**a**) Merkel cell cancers tend to invade locally, infiltrating the skin tissue and underlying subcutaneous fat and fascia. The tumor cells share histopathologic features with Merkel cells. They are small blue cells with basophilic nuclei and minimal cytoplasm. Mitoses are frequent and the apoptosis index is high. Three histologic subtypes have been recognized: (**b**) small-cell variant, histologically indistinguishable from bronchial small-cell carcinoma; (**c**) intermediate variant of MCC showing vesicular, basophilic nuclei with prominent nucleoli and high mitotic activity; (**d**) trabecular variant which is rare and normally only seen as a small component of a mixed variant. (Courtesy Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland)

intermediate variant of Merkel cell carcinoma (MCC) showing vesicular, basophilic nuclei with prominent nucleoli and high mitotic activity (Fig. 7.6d); and trabecular variant which is rare and normally only seen as a small component of a mixed variant. Of these, the trabecular form is discussed as the best differentiated with a better prognosis, while the small cell form is relatively undifferentiated and has a worse prognosis. But comprehensive data are missing, and mixed and transitional forms are frequent, so there is no clear histologic-prognostic association.

Of 2104 Merkel cell carcinoma patients identified in a retrospective analysis of a large population database, 61.0% were men. The mean age at diagnosis was 77.5 years. Scalp tumors were significantly larger (10.4% >5 cm, $P = 0.0001$) and more likely to present with distant metastasis (8.7%, $P = 0.07$) than other head and neck tumors [80].

With regard to treatment of Merkel cell carcinoma, expedient referral to radiation oncology is critical. Merkel cell carcinoma will quickly relapse following any attempted excisional biopsy. Radiation therapy is the primary management of Merkel cell carcinoma, since the tumor is exquisitely radiosensitive [81]. Because of its significant adverse effects, traditional chemotherapy has been saved for late-stage highly metastasized cases of Merkel cell carcinoma. While some chemotherapeutic regiments have been shown to have transient effects, studies have not found any significant long-term effect on recurrence rate or life expectancy [82]. As of 2015, there were no FDA-approved standard chemotherapy regimens for MCC treatment [83]. The most recent American guidelines do not recommend adjuvant chemotherapy, citing a lack of evidence to suggest improved outcomes. Instead, consideration of the need for chemotherapy on a case-by-case basis is recommended [84]. Immunotherapies, namely, inhibitors of the PD1-PDL1 checkpoint signaling pathway, are novel anticancer agents that have shown benefit in advanced-stage or chemotherapy-resistant Merkel cell carcinoma [85]. Studies to date have shown a clinical response rate between 50 and 65% for MCC treated with PD-1 pathway inhibitors. The antibody titer in the blood to the Merkel cell polyomavirus oncoprotein can be used as a treatment response biomarker in people that have detectable antibodies at the time of diagnosis [86, 87].

Ferrau et al. reported on a case of dramatic resolution of a Merkel cell carcinoma of the scalp with primary chemotherapy which allowed surgical removal of a tumoral mass involving the frontal and parieto-occipital area. The patient was treated with combination chemotherapy of cyclophosphamide (75 mg/m$^2$) and epidoxorubicin (75 mg/m$^2$), both given on day 1. Etoposide (150 mg/m$^2$) was added on days 1 and 2. The therapy was repeated for a total of three cycles with a 21-day interval in between. After the first cycle, a regression of the tumor mass was noted, with complete clinical remission, including regional lymph nodes at the end of the third cycle. After surgery, the patient was again treated with chemotherapy for two more cycles, and at the same time, radiotherapy to the scalp and cervical lymph nodes was given. The patient remained disease free for 2 months, when hepatic and bone metastases appeared [88].

In most cases, a common wart is diagnosed with one or more of the following methods:

- Examining the wart
- Scraping off the top layer of the wart to check for signs of dark, pinpoint dots—clotted blood vessels—which are common in warts
- Removing a small section of the wart (shave biopsy) and sending it to a laboratory for analysis to rule out other types of skin growths

Most common warts disappear spontaneously, though it may take a year or 2, and new ones may develop nearby. The goals of treatment are to destroy the wart and stimulate an immune system response against the virus, or both. Based on the location of the warts, the symptoms, and the physician's or the patient's preference, the following treatment modalities are practiced alone or in combination:

- Salicylic acid. Prescription-strength wart medications with salicylic acid work by removing layers of a wart a little bit at a time.
- Cryotherapy. Freezing works by causing a blister to form under and around the wart. Then, the dead tissue sloughs off within a week or so. Salicylic acid is more effective when combined with cryotherapy.
- Other acids. If salicylic acid or freezing isn't working, trichloroacetic acid is an option. With this method, the surface of the wart is first shaved, and then the acid is applied to the wart with a wooden toothpick. It requires repeat treatments every week or so.
- Minor surgery. It may leave a scar in the treated area.
- Curettage is scraping off the wart with a sharp knife or small, spoon-shaped tool. Another option is excision, slicing the wart off or cutting it out with a sharp blade.
- Electrosurgery burns the wart with an electric charge through the tip of a needle. It's good for common warts, filiform warts, and foot warts. The $CO_2$ laser is an alternative.
- Pulsed-dye laser treatment cauterizes tiny blood vessels. The infected tissue eventually dies, and the wart falls off.
- Diphencyprone (DCP) and more recently imiquimod act as immune response modifiers. Imiquimod stimulates the innate immune system by activating the toll-like receptor 7 (TLR7), commonly involved in pathogen recognition [89, 90]. Cells activated by imiquimod via TLR-7 secrete cytokines, primarily interferon-α (IFN-α), interleukin-6(IL-6), and tumor necrosis factor-α (TNF-α) [91]. There is evidence that imiquimod, when applied to skin, can lead to the activation of Langerhans cells, which subsequently migrate to local lymph nodes to activate the adaptive immune system. Other cell types activated by imiquimod include natural killer cells, macrophages, and B lymphocytes [92]. Local hyperthermia of target lesions at a surface temperature of 44 °C for 30 min combined with 5% topical imiquimod cream cleared extensive and recalcitrant common warts on the scalp in one case [93]. Side effects of imiquimod therapy include local inflammatory reactions, such as blisters, a burning sensation, skin redness, dry skin, itching, skin breakdown, skin crusting or scabbing, skin drainage, skin flaking or scaling, skin ulceration, sores, swelling, as well as systemic reactions, such as fever, flu-like symptoms, headache, and tiredness. Also, imiquimod-induced alopecia has been reported [94] and erosive pustular dermatosis of the scalp [95].

## 7.5 Molluscum Contagiosum and Other Poxviruses

Molluscum contagiosum is a viral infection of the skin that results in small raised pink lesions with a dimple in the center that occur singularly or in groups. The infection is caused by a DNA poxvirus called the molluscum contagiosum virus (MCV).

The poxvirus family uniquely contains both non-enveloped particles (mature virions) and enveloped particles (extracellular virions). The virion is exceptionally large, its size is around 200 nm in diameter and 300 nm in length, and its structure is consistent with that of others in the poxvirus family: they are composed of a nucleocapsid, core envelope, lateral body, and an extracellular envelope. Like other poxviruses, MCV is a DNA virus that replicates in the cytoplasm instead of the nucleus. Because of this, the virus must bring all necessary enzymes for replication with it or encode the enzymes in its genome. Four genera of poxviruses may infect humans:

- Orthopox: smallpox virus (variola), vaccinia virus, cowpox virus, monkeypox virus, rabbitpox virus
- Parapox: orf virus, pseudocowpox, bovine papular stomatitis virus
- Yatapox: tanapox virus, Yaba monkey tumor virus
- Molluscipox: molluscum contagiosum virus

The most common are vaccinia seen on the Indian subcontinent and molluscum contagiosum, but monkeypox infections are rising, seen in West and Central African rainforest countries. The similarly named disease chickenpox is not a true poxvirus and is actually caused by the herpesvirus varicella-zoster.

MCV is spread either by direct contact, including sexual activity, or via contaminated objects such as towels. The condition can also be spread to other areas of the body by the person themselves. Risk factors include a weak immune system, atopic dermatitis, and crowded living conditions. Following one infection, it is possible to get reinfected.

The usual sites of occurrence of molluscum contagiosum lesions in an adult are the abdomen, legs, arms, neck, genital area, and face being the most common. In the face, the beard is particularly prone to spreading of lesions by autoinoculation from shaving. Molluscum contagiosum may occur less commonly in other sites of skin, including the scalp, along with lesions on other sites, but lesions localized only to the scalp are quite infrequent. However, lesions over the scalp have been described in the past in a newborn [96], in children [97, 98], and in adults [99]. An increase in these cases could be linked to increased use of electric trimmer/clippers acting as fomites in the transfer of the virus [100].

It has been long known that the human papillomavirus, which causes genital warts, can be vertically transmitted through an infected genital tract. Congenital molluscum appears to be a more common entity than previously reported. Vertical

transmission of molluscum should be considered for all infantile cases of molluscum [101].

With advanced age, human T cells reveal reductions in the proliferative response to activation, in diversity of the T-cell receptor antigen repertoire, and in cytolytic activity. B cells of aging individuals show reduced response to certain viral infections or vaccinations. Thus, the atypical clinical manifestation of giant molluscum contagiosum on the scalp may be attributable to a possible decline in immune function due to advanced age [102].

Diagnosis of molluscum contagiosum is typically based on the appearance of the lesions. They typically present as small raised pink lesions with a dimple in the center (Fig. 7.7a, b). Again, lesions can be spread through autoinoculation during the shaving process in the beard area (Fig. 7.7c). Presence of multiple nodular lesions, some of which may be notably large (greater than 15 mm), is observed in the immunodeficient, particularly in AIDS [103] (Fig. 7.7d).

The diagnosis can be confirmed by excisional biopsy. Histologically, molluscum contagiosum is characterized by molluscum bodies (Henderson-Paterson bodies) in the epidermis, above the stratum basale, which consist of cells with abundant large granular eosinophilic cytoplasmic inclusion bodies (accumulated virions) and a small nucleus that has been pushed to the periphery (Fig. 7.7e, f).

Mimickers of molluscum contagiosum have been: cutaneous cryptococcosis in patients with AIDS [104], preputial ectopic sebaceous glands [105], multiple eruptive histiocytoma cutis [106], infantile gluteal granulomata [107], histoid leprosy [108], juvenile xanthogranulomas [109], Langerhans cell histiocytosis [110], and secondary syphilis in the beard area of an AIDS patient [111].Treatment of molluscum contagiosum includes cryosurgery, as well as scraping molluscum contagiosum lesions off with a curette. Most typical therapies are ineffective in treating individuals with severely weakened immune systems. The recommended treatments in this case are therapies that help boost the immune system.

Orf (ecthyma contagiosum) is an exanthematous disease caused by a parapoxvirus and occurring primarily in sheep and goats. It is a zoonotic disease, meaning humans can contract it through direct contact with infected sheep and goats or with fomites carrying the orf virus. It causes a rapidly growing, red, and elevated papulovesicular lesion locally and generally no systemic symptoms. The condition has been recorded since the late nineteenth century and has been reported from most sheep- or goat-raising areas, including those in Europe, the Middle East, the United States, Africa, Asia, South America, Canada, New Zealand, and Australia. In some environments, infection is injected by scratches from thistles of both growing and felled plants. The virus can survive in the soil for at least 6 months. In animals, symptoms include papules and pustules on the lips and muzzle and less commonly in the mouth of young lambs and on the eyelids, feet, and teats of ewes. The lesions progress to thick crusts which may bleed. Infected locations in the human can include the finger, hand, arm, face, and even the penis, caused by infection either from contact with the hand during urination or from bestiality. Consequently, it is important to observe good personal hygiene and to wear gloves when treating infected animals. While orf is usually a benign self-limiting illness which resolves

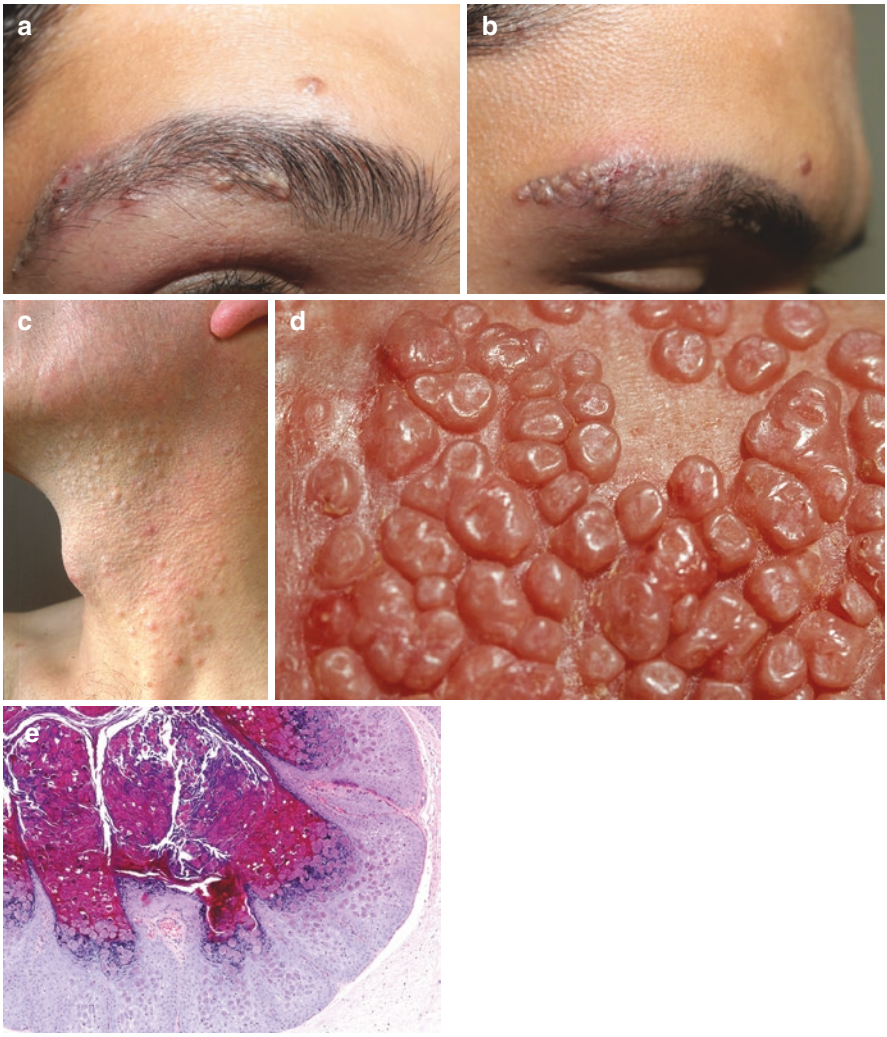


**Fig. 7.7** (**a**–**f**) Molluscum contagiosum: (**a**, **b**) small raised lesions with a dimple in the center, courtesy Prof. Fábio Francesconi, Federal University of Amazonas, Brazil, (**c**) spread through autoinoculation in the beard area, (**d**) multiple nodular lesions, some of which may be notably large (greater than 15 mm) in a patient with AIDS. (**e**, **f**) Histopathology: Henderson-Paterson bodies consist of cells with abundant large granular eosinophilic cytoplasmic inclusion bodies (accumulated virions) and a small nucleus that has been pushed to the periphery. Courtesy Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland

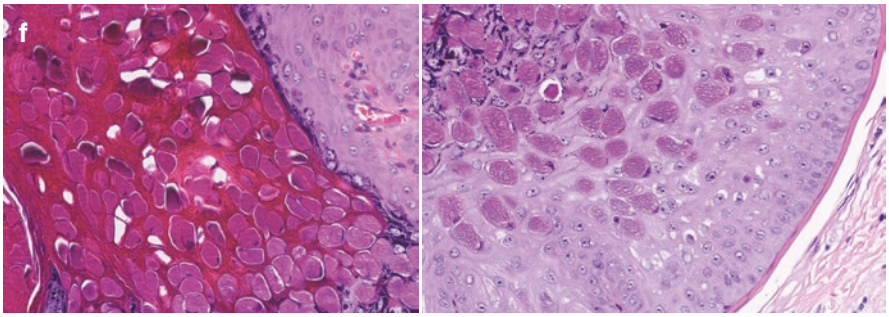


**Fig. 7.7** (continued)

in 3–6 weeks, in the immunocompromised it can be very progressive and even life-threatening [112].

Two cases of virologically proven orf of the scalp following scalp trauma produced by an inanimate object have been reported [113].

The diagnosis of orf is established by a history of contact with infected animals or trauma in a respective environment and electron microscopy of vesicular fluid. The histologic findings of early orf lesion are characterized by epithelial hyperplasia, intracytoplasmic eosinophilic inclusions, and an edematous, vascular dermis.

Treatment is nonspecific. Compresses, bacterial culture and sensitivity testing with appropriate antibiotics are of value in secondary bacterial infection. After excision and cautery, lesions usually heal uneventfully with 2–3 weeks. One percent topical cidofovir cream has been successfully used in immunocompromised patients with progressive disease [114, 115].

Other diseases caused by pox viruses, especially smallpox (variola), have been known about for centuries. One of the earliest suspected cases is that of Egyptian pharaoh Ramses V who is thought to have died from smallpox circa 1150 years BCE. By special permission of Egyptian President Anwar el Sadat (1918–1981), Dr. Donald R. Hopkins "was allowed to examine the front upper half of Ramses V's unwrapped mummy in the Cairo Museum in 1979. Inspection of the mummy revealed a rash of elevated pustules, each about two to four millimeters in diameter. …The appearance of the larger pustules and the apparent distribution of the rash were similar to the smallpox rashes he had seen in more recent victims of the disease" [116]. From 1984 to 1987, Hopkins was deputy director and acting director of the Centers for Disease Control and Prevention, thereafter, assistant professor of tropical public health at Harvard School of Public Health. He directed the Smallpox Eradication/Measles Control Program in Sierra Leone and served as a consultant to the World Health Organization. His book, *Princes and Peasants: Smallpox in History* was nominated for the Pulitzer Prize in 1983.

Smallpox was thought to have been transferred to Europe around the early eighth century and then to the Americas in the early sixteenth century, resulting in the deaths of 3.2 million Aztecs within 2 years of introduction attributed to the American population's complete lack of exposure to the virus over millennia. A century after

Edward Jenner (1749–1823) showed that the less potent cow pox could be used to effectively vaccinate against the more deadly smallpox, a worldwide effort to vaccinate everyone against smallpox began with the ultimate goal to rid the world of the plague-like epidemic. The last case of endemic smallpox occurred in Somalia in 1977.

The prototypical poxvirus is vaccinia virus, known for its role in the eradication of smallpox. The vaccinia virus is an effective tool for foreign protein expression, as it elicits a strong host immune response.

Vaccinia virus infection is typically very mild and often does not cause symptoms in healthy individuals, although it may cause rash and fever. Immune responses generated from a vaccinia virus infection protect the person against a lethal smallpox infection. For this reason, vaccinia virus has been used as a live virus vaccine against smallpox. The original vaccine for smallpox, the origin of the idea of vaccination, was cowpox, described by Edward Jenner in 1798. Noting the common observation that milkmaids were generally immune to smallpox, Jenner postulated that the pus in the blisters that milkmaids received from cowpox, a disease similar to smallpox, but much less virulent, protected them from smallpox. On May 14, 1796, Jenner tested his hypothesis by inoculating James Phipps, an 8-year-old boy who was the son of Jenner's gardener. He scraped pus from cowpox blisters on the hands of Sarah Nelmes, a milkmaid who had caught cowpox from a cow called Blossom, whose hide now hangs on the wall of the St. George's Medical School library. Jenner inoculated Phipps in both arms that day, subsequently producing in Phipps a fever and some uneasiness, but no full-blown infection. Later, he injected Phipps with variolous material, the routine method of immunization at that time. No disease followed. The boy was later challenged with variolous material and again showed no sign of infection. The Latin term used for cowpox was variolae vaccinae, Jenner's own translation of smallpox (variola) and of the cow (vacca). His tribute to the source of his discovery lives on in our modern usage of the words vaccine and vaccination [117]. When it was realized that the virus used in smallpox vaccination was not, or was no longer, the same as cowpox virus, the name vaccinia was used for the virus in smallpox vaccine.

Vaccination is the administration of a vaccine to help the immune system develop immunity from a disease. Vaccines contain a microorganism or virus in a weakened, live or killed state, or proteins or toxins from the organism. In stimulating the body's adaptive immunity, they help prevent sickness from an infectious disease.

The scientific consensus that vaccines are generally safe and effective is overwhelming. Vaccination is the most effective method of preventing infectious diseases. Widespread immunity due to vaccination is largely responsible for the worldwide eradication of smallpox and the elimination of diseases such as polio and tetanus from much of the world. However, some diseases, such as measles outbreaks in America, have seen rising cases due to relatively low vaccination rates in the 2010s attributed, in part, to vaccine hesitancy [118].

Vaccine hesitancy is a delay in acceptance, or refusal of vaccines despite the availability of vaccine services. The term covers outright refusals to vaccinate, delaying vaccines, accepting vaccines but remaining uncertain about their use, or

using certain vaccines but not others. Vaccine hesitancy is complex and context-specific, varying across time, place, and vaccines. It can be influenced by factors such as lack of proper scientifically based knowledge and understanding about how vaccines are made or work, as well as psychological factors including fear of needles [119], and distrust of public authorities, a person's lack of confidence in the vaccine and/or healthcare provider, complacency (the person does not see a need for the vaccine or does not see the value of the vaccine), and convenience (access to vaccines) [120]. It has existed since the invention of vaccination and predates the coining of the terms vaccine and vaccination by nearly 80 years.

After Edward Jenner introduced the smallpox vaccine in 1798, William Rowley published illustrations of deformities allegedly produced by vaccination, lampooned in English caricaturist James Gillray's (1756–1815) famous caricature "The Cow-Pock – or – The Wonderful Effects of the New Inoculation!" (1802). This 1802 cartoon is a striking reminder that the controversy surrounding vaccination is as old as the earliest days of the procedure itself. The print, which was bequeathed to the Morgan Library & Museum in 1986 by the collector Gordon N. Ray (1915–1986), was issued only 4 years after English physician Edward Jenner (1749–1823) privately published his landmark "An Inquiry into the Causes and Effects of the Variolae Vaccinae : A Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire and Known by the Name of the Cow Pox" that summarized his success in imparting immunity to the deadly disease of smallpox by inoculating patients with cowpox, a relatively benign virus of cattle and other livestock. The discovery would pave the way for the prevention of a disease responsible for an estimated 400,000 deaths per year in Europe alone during the eighteenth century. Where the smallpox was endemic, as it was in Jenner's England, it was a perennial killer, particularly of children. In regions previously unexposed to the virus, such as Oceania and the Americas, it was the cause of historically catastrophic epidemics, devastating human populations on a scale that is difficult if not impossible to calculate to this day. By relying upon a similar but far less virulent infection associated with an animal host, Jenner's vaccine held a key advantage over the previous and dangerously unpredictable practice of variolation, a technique which conferred immunity to the disease through inoculation with a mild strain of the smallpox virus.

As Gillray's cartoon suggests, opposition to Jenner's vaccine was quick to emerge, with its bovine origins often provoking some of the most vehement criticism. Objections were made on both medical and religious grounds, condemning vaccination as a dangerous and unsanitary procedure involving the forbidden mingling of animal matter with human flesh. Outspoken opponents such as the physician Benjamin Moseley (1742–1819) sought to alarm readers with luridly worded arguments against the abominable practice of introducing a "bestial humour into the human frame," while hinting darkly at the "strange mutations from quadruped sympathy" that might result as well as relating fantastical accounts of vaccinated children sprouting cow hair or developing facial features distorted "to resemble that of an Ox." With his inventive flair for the grotesque, Gillray clearly recognized in the vaccine controversy an excellent opportunity to exercise his comic gifts as a visual

artist. The result was a cartoon that succeeded in both ridiculing the credulity and absurdity of the most extreme anti-vaccination polemics and effectively illustrating the innate anxiety and even revulsion inspired by the debate. The setting has been identified as London's Smallpox and Inoculation Hospital at St. Pancras. A figure probably intended to represent Jenner himself is shown presiding over the scene as he makes an incision in the arm of a young woman who shrinks away in fear as he prepares to inoculate the small wound with infectious lymph from a bucket labeled "Vaccine Pock hot from ye Cow." A picture depicting the worship of the golden calf adorns the wall behind them. The doctor appears blandly indifferent to the plight of the newly vaccinated, who panic as miniature cows burst forth from their bodies and one unfortunate man sprouts a pair of horns.

Despite decades of debate, however, it only took one smallpox death to settle the inoculation question in France once and for all. On May 10, 1774, King Louis XV (1710–1774) died after a 2-week illness an inexorable, excruciating, and very public demise. The new king, Louis XVI (1754–1793), was sufficiently alarmed that he took the controversial step of submitting to inoculation on June 18, 1774. His two younger brothers, the Comte de Provence and the Comte d'Artois, were inoculated at the same time, in other words, the entire line of succession. The procedures were a success. The milliners of Paris, attuned to current events that could be translated into quick profits, commemorated the momentous event with an allegorical headdress dubbed the *pouf à l'inoculation*. Perched atop a woman's powdered and pomaded coiffure, it depicted the serpent of Asclepius, representing medicine; a club, representing conquest; a rising sun, representing the king; and a flowering olive branch, symbolizing the peace and joy resulting from the royal inoculation.

In fact, smallpox inoculation which by then was the norm across Asia and the Middle East was introduced in the West by Lady Mary Wortley Montagu (1689–1762). Herself a smallpox survivor, the English ambassadress to Turkey had witnessed the practice in Constantinople, and upon her return to England in 1718, she became its biggest advocate. Initially, London society found the practice shocking, and France was one of the last holdouts. Though inoculation was common in northern Europe by the early 1770s, it was still regarded with suspicion in France, and with good reason: improperly performed, it could result in infection and even death. Before Edward Jenner developed the first vaccine to combat smallpox in 1798 with a cowpox-based vaccine, the practice of inoculation involved injecting a small amount of pus from the lesions of a smallpox sufferer under the skin of a healthy patient, just enough to stimulate the production of antibodies without triggering a full-blown case. While the likes of French Enlightenment writers Voltaire (1694–1778) and Diderot (1713–1784) championed inoculation, the conservative French medical establishment resisted the new and as yet risky practice.

In commemorating the royal inoculation, the milliners and their female clients helped to publicize it, and the practice, like the *pouf*, instantly became all the rage. Crucially, the *pouf à l'inoculation* wasn't an explicit critique of the eighteenth-century anti-vaxxers but simply a visible expression of support for inoculation. Instead of picking a fight, it presented inoculation as something normal and

harmless. And because the *pouf* was worn by the fashionable elite of society, it went one step further, making inoculation look not just normal but also stylish.

Finally, while myths, conspiracy theories, and misinformation spread by the anti-vaccination movement and fringe doctors lead to vaccine hesitancy and public debates around the medical, ethical, and legal issues related to vaccines, there is no serious hesitancy or debate within mainstream medical and scientific circles.

Although opposition to vaccination has existed for centuries, the Internet and social media have recently facilitated the spread of vaccine-related misinformation [121]. Unsubstantiated safety concerns related to vaccines are often presented on the Internet as scientific information. The World Health Organization has classified vaccine-related misinformation into five topic areas. These are threat of disease (vaccine preventable diseases are harmless), trust (questioning the trustworthiness of healthcare authorities who administer vaccines), alternative methods (such as alternative medicine to replace vaccination), effectiveness (vaccines do not work), and safety (vaccines have more risks than benefits) [121].

Misinformation that forced vaccination could be used to depopulate the earth circulated in 2011 by misquoting Bill Gates. There is misinformation implying that vaccines, particularly the mRNA vaccine, could alter DNA in the nucleus. However, mRNA in the cytosol is very rapidly degraded before it would have time to gain entry into the cell nucleus. Retrovirus can be single-stranded RNA, just as SARS-CoV-2 vaccine is single-stranded RNA, which enters the cell nucleus and uses reverse transcriptase to make DNA from the RNA in the cell nucleus. A retrovirus has mechanisms to be imported into the nucleus, but other mRNAs lack these mechanisms. Once inside the nucleus, creation of DNA from RNA cannot occur without a primer, which accompanies a retrovirus, but which would not exist for other mRNA if placed in the nucleus [122]. Thus, mRNA vaccines cannot alter DNA because they cannot enter the nucleus and because they have no primer to activate reverse transcriptase.

Contemporary anti-vaxxers emphasize that the components in vaccines such as thiomersal and aluminum are capable for causing health hazards. However, thiomersal is a harmless component in vaccines which is used to maintain its sterility, and there are no known adverse effects due to it. Aluminum is included in the vaccine as an adjuvant, and it has low toxicity even in large amounts. Formaldehyde included in some vaccines is in negligibly low quantities and it is harmless.

The Big Pharma conspiracy theory, which pharmaceutical companies operate for sinister purposes and against the public good, has been used in the context of vaccination [123].

The conspiracy theory that COVID-19 vaccines contain injectable microchips to identify and track people started circulating in 2020 claiming the COVID-19 pandemic was a cover for a plan to implant trackable microchips and Bill Gates, co-founder of Microsoft, was behind it. Table 7.3 summarizes a list of current popular misinformation regarding the COVID-19 vaccines.

**Table 7.3** List of popular vaccination misinformation

| |
|---|
| • Vaccination causes idiopathic illnesses, such as autism |
| • Vaccines can cause the same disease that one is vaccinated against |
| • Vaccines cause harmful side effects and even death |
| • Vaccines will cause infertility |
| • Vaccination as genocide |
| • Vaccine components contain forbidden additives |
| • Vaccines are part of a governmental/pharmaceutical conspiracy |
| • Vaccine preventable diseases are harmless |
| • Personal anecdotes about harmed individuals |
| • Other conspiracy theories: polio is not a real disease, and the symptoms are actually due to DDT poisoning; the COVID-19 vaccines contain injectable microchips to identify and track people, a story about COVID-19 being spread by 5G |

## 7.6 Trichodysplasia Spinulosa

Trichodysplasia spinulosa is a rare condition that has been described almost exclusively in immunocompromised patients, usually organ transplant recipients on regimens of immunosuppressive drugs. Despite its rarity, the condition is believed to be underdiagnosed, and the growing population of patients on immunosuppressive drug regimens suggests its incidence may rise.

Trichodysplasia spinulosa was first described in a 1995 case report as ciclosporin-induced folliculodystrophy, initially considered to be an adverse effect of ciclosporin treatment [124]. A subsequent report in 1999, which introduced the term trichodysplasia spinulosa, used electron microscopy to identify the presence of virus particles in affected cells consistent with what were at the time known as papovaviruses [125]. The group has since been divided into the papillomavirus and polyomavirus families. In 2010, researchers recovered viral DNA from trichodysplasia spinulosa lesions used rolling circle amplification and thus discovered a novel polyomavirus, trichodysplasia spinulosa polyomavirus (TSPyV), while establishing the evidence that TSPyV is the causative agent of trichodysplasia spinulosa [126, 127]. TSPyV appears to actively replicate in the hair follicle inner root sheath cells, where it causes hyperproliferation and enlargement of hair follicles by modulating PP2A protein phosphatase signaling pathways [128]. Eventually, trichodysplasia has been described as an emerging infectious disease with cutaneous manifestations [129].

Trichodysplasia spinulosa typically presents as an eruption of flesh-colored follicular papules 1 to 3 mm in size, each with a central keratinous spine, usually located over the nose and forehead, less frequently other areas of the body including the ears and trunk, and can result in localized alopecia. This most commonly affects the eyebrows but can also affect eyelashes (madarosis) and the scalp.

Trichodysplasia spinulosa is suspected on clinical observation and is usually confirmed by histopathology of a lesional biopsy or a plucked spicule. Typical

histopathological features include large and distended hair follicles, which are often plugged with keratin and other debris. The hair follicles are abnormally organized with hyperproliferation of the inner hair root sheath cells containing large eosinophilic trichohyalin granules. Antibodies against major capsid protein VP1, the major component of the viral capsid, can be used to confirm the presence of viral particles in cell nuclei. Electron microscopy can also be used to detect viral particles.

As trichodysplasia spinulosa is rare, there is limited data on treatment and long-term outcome. Unlike Merkel cell carcinoma caused mostly by Merkel cell polyomavirus, trichodysplasia spinulosa is a dysplasia rather than a neoplasia [130]. In some cases, improvement in immune function has been noted to produce spontaneous improvement of symptoms. This pattern is consistent with the behavior of other viral diseases found in immunocompromised patients. Success has been reported from:

- Reduction or change in immunosuppressive medications [131]
- Physical extraction of keratin spicules [132]
- Compounded topical cidofovir cream [133]
- Oral valganciclovir [134]
- Treatment with antiviral drugs improves symptoms only as long as treatment continues
- Others: leflunomide [135]. Treatment with topical or oral retinoids has proven unsuccessful [136]

Differential diagnosis includes other visually similar conditions affecting the hair follicles of a group of cutaneous conditions with similar manifestations and distinct etiologies, collectively called the digitate keratoses [137].

Among others, multiple digitate hyperkeratosis (Fig. 7.8a–c) has been reported in association with paraproteinemia (Fig. 7.8d) [138] and due to follicular accumulation of IgG dysprotein (Fig. 7.8e) and cryoglobulin [139]. Histopathologic study of the follicular lesions shows follicular plugs of compact homogeneous eosinophilic material (Fig. 7.8f), and biochemical investigation reveals that skin matter from spicules is made up of monoclonal dysprotein with electrophoretic characteristics identical to those found in patient serum (Fig. 7.8g).

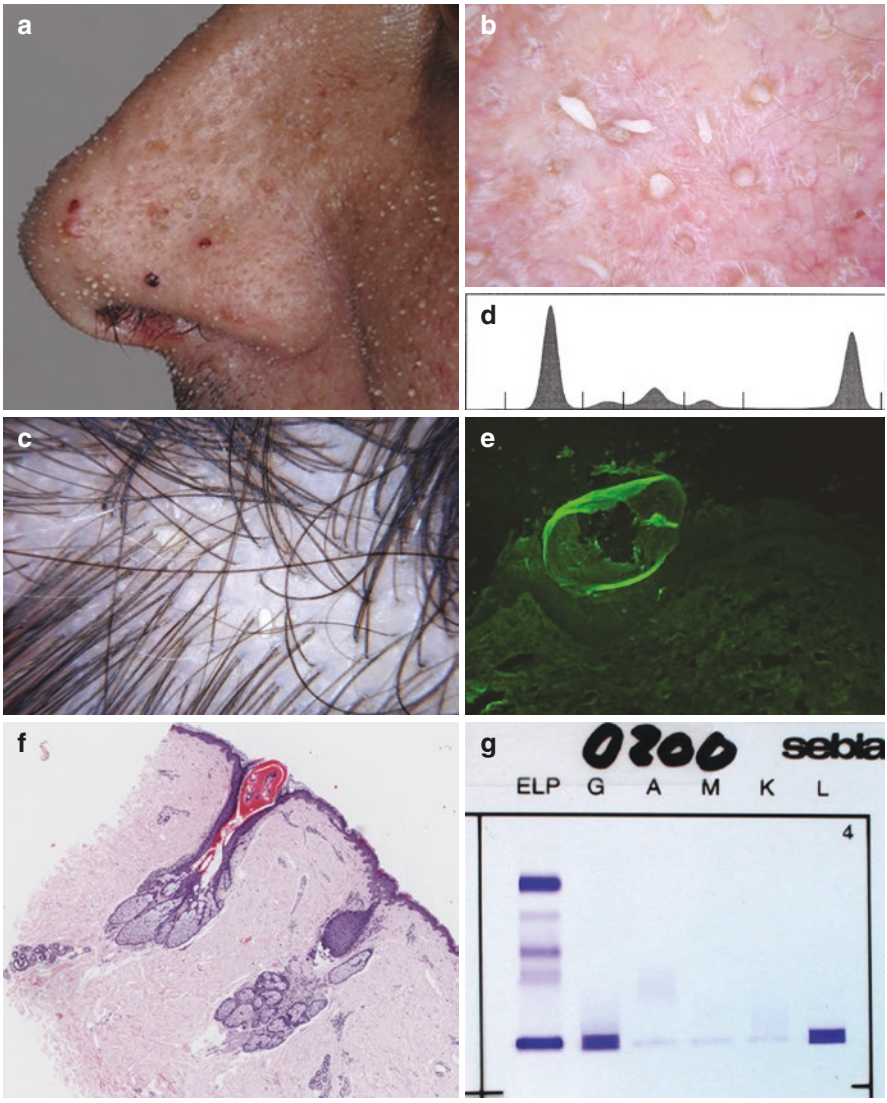


**Fig. 7.8** (**a**–**g**) Digitate keratosis: (**a**–**c**) follicular spiculae, (**b**) detail, (**c**) on scalp, (**d**) immune electrophoresis: paraproteinemia, (**e**) immunofluorescence: IgG dysprotein, (**f**) histopathology: eosinophilic follicular plug, (**g**) immunoblot: monoclonal dysproteins

## 7.7 Common Latent Viruses, Microcompetition, Androgenetic Alopecia, and the Aging Phenotype

With at least 315 different cellular and viral interacting proteins, CBP and p300 are considered the most heavily connected coactivators in the mammalian protein-protein interaction network [140, 141]. Both are histone acetyltransferases that control the transcription of numerous genes. Although two separate genes encode CBP and p300, they share a 61% sequence identity and are therefore often mentioned together as p300/CBP [142]. p300/CBP is a 300-kDa protein that has a CH2 domain, which contains its acetyltransferase activity, and five protein-binding domains [142]. Many studies have shown that competition for the limiting p300/CBP is an important mechanism that regulates transcription and cellular activities. These showed that competition between cellular transcription factors to bind the limiting p300/CBP is an important regulator of transcription. According to the microcompetition model, disrupting this regulation may cause disease. The microcompetition model was first described in the book *Microcompetition with Foreign DNA and the Origin of Chronic Disease* [143]. It centers on a specific type of disruption of this regulation: the one caused by the viruses with an N-box, which is a strong cis-regulatory element found on their promoters/enhancers. Accordingly, the viral N-boxes decrease the availability of GABP•p300/CBP in the cell. The result is abnormal expression of the cellular genes that bind GABP•p300/CBP. The genes that are transactivated by the GABP•p300/CBP complex synthesize fewer proteins, while those that are transrepressed by the complex synthesize more proteins. The abnormal levels of these cellular proteins can cause disease [144]. Some common viruses with an N-box are the cytomegalovirus, Epstein-Barr virus, herpes simplex virus 1, human T-cell lymphotropic virus, and human immunodeficiency virus. These viruses are highly prevalent. Since the virus is highly prevalent and only a fraction of infected people develop disease, it has been postulated that the copy number during latency matters. Only a high-enough copy number produce the strong enough sequestering effect that causes a disease, while the copy number of a virus during its latent phase is determined by the balance between the efficiency of the immune system and the copy number of latent viruses. Many events can cause immunodeficiency, including aging [145] and stress [146].

In androgenetic alopecia, androgens suppress growth on the scalp in those genetically predisposed. Studies have demonstrated both excess levels of dihydrotestosterone (DHT) [147] and an elevated expression of the androgen receptor (AR) [148] in the balding scalp. The reason for this increase in DHT levels is the increase of activity of 5-alpha reductase, the enzyme that converts testosterone to DHT. Elevated levels of 5-alpha reductase and AR in androgenetic alopecia have been explained by the microcompetition model: accordingly, the GABP•p300/CBP transcription complex normally suppresses both 5-alpha reductase and AR expression. Therefore, microcompetition between these genes and a latent virus, which also binds the complex, reduces the suppression and causes overexpression of 5-alpha reductase and AR. Excess 5-alpha reductase activity increases the conversion of testosterone to DHT, which binds to excess AR, resulting in a progression of androgenetic

alopecia. While 5-alpha reductase and the AR currently are the pharmaceutic industry's main target for drug development in androgenetic alopecia, the authors of the model suggest that a treatment that targets the latent virus, that is, the cause rather the than the consequence of microcompetition, may serve as a more effective strategy for treatment of androgenetic alopecia [149].

Reduced telomere length has been associated with aging as well as age-related diseases, including cardiovascular disease, diabetes, and cognitive decline [150]. Telomeres, stretches of DNA at the ends of chromosomes, provide protection against inappropriate DNA repair, recombination, and loss of genetic information after cell division.

Van de Berg et al. measured the relationship between telomere length in T cells and CMV infection [151]. They report that 1 year postprimary CMV infection, that is, during the latent phase, the cells exhibited shorter telomeres.

According to the microcompetition model, latent CMV infection may cause reduced telomere length via GABP transcription factor deficiency and contribute to the aging phenotype and aging-related diseases [152]. Microcompetition and viral-induced transcription factor deficiency are important since seroprevalence of CMV is greater than 70–80% by the age of 50 [153].

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# Parasitic Diseases and Infestations of the Hair and Scalp

8

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## Contents



First used in the English language in 1539, the word parasite comes from the Medieval French parasite, from the Latin parasitus, the latinization of the Greek παράσιτος, meaning "one who eats at the table of another," i.e., from παρά (para), "beside, by" + σῖτος (sitos), and "wheat," hence "food."

In contemporary popular language, the word parasitism has a derogatory sense. In everyday speech, a parasite is a sponger, a lazy profiteer, and a drain on society. However, in the Classical era, the concept of the parasite was not strictly pejorative: the parasitus was an accepted role in Roman society, in which a person could live

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off the hospitality of others, in return for flattery, simple services, and a willingness to endure humiliation. In English writer and physician John William Polidori's (1795–1821) original Gothic horror novel *The Vampyre* (1816), Lord Ruthven is the prototype and antecedent to Bram Stoker's Dracula (1897). As a thief, seducer, creator, and mimic, the eponymous Count is the ultimate parasite. The whole point of vampirism is sucking other people's blood, living at other people's expense [1]. Finally, revolting and horrifying parasitic alien species have become widespread in modern science fiction, with Swiss surrealist painter H.R. Giger (1940–2014) winning an Academy Award for Best Achievement for Visual Effects for his respective design work on the movie *Alien* (1979).

Parasitism represents a close and persistent long-term biological interaction between the parasite and its host. Unlike saprophytes, parasites feed on living hosts, and unlike commensalism, the parasitic relationship harms the host, either feeding on it or consuming some of its food.

Because parasites interact with other species, they can also act as vectors of pathogens, transmitting specific infectious diseases.

Parasitism has an extremely wide taxonomic range, including protozoans, animals, fungi, and plants. Many bacteria are parasitic, though they are more generally thought of as pathogens causing disease [2]. Viruses are obligate intracellular parasites, characterized by extremely limited biological function, lacking all the usual machinery of the cell such as enzymes, relying entirely on the host cell's ability to replicate DNA and synthesize proteins.

Parasitism is a major aspect of evolutionary ecology. As hosts and parasites evolve together, their relationships often change. When a parasite is in a sole relationship with a host, selection drives the relationship to become more benign, even mutualistic, as the parasite can reproduce for longer if its host lives longer. But where parasites are competing, selection favors the parasite that reproduces fastest, leading to increased virulence. There are thus varied possibilities in host-parasite coevolution.

Parasites can exploit their hosts to carry out a number of functions that they would otherwise have to carry out for themselves. Parasites which lose those functions then have a selective advantage, as they can divert resources to reproduction. Many insect ectoparasites including bedbugs, lice, and fleas have lost their ability to fly, relying instead on their hosts for transport.

The sensory inputs that a parasite employs to identify and approach a potential host are known as host cues. Such cues can include, for example, exhaled carbon dioxide, skin odors, visual and heat signatures, and moisture [3].

Hosts have evolved a variety of defensive measures against their parasites, including physical barriers like the skin and the reaction of the immune system. Once inside the body, parasites must overcome the immune system's serum proteins and pattern recognition receptors, intracellular and cellular, that trigger the adaptive immune system's lymphocytes such as T cells and antibody-producing B cells. The skin reactions to parasites can be either due to irritant effects of the contents of the parasite's saliva or the results of development of an immunologically mediated response to parasitic antigens. Secondary bacterial infections of scratch

excoriations on the skin are common, especially in warm humid climates, and depending on hygiene.

*Entomology* from Ancient Greek ἔντομον "insect" and -λογία "study of" is the scientific study of insects. Like other fields that are categorized within zoology, entomology is a taxon-based category. Any form of scientific study in which there is a focus on insect-related inquiries is, by definition, entomology.

The discipline of medical entomology, or public health entomology, and also veterinary entomology is focused upon insects and arthropods that impact human health. Veterinary entomology is included in this category, because many animal diseases can jump species and become a human health hazard. Medical entomology also includes scientific research on the behavior, ecology, and epidemiology of arthropod disease vectors and involves a tremendous outreach to the public, including local and state officials and other stake holders in the interest of public safety. There are many insects that affect human health. They can parasitize, bite, sting, and cause allergic reactions and/or vector disease to humans. Medical entomologists worldwide are working to combat the known effects in order to improve public health.

Dermatological entomology represents the branch of medical entomology that applies to the skin and its appendages [4]. Entodermoscopy is the term that has been proposed for the use of the dermatoscope in the diagnosis of skin infestations [5] although as yet dermoscopy is of minor importance in the diagnosis and management of infections and infestations of the skin and hair. Examples have been scabies, tungiasis, larva migrans, ticks, lice, myiasis, and urticating hairs of the tarantula. With some sarcasm indeed, trichological entomology could be proposed to include the science of insects as they relate to diseases of the hair and scalp and entodermoscopy, underlining the problem of extreme specialization in medicine with its propensity for neologisms of little practical value, while as dermatologists and physicians, we should rather maintain a broad view on health and disease.

Personal pests such as lice, fleas, bedbugs, ticks, and scabies mites may vector pathogens. They are hematophagous, meaning they feed on the blood of their host. Nearly all personal pests can be transmitted to an uninfected host with prolonged exposure to an infected host. Lice, fleas, bedbugs, and ticks are known as ectoparasites. Ectoparasites live on the skin of their host. They have adaptations that allow them to access the nutrients inside of the host, such as methods to penetrate skin, insert digestive enzymes, and a gut microbiome that can digest the nutrients received from the host. While these ectoparasites feed, the transfer of fluids may transmit diseases such as typhus, plague, and Lyme disease.

## 8.1 Lice

Lice are hematophagous, wingless insects. Pediculosis, the infestation of the human with lice, has been documented for thousands of years. They are very host-specific; therefore human lice are not transmitted to or from pets or other animals. There are three species of lice that infest humans with particularities in body size, form, and

preferred regions of infestation: *Pediculus humanus humanus* the body or clothing louse; *Pediculus humanus capitis*, the head louse; and *Pthirus pubis*, the pubic or crab louse.

The anticoagulant together with a vasodilator in lice saliva produces irritation and pruritus in most individuals. Lice, like most insects, harbor symbiotic bacteria. In the body lice, these produce necessary B vitamins specifically nicotinic acid, pantothenic acid, and biotin to meet the louse's nutritional requirements. Therefore, body lice are capable of inhabiting a host that is nutritionally deficient. However, the symbiotes of head lice do not possess these nutritional-enhancing capabilities; therefore head lice seek out healthy, well-nourished children as host.

Unfortunately, body lice have erroneously given all human lice a connotation of filth and poor hygiene. In fact, head lice prefer clean and healthy heads.

Finally, body lice are vectors of diseases such as epidemic typhus (*Rickettsia prowazekii*). Epidemics occurred routinely throughout Europe from the 16th to the 19th centuries, particularly during the English Civil War, the Thirty Years' War, and the Napoleonic Wars, and accounted for a significant proportion of casualties among the combatants. In fact, during Napoleon's retreat from Moscow in 1812, more French soldiers died of typhus than were killed by the Russians [6]. Also, trench fever caused by *Bartonella (rochalimaea) quintana* is transmitted by the body louse, and louse-borne relapsing fever (LBRF) is caused by *Borrelia recurrentis*. Lice prefer a narrow range of temperature and will leave a febrile person in search of another individual with a more suitable microclimate. Thus, there is an additional risk of migration of lice from the sick to the healthy. In the case of death of the host, lice quickly leave the cooling body in search of a new host.

The role of head lice and pubic lice as transmitters of disease has not been scientifically confirmed. However, head lice have been shown to transmit *Staphylococcus aureus* and group A *Streptococcus pyogenes* resulting in pyoderma of the scalp. In these cases, treatments with antibiotics are only temporary cures unless the causative agent, the louse, is effectively eradicated.

### 8.1.1 Head Lice

Head lice infest all levels of society and most ethnic groups. The mechanisms of transmission and the habits of head lice differ between cool and warm climates. Maximum egg production occurs at optimum temperatures of 29–30 °C with an ample supply of food. For these reasons it is commonly held that most eggs are laid close to the scalp.

Robert Hooke's 1667 book, *Micrographia: Or Some Physiological Descriptions of Minute Bodies Made by Magnifying Glasses with Observations and Inquiries Thereupon*, illustrated a human louse (Observation 54), drawn as seen down an early microscope (Fig. 8.1a). Lice, like all other insects, have six legs. These project from the fused segments of the thorax, are short and terminate with a single claw and opposing "thumb". Between its claw and thumb, the louse grasps the hair of its

host. With their short legs and large claws, lice are well adapted to clinging to the hair of their host.

Body lice and head lice (Fig. 8.1b, c) are almost identical in appearance except for size. Head lice are shorter and narrower across the abdomen than body lice. Adult head lice are small (2.5–3 mm long), dorsoventrally flattened (see anatomical terms of location), and wingless. The thoracic segments are fused but otherwise distinct from the head and abdomen, the latter being composed of seven visible segments. One pair of antennae, each with five segments, protrudes from the insect's head. Head lice also have one pair of eyes. Head louse mouthparts are highly adapted for piercing the skin and sucking blood. These mouth parts are retracted into the insect's head except during feeding.

Like most insects, head lice are oviparous. Females lay about three or four eggs per day. Louse eggs, also known as nits, are attached near the base of a host hair shaft. Eggs are usually laid on the base of the hair, 3–5 mm off the scalp surface.

The nits (Fig. 8.1d, e) are oval-shaped and about 0.8 mm in length. They are bright, transparent, and tan to coffee-colored so long as they contain an embryo but appear white after hatching. Head lice hatch typically 6–9 days after oviposition. After hatching, the louse nymph leaves behind its egg shell, still attached to the hair shaft. The empty egg shell remains in place until physically removed by abrasion or the host, or until it slowly disintegrates, which may take 6 or more months.

The nape of the neck and behind the ears are their favorite places because these areas are more protected from extreme temperatures. Pruritus is the primary complaint. The intense itching forces the host to scratch, often excoriating the skin (Fig. 8.1f). Secondary bacterial infections are common.

Lice have no wings or powerful legs for jumping, so they move using the claws on their legs to move from hair to hair. Normally, head lice infest a new host only by close contact between individuals, making social contacts among children and parent-child interactions more likely routes of infestation than shared combs, hats, brushes, towels, clothing, beds, or closets. Head-to-head contact is by far the most common route of lice transmission. The number of children per family; the sharing of beds and closets; hair washing habits; local customs and social contacts; healthcare in a particular area, such as school; and socioeconomic status were found to be significant factors in head louse infestation. Girls are two to four times more frequently infested than boys. Children between 4 and 14 years of age are the most frequently infested group. Children with long- and medium-length hair are more often infested than children with short hair [7]. Finally, there appears to be an unknown element that causes some children to be more prone to repeated infestations than others. Whether blood type [8] or scalp microbiomata [9] plays a role is as yet to be further elucidated.

Many options for the treatment of head lice infestation exist. Nonprescription topical permethrin and pyrethrin are available. Prescription topical products include lindane, malathion, benzyl alcohol, carbaryl, and ivermectin.

Although treatment options are available, many have become less efficacious due to emergence of resistance with regional variety of prevalence and types of resistance.

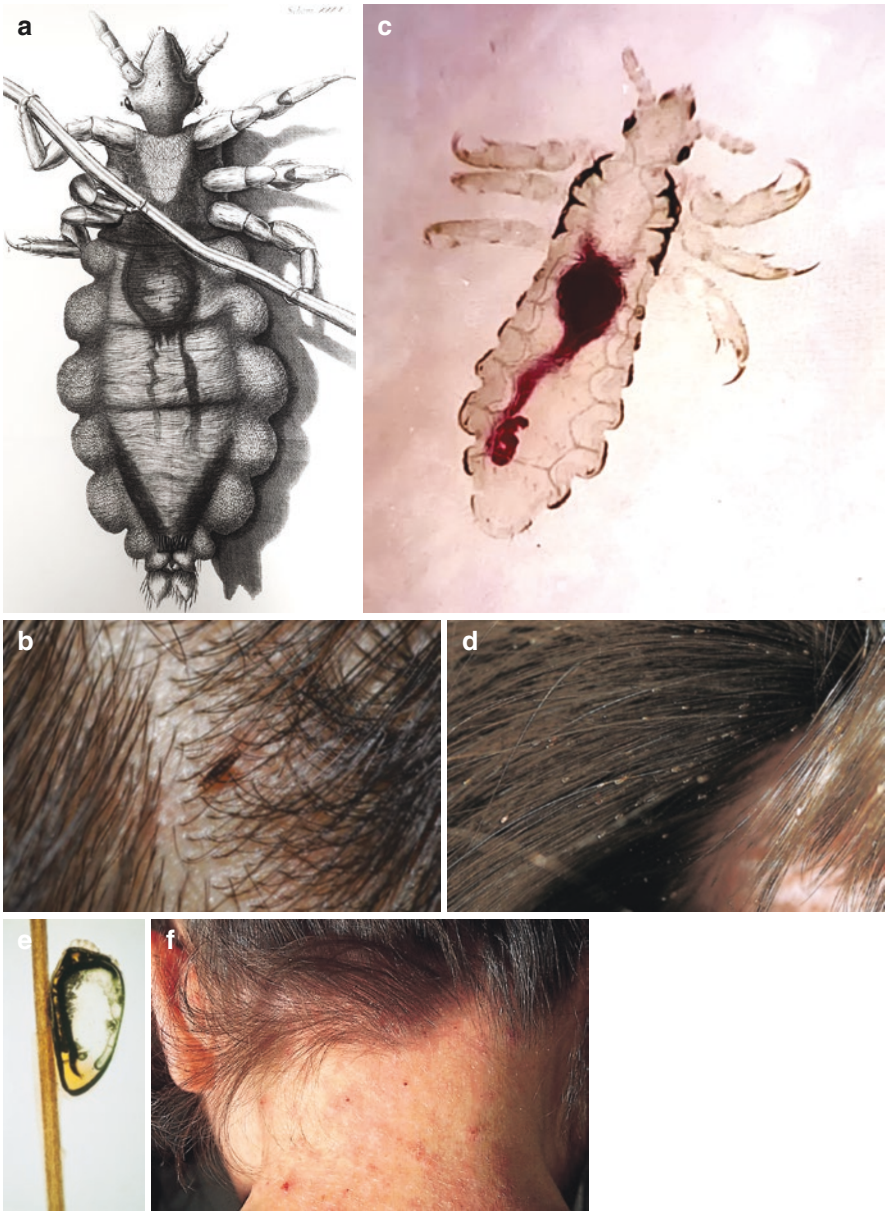


**Fig. 8.1** (**a**–**c**) Pediculosis capitis: (**a**) the head louse, as originally drawn by Robert Hooke (from facsimile of the 1667 book *Micrographia* in the author's personal library), (**b**) head louse (courtesy Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), (**c**) magnified, (**d**) nits attached to the hair, (**e**) magnified, and (**f**) excoriations of the skin in the nape of the neck

Two treatments 1 week apart are necessary for all topical pediculides, given their poor ovicidal activity. Because no product is 100% ovicidal, it is important to concentrate on grooming and nit removal in the period between treatments to enhance efficacy.

Many parents are reluctant to apply pesticides to their children's heads and are turning to alternative therapies. Some have claimed to have successfully cured their infestation by using inexpensive, non-pesticide products, including Vaseline petrolatum jelly, hair pomade, olive oil, mayonnaise, vinegar, mineral oil, or essential oils from the health food store. However, these require repeated overnight treatments because they are not as effective as the currently available products, and they usually require many hours of painstaking combing. Noninsecticidal agents, including dimethicone and isopropyl myristate, show promise in the treatment of pediculosis [10].

Extensive environmental decontamination is not necessary after pediculosis is diagnosed. However, some school authorities may insist on a "no nit" policy to ensure freedom from infestation and proof of adequate treatment. This requires physically removing the nits form the hair. Although time-consuming, it relieves school authorities, nurses, and physicians of the difficulty of deciding whether eggs are viable, but it puts a burden on the parents, especially if they have a few children. Nit combs are constantly being improved on. The task of removing nits is made easier when the hair is wet, and the additional use of a detangler, crème rinse, light oil, or condition facilitates combing.

Cotrimoxazole (CTM) has been observed to be an effective treatment for pediculosis given orally [11]. So far, the use of antibiotics for the treatment of pediculosis capitis has been regarded appropriate only for infested children who have secondary bacterial infections of the scalp. The rationale behind this treatment is that, because lice are obligate blood feeders and are dependent on their symbiotic bacteria for survival, a blood meal containing antibiotic will kill their symbiotes. The minimal effective dose of CTM in pediculosis was found to be one tablet containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole taken twice daily for 3 days. Patients are retreated with CTM twice daily for 3 days, 10 days after completion of the initial CTM therapy, by which time nits had hatched.

Oral ivermectin is an option for the treatment of head lice infestation, especially in individuals who have experienced a treatment failure. Published evidence from clinical trials indicates that oral ivermectin at a 2 × 200 μg/kg dosage given at day 1 and 7 is as effective as currently available topical treatments [12].

### 8.1.2 Crab Lice

The crab louse usually is found in a person's pubic hair. Although the louse cannot jump, it can also live in other areas of the body that are covered with coarse hair, such as the perianal area, the entire body in men, and the eyelashes (phthiriasis palpebrarum). Pubic lice have wide, short bodies resembling a tiny crab (Fig. 8.2). An adult crab louse is about 1.3–2 mm long and slightly smaller than the body louse

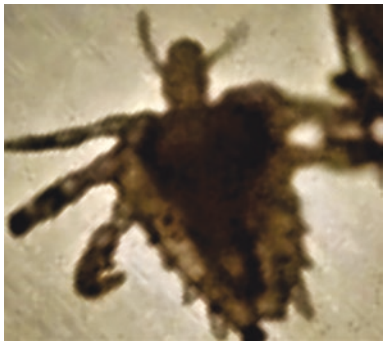

**Fig. 8.2** Crab louse (pediculosis pubis)

and head louse and can be distinguished from those other species by its almost round body. Another distinguishing feature is that the second and third pairs of legs of a crab louse are much thicker than the front legs and have large claws.

The eggs of the crab louse are laid usually on the coarse hairs of the genital and perianal regions of the human body. The female lays about three eggs a day. The eggs take 6–8 days to hatch, and there are three nymphal stages which together take 10–17 days before the adult develops, making a total life cycle from egg to adult of 16–25 days. Adults live for up to 30 days. Crab lice feed exclusively on blood and take a blood meal four to five times daily. Outside the host they can survive for 24–48 h. Crab lice are transmitted from person to person most commonly via sexual contact.

The main symptom of infestation with crab lice is itching, usually in the pubic hair area, resulting from hypersensitivity to louse saliva, which can become stronger over 2 or more weeks following initial infestation. In some infestations, a characteristic gray-blue or slate coloration appears (maculae ceruleae) at the feeding site, which may last for several days.

Crab louse infestation can be suspected through the presence of the maculae ceruleae and diagnosed by identifying the presence of active stages of the louse, as well as of nits on the pubic hair or other hairs of the body.

Crab lice prefer hair that is widely spaced because the usually grasp one hair with the claws on one side of their body and another hair with the claws on the other side. Crab lice are relatively rare in Asians, perhaps because of sparser genital hairs. Infestation with pubic lice is relatively common among homosexual man. Crab lice found on the head or eyelashes of children may be an indication of sexual exposure or abuse [13]. And yet, although pediculosis pubis is considered a sexually transmitted disease, fomite transmission (bedding, clothing) may play a larger role than originally supposed. It has been suggested that an increasing percentage of humans removing their pubic hair, especially in women, has led to reduced crab louse populations in some parts of the world [14].

The role of pubic lice as transmitter of infectious disease has not been scientifically confirmed. And yet, the possibility of co-infection with another sexually

transmitted disease must be taken into consideration in the particular individual depending on behavioral risk factors. Crab lice collected from human immunodeficiency virus (HIV)-positive and HIV-negative volunteers were tested by stands for polymerase chain reaction (PCR) for the human immunodeficiency virus (HIV). All specimens obtained from HIV-1-positive individuals were found positive by ethidium bromide gel and confirmed on Southern blot [15]. As yet, HIV transmission by crab lice has not been demonstrated.

First-line pharmacologic treatment for pediculosis pubis is permethrin 1% lotion or shampoo. In adults, the presence of pubic lice should prompt an evaluation for sexually transmitted infections [16]. Pubic lice have always appeared to be among the hardiest of human lice when it comes to treatment. It is important to treat all hairy areas of the body since it is not uncommon to have other body areas infested without the patient being aware of it, and lice will wander away from a treated area in search of a more suitable environment.

Products for head and pubic lice are too irritating to use in the sensitive eye region. Although a safe and effective treatment for eyelash involvement with crab lice (phthiriasis palpebrarum) has been petrolatum jelly (Vaseline), it is slow and needs to be applied at least five times a day for 10 days. A course of oral tetracycline can be useful in killing the lice sooner. Finally, physostigmine 0.2% eyedrop, a pupillary dilator, has also been used successfully when applied to eyelashes; however, again the application must be repeated several times over a 3-day period.

## 8.2 Scabies

Scabies is one of the three most common skin disorders in children, along with ringworm and bacterial skin infections.

The Italian physician Giovanni Cosimo Bonomo (16666–1696) and biologist and entomologist Diacinto Cestoni (1637–1718) showed in the seventeenth century that scabies is caused by *Sarcoptes scabiei*, this discovery of the itch mite in 1687 marking scabies as the first disease of humans with a known microscopic causative agent.

Human scabies is caused by the female itch mite *Sarcoptes scabies* var. *hominis*, family Sarcoptidae, class Arachnida, and as such has four pairs (eight) of legs (two pairs in front and two pairs behind). Adult scabies mites are spherical, eyeless mites that are recognizable by their oval, ventrally flattened and dorsally convex tortoise-like bodies and multiple cuticular spines. No demarcation into cephalothorax or abdomen occurs, and the mite's surface has folds covered with short bristles. The front legs end in long, tubular processes known as suckers, and the hind legs end in long bristles (Fig. 8.3a). When placed on the skin, the female mite exudes a fluid that dissolves the skin surface, forming a well into which she sinks. In cool climates,

the female scabies mite forms a tunnel or burrow that may extend a distance of 0.5–5 mm per day. Gravid females lay the first egg within hours of burrowing and 2–3 eggs a day. The eggs hatch within 2.5–4 days. The six-legged larvae, which hatch in 3 to 10 days, move about on the skin, molt into a nymphal stage, and then mature into the eight-legged adult mites. The adult mites live 3–4 weeks in the host's skin. The male mites which are only half the size of females do not burrow, however do enter the females' residence shortly to copulate, leaving irritant antigenic matter. In fact, the pruritic eruption of the skin is caused by both the burrowing and release of irritant and antigenic secretions and excretions of the mite.

Scabies represents a contagious skin infestation, the most common skin symptoms being severe itchiness often worse at night, causing papular pustular-vesicular eruptions of the skin. Although the life cycle of the scabies mite is only about 2 weeks, individual patients are seldom found to have more than about a dozen mites on them. Even so, this number is sufficient to cause agonizing itching and severe damage to the skin as a result of scratching, in particular by the introduction of infective bacteria, which may lead to impetigo or eczema. A delayed type IV hypersensitivity reaction to the mites, their eggs, or packets of feces (skybala) occurs approximately 30 days after infestation. The presence of the eggs produces a massive allergic response that, in turn, produces more itching. Individuals who already are sensitized from a prior infestation can develop symptoms within hours.

Crusted scabies (Fig. 8.3b–e), also called Norwegian scabies, is an infestation characterized by thick crusts of skin that contain large numbers of scabies mites and eggs. It represents a severe form of the disease that occurs most often elderly, disabled, and people with impaired immune systems, such as those with HIV/AIDS or cancer or those on immunosuppressive medications. On those with weaker immune systems, the host becomes a more fertile breeding ground for the mites, which spread over the host's body, including the scalp [17–23]. The mites in crusted scabies are not more virulent than in non-crusted scabies; however, they are much more numerous (up to two million). People with crusted scabies exhibit scaly rashes, slight itching, and thick crusts of skin that contain large numbers of scabies mites. For this reason, persons with crusted scabies are more contagious to others than those with typical scabies. Such areas make eradication of mites particularly difficult, as the crusts protect the mites from topical scabicides, necessitating prolonged treatment of these areas and/or oral treatment.

The mite is found in all parts of the world. Scabies may be diagnosed clinically in geographical areas where it is common when diffuse itching presents along with either lesions in two typical spots or itchiness is present in another household member.

The classical sign of scabies is the burrow made by a mite within the skin. To detect the burrow (Fig. 8.3f), the suspected area is rubbed with ink from a fountain pen or a topical tetracycline solution, which glows under a special light. The skin is then wiped with an alcohol pad. If the person is infected with scabies, the characteristic zigzag or S pattern of the burrow will appear across the skin; however, interpreting this test may be difficult, as the burrows are scarce and may be obscured by scratch marks.

A definitive diagnosis is made by finding either the scabies mites or their eggs and fecal pellets (Fig. 8.3g). Searches for these signs involve either scraping a suspected area, mounting the sample in xyline, and examining it under a microscope.

On histopathology, scanning power view of scabies shows a pattern of an epidermal and wedge-shaped dermal inflammatory process (Fig. 8.3h). The epidermal histological findings in the primary scabetic lesion are hyperkeratosis, acanthosis, and spongiotic edema and vesiculation. The dermal changes consist of perivascular and diffuse cell infiltrates, mainly mononuclear cells, and sometimes eosinophilic

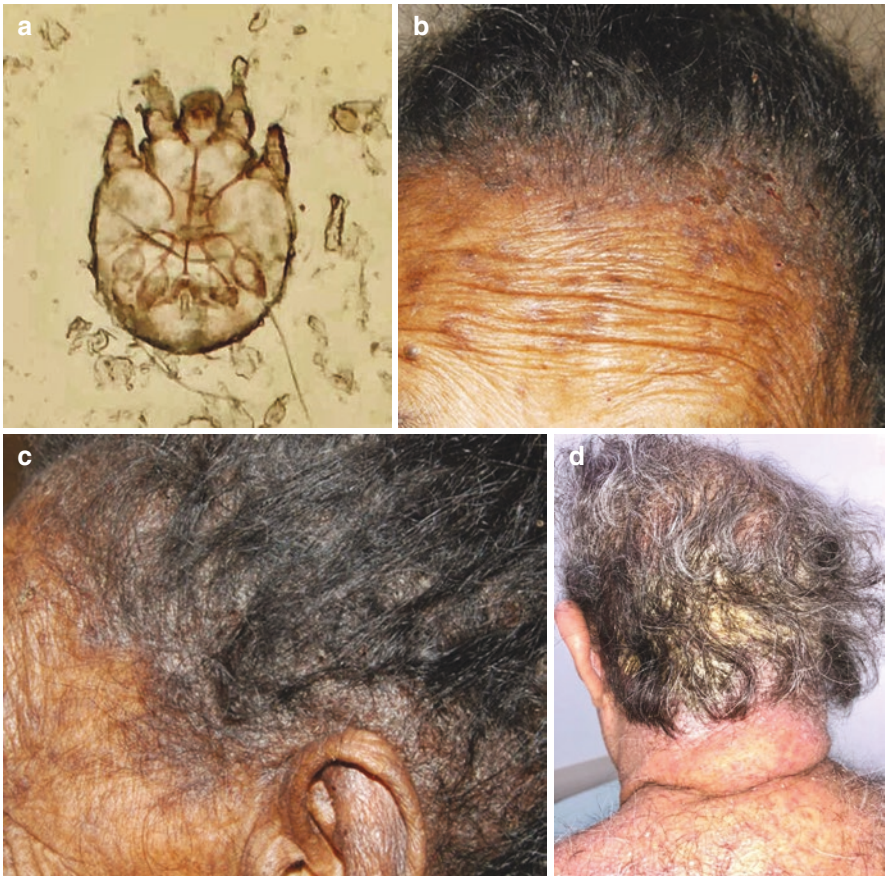


**Fig. 8.3** (**a**–**i**) Scabies: (**a**) Scabies mite (*Sarcoptes scabies*), courtesy Dr. Marcelo Teixeira, Dermatologist, Brazil, (**b**–**e**) crusted scabies of the scalp (courtesy Dr. Marcelo Teixeira, Dermatologist, Federal Fluminense University, Brazil, and Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), (**f**) dermoscopy of scabies burrow, (**g**) scabies fecal pellets (skybala) (arrows), (**h**–**j**) histopathology: (**h**) pattern of an epidermal and wedge-shaped dermal inflammatory process, (**i**) perivascular and diffuse mainly mononuclear cell infiltrates with eosinophilic granulocytes, (**j**) presence of scabies parts evident as solid fragments representing the chitinous exoskeleton of the *Sarcoptes scabiei* within the epidermis (courtesy Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland)

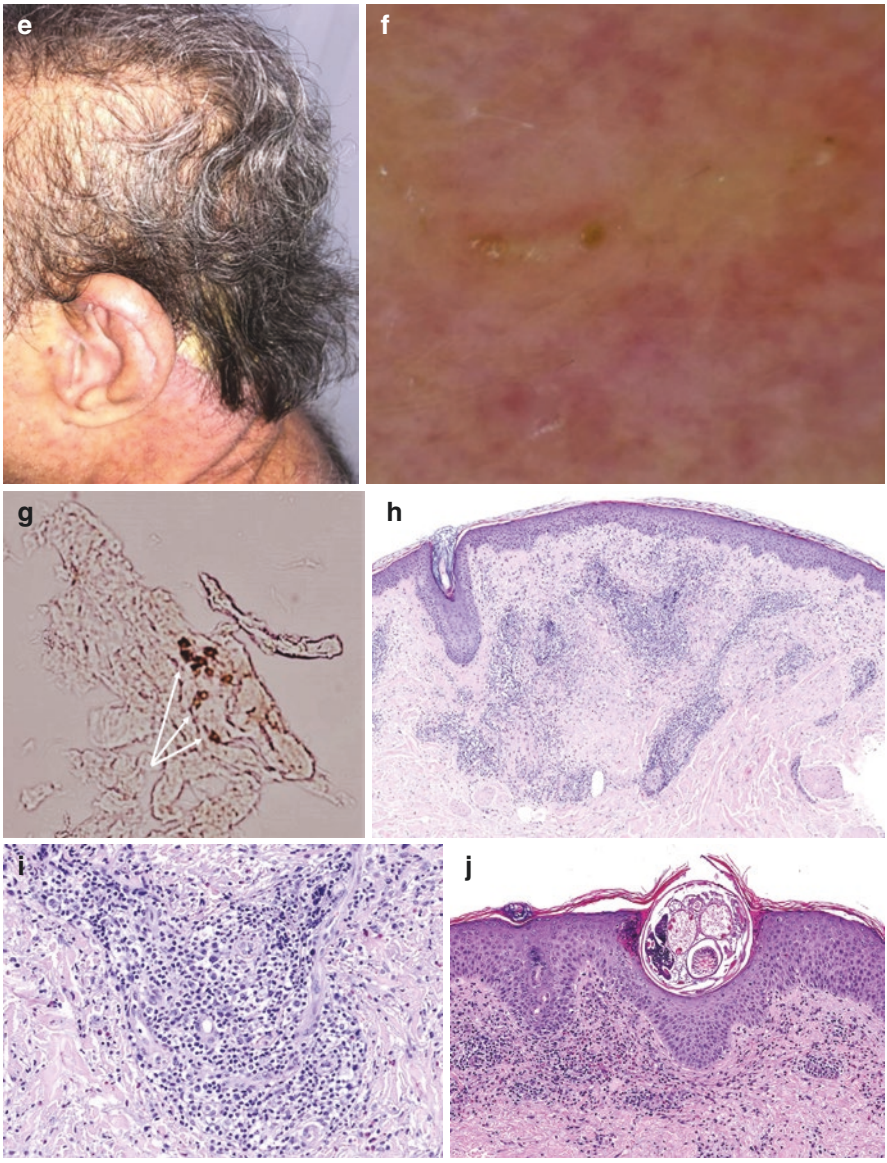


**Fig. 8.3** (continued)

granulocytes (Fig. 8.3i). Deep interstitial eosinophils are an important clue to an arthropod bite reaction. Ultimately, the presence of scabies parts evident as solid pink eosinophilic fragments representing the chitinous exoskeleton of the *Sarcoptes scabiei* mite is diagnostic (Fig. 8.3j).

Several medications are effective in treating scabies. The simultaneous treatment of all close contacts is recommended, even if they are asymptomatic, to reduce rates of recurrence. Bedding, clothing, and towels used during the previous 3 days should be washed in hot water and dried in a hot dryer. Treatment protocols for crusted scabies are significantly more intense than for common scabies.

Permethrin 5% dermal cream is the most effective treatment for scabies and remains the treatment of choice. It is applied from the neck down, usually before sleep, and left on for about 8 to 14 h, then washed off in the morning. Care should be taken to coat the entire skin surface, not just symptomatic areas. Any patch of skin left untreated can provide a safe haven for one or more mites to survive, particularly the nails. These are important as the principal tools for scratching and may also act as a reservoir for mites and their eggs. One application is normally sufficient, as permethrin kills eggs and hatchlings, as well as adult mites, though many physicians recommend a second application 3–7 days later as a precaution.

Oral ivermectin at a single 200 μg/kg dose and at two doses in patients with crusted scabies, respectively, is effective in eradicating scabies. It is the treatment of choice for crusted scabies and is sometimes prescribed in combination with a topical agent. One review found that the efficacy of permethrin is similar to that of systemic or topical ivermectin. A separate review found that although oral ivermectin is usually effective for treatment of scabies, it does have a higher treatment failure rate than topical permethrin. Another review found that oral ivermectin provided a reasonable balance between efficacy and safety. A study has demonstrated that scabies is markedly reduced in populations taking ivermectin regularly. The drug is widely used for treating scabies and other parasitic diseases particularly among the poor and disadvantaged in the tropics [24–32].

Other treatments of the past have included lindane (1% lotion), benzyl benzoate (25% to 30% to be applied for 3 alternate or consecutive days), crotamiton (10% cream), and sulfur preparations (at concentrations of 6% or less in several applications over 2 or 3 days). Today, lindane is not recommended for its neurotoxicity and emergence of lindane-resistant scabies and crotamiton for lack of efficacy and lack of toxicity data. Because permethrin cream is approved for use on infants aged 2 months or older, it has largely replaced sulfur in pediatric practice.

Mass treatment programs that use topical permethrin or oral ivermectin have been effective in reducing the prevalence of scabies in a number of populations. Since mites can survive for only 2–3 days without a host, other objects in the environment pose little risk of transmission except in the case of crusted scabies. Therefore, cleaning is of little importance. However, rooms used by those with crusted scabies require thorough cleaning. Particularly nursing homes and hospital staff have notably become infested by changing bedding, even with no patient contact.

Among the famous people who have allegedly suffered of scabies, Napoleon (1769–1821) has been the most notorious. And yet there are no authentic records to prove that he ever had this disease. Considering the emperor's habits of hygiene; the


**Fig. 8.4** (**a**–**c**) Solar-powered scratching Napoleon by Kikkerland. Solar cell is at the top of his hat. Napoleon's characteristic pose with his hand beneath his shirt was rather a mannerism than due to itching form scabies

long duration of his skin condition, which began with the siege of Toulon (1793) and lasted for 9 or 10 years; and the numerous sulfur baths which he took, it seems improbable that he should have suffered of scabies. Moreover, the remedy consisting of a concoction of ointments and salves containing olive oil, alcohol, and powdered "cevilla," which his personal physician Jean-Nicolas Corvisart (1755–1821) used successfully, would have been practically useless for the treatment of scabies. In fact, Friedman in his book, *The Emperor's Itch: The Legend Concerning Napoleon's Affliction with Scabie*s, suggests that Napoleon may have actually suffered from dermatitis herpetiformis. The author also thinks that Napoleon's characteristic pose with his hand beneath his shirt was rather a mannerism possibly cultivated in his youth (Fig. 8.4a–c) than due to itching from cutaneous disease [33].

## 8.3 Demodex

Demodex is a genus of microscopic mites that live in or near hair follicles of mammals. Around 65 species of Demodex are known. Two species live on humans: *Demodex folliculorum* and *Demodex brevis*, both frequently referred to as eyelash mites, alternatively face mites or skin mites. *D. folliculorum* is found in hair follicles, while *D. brevis* lives in sebaceous glands connected to hair follicles. Both

species are primarily found in the face near the nose, the eyelashes, and eyebrows but also occur elsewhere on the body, including the scalp.

The adult mites are only 0.3–0.4 mm long, with *D. brevis* slightly shorter than *D. folliculorum* [34]. Each has a semitransparent, elongated body that consists of two fused segments. Eight short, segmented legs are attached to the first body segment (Fig. 8.5). The body is covered with scales for anchoring itself in the hair follicle, and the mite has pin-like mouthparts for eating skin cells and oils that accumulate in the hair follicles. The mites can leave the hair follicles and slowly walk around on the skin, at a speed of 8–16 mm per hour, especially at night, as they try to avoid light. The mites are transferred between hosts through contact with hair, eyebrows, and the sebaceous glands of the face.

Older people are much more likely to carry the mites; about a third of children and young adults, half of adults, and two-thirds of elderly people carry them [35]. The lower rate in children may be because children produce less sebum or simply have had less time to acquire the mite.

29% of unselected pathological and forensic autopsy cases revealed *Demodex folliculorum* and *brevis* in hair follicles and sebaceous glands of the scalp. The

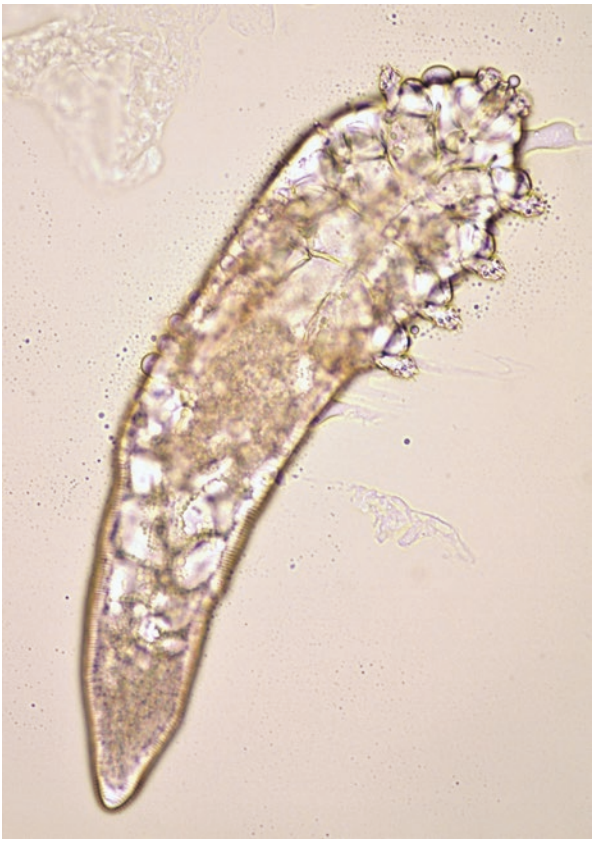

**Fig. 8.5** *Demodex folliculorum*

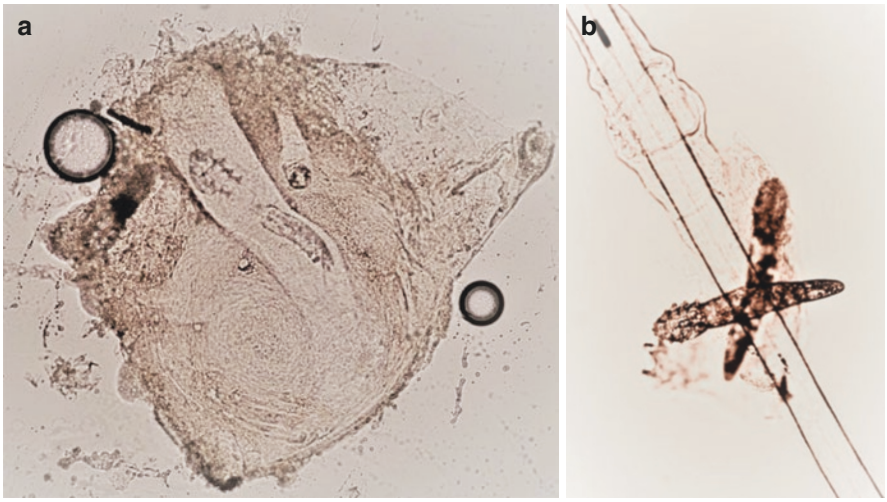


**Fig. 8.6** (**a**, **b**) Demodex mites are common (**a**) commensals of the pilosebaceous unit, and often (**b**) found in plucked hair mounted for the trichogram examination

frequency was equal in male and female subjects and correlated to the number of sebaceous glands, and not to the density of hair follicles. However, there was a tendency to an increased number of parasites inhabiting the scalp of people of advanced age, or with a bald head. A chronic lymphocytic infiltration of the skin was conspicuous in more than 70% of cases [36].

A 2014 study of $n = 29$ people in North Carolina, USA, found that all the adults ($n = 19$, over 18 years of age) carried mites and that 70% of those under 18 years of age carried mites [37]. This study using a DNA detection method, more sensitive than traditional sampling and observation by microscope, along with several studies of cadavers, suggests that previous work might have underestimated the mites' prevalence. However, the small sample size and small geographical area involved prevent drawing broad conclusions from these data.

Demodex infestation of the scalp has previously been put forward as a possible etiological factor in some cases of scalp rosacea [38]. However, demodex mites are common commensals of the pilosebaceous unit (Fig. 8.6a), often found in plucked hair mounted for the trichogram examination (Fig. 8.6b) However, there has been a controversy to what degree demodex mites are causative of skin pathology and how they might contribute to disease in humans until topical ivermectin has successfully been introduced for treatment of rosacea [39].

*Demodex folliculorum* and *D. brevis* have been identified and implied to play a role in pustular folliculitis of the face (Fig. 8.7a, b) [40], papulopustular scalp eruptions (Fig. 8.7c, d) [41], eosinophilic follicular reaction [42], and blepharitis (Fig. 8.7e) [43]. In general, the clinical presentations of demodicidosis have been classified into three main groups:

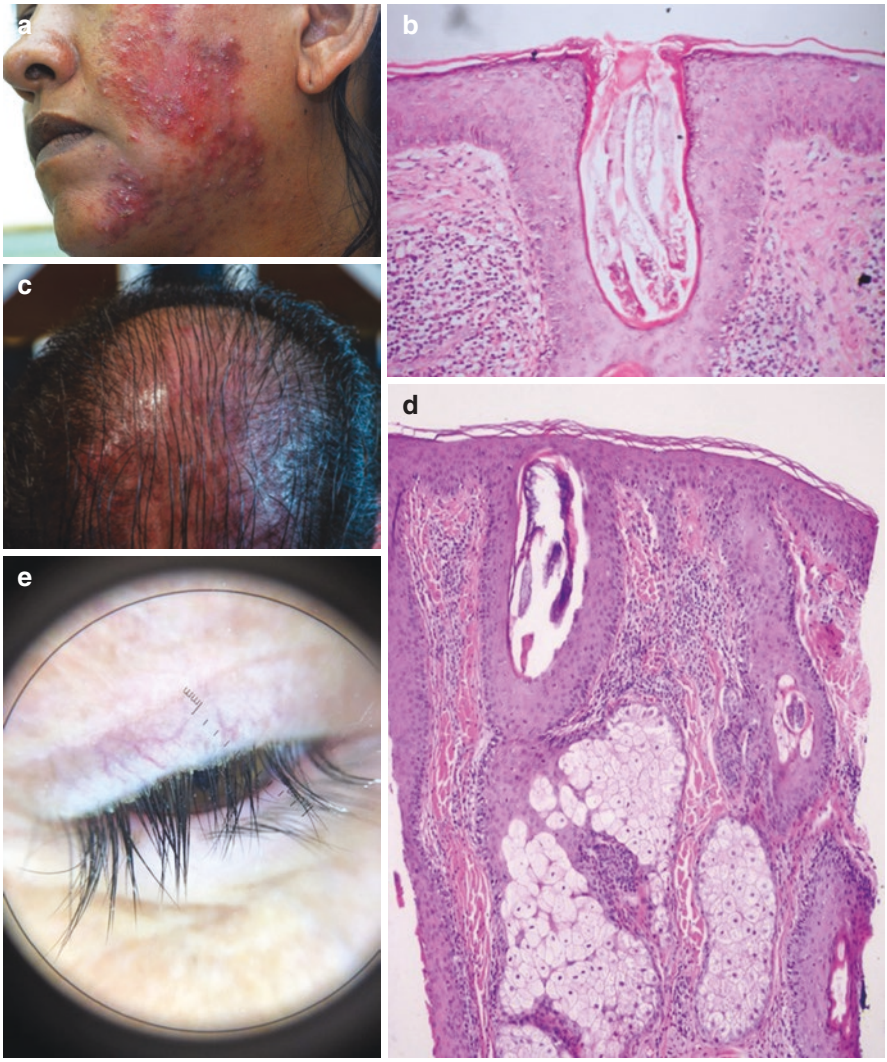


**Fig. 8.7** (**a**–**e**) Demodicidosis: (**a**) pustular folliculitis of the face, (**b**) histopathology (courtesy Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), (**c**) papulopustular scalp eruptions, (**d**) histopathology, (**e**) blepharitis

- Pityriasis folliculorum
- Rosacea-like demodicidosis
- Granulomatous rosacea-like demodicidosis gravis

A case of scalp demodicosis in a patient with frontal fibrosing alopecia dermoscopically mimicking active disease was reported. A 78-year-old Caucasian male with a previous history of a well-controlled frontal fibrosing alopecia with high-potency topical corticosteroids presented with scalp itching, follicular hyperkeratosis, and erythema. A scalp biopsy of this area revealed numerous mites in the follicular openings. Based on these findings and the history of chronic use of topical corticosteroids, a diagnosis of secondary scalp demodicosis was made. Discontinuation of topical corticosteroid treatment was recommended, and four doses of oral ivermectin 200 mcg/kg on a weekly basis were prescribed. One month later, dermoscopic signs suggestive of demodicosis as well as pruritus resolved [44]. It is also our observation that sometimes persistent follicular inflammation, scaling, and pruritus in patients with frontal fibrosing alopecia despite topical corticosteroid treatment may sometimes resolve upon a trial with topical 5% permethrin cream [unpublished data], while we alternatively interpreted this observation as an abnormal reaction of the hair follicle on commensal demodex mites.

Methods used for diagnostic purposes in demodicosis include cyanoacrylic adhesives, comedone extractor, cellophane tape preparations, skin scraping, punch biopsy, and standardized surface skin biopsy [45].

Therapy includes oral metronidazole (250 mg bid for 30 days), 5% topical permethrin cream once daily (Fig. 8.8a, b), or oral permethrin (200 micrg/kg) followed by maintenance therapy with 5% topical permethrin cream weekly [46].

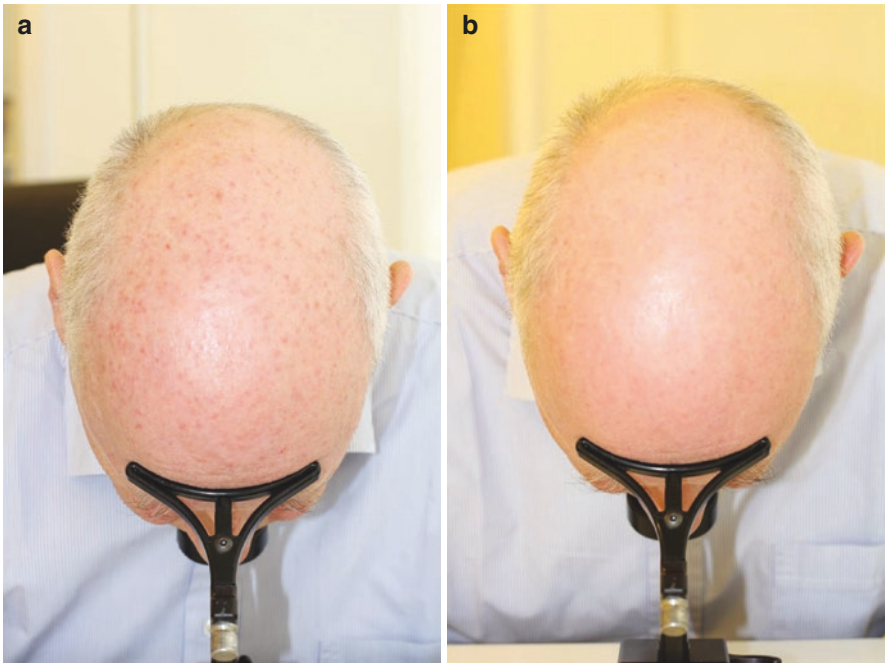


**Fig. 8.8** (**a**, **b**) Scalp demodicidosis (**a**) before, and after (**b**) successful treatment with 5% topical permethrin cream daily

## 8.4 Tick

Ticks (order Ixodida) are parasitic arachnids that are part of the mite superorder *Parasitiformes.* Ticks are ectoparasites and consume blood to satisfy all of their nutritional requirements. They are obligate hematophages and require blood to survive. On locating a suitable feeding spot, the tick grasps the host's skin and cuts into the surface. It extracts blood by cutting a hole in the host's epidermis, into which it inserts its hypostome and prevents the blood from clotting by excreting an anticoagulant or platelet aggregation inhibitor [47]. Ixodidae remain in place until they are completely engorged. Tick saliva contains about 1500 to 3000 proteins, depending on the tick species. The proteins with anti-inflammatory properties, called evasins, allow ticks to feed for 8–10 days without being perceived by the host animal.

Ticks are implicated in the transmission of a number of infections caused by pathogens such as bacteria, viruses, and protozoa. Species of the bacterial genus *Rickettsia* are responsible for typhus, rickettsial pox, boutonneuse fever, African tick bite fever, Rocky Mountain spotted fever, Flinders Island spotted fever, and Queensland tick typhus (Australian tick typhus). Other tick-borne diseases include Lyme disease and Q fever, Colorado tick fever, Crimean-Congo hemorrhagic fever, tularemia, tick-borne relapsing fever, babesiosis, ehrlichiosis, Bourbon virus, and tick-borne meningoencephalitis, as well as bovine anaplasmosis and the Heartland virus. In the United States, Lyme disease is the most commonly reported vector-borne disease in the country. Finally, a tick can harbor more than one type of pathogen, making diagnosis more difficult.

Not all ticks in an infective area are infected with transmittable pathogens, and both attachment of the tick and a long feeding session are necessary for diseases to be transmitted. Consequently, tick bites often do not lead to infection, especially if the ticks are removed within 36 h. While adult ticks can be removed with fine-tipped tweezers or proprietary tick removal tools then disinfecting the wound, there is growing consensus that ticks should be killed in situ and frozen with either a custom spray or medical wart remover and left to fall out to avoid anaphylactic/allergic reactions.

Tick bite alopecia represents a distinctive tick bite-related condition characterized by a solitary oval zone of alopecia with a central eschar. Histologic findings are not well described but generally indicate dense perifollicular lymphocytic inflammation. The mechanism for hair loss is poorly understood, but the prognosis for hair regrowth appears to be favorable [48]. As anticoagulants may cause alopecia, it has been speculated on the possibility that their presence may be responsible for the depilating effect of tick saliva [49]. In view of the histological findings, however, it is more likely that alopecia is the result of the joint effect of tick saliva and host reaction. Tissue necrosis in the immediate vicinity of the attachment site of the tick probably accounts for the central eschar and initial central hair loss. Dilution of the salivary juice as is spreads through the host tissue would result in progressive loss of activity with diminishing destructive power [50].

The scarring form of tick bite alopecia is characterized by the formation of an eschar that progresses to patches of cicatricial alopecia. This scarring form of tick

bite alopecia histologically is characterized by a loss of hair follicles with fibrosis, periadnexal lymphocytic inflammation, and an interstitial eosinophilic or granulomatous infiltrate. The etiology of the hair loss may be related to the host response to tick saliva, external forces, and, in some scarring cases, rickettsial infection [51]. Tick-borne lymphadenopathy syndrome, classically transmitted by ticks of the genus *Dermacentor* and caused by *Rickettsia slovaca* infection, is an entity typically seen in Europe and highly associated with alopecic eschar, fever, malaise, and painful nuchal lymphadenopathy [52, 53]. Doxycycline is the treatment of choice.

Both, pseudopelade Brocq [54] and acute diffuse and total alopecia of the female scalp [55] have been reported as possible sequelae of stage III Borrelia infection. In both cases, treatment with intravenous cefotaxime and ceftriaxone, respectively, were successful in arresting progression of scarring alopecia and recovering hair in the diffuse and total alopecia.

Besides several reports of localized alopecia after tick bites, there have also been few reports of ant-induced alopecia in the literature [56–58]. Ant-induced alopecia should be considered in the differential diagnosis of localized sudden onset alopecia, at least in some geographic areas of the world.

## 8.5 Furunculoid Myiasis

Cutaneous myiasis is a parasitic infestation that is caused by developing larvae (maggots) of a variety of fly species which are classified within the arthropod order Diptera [59–61]. Although flies are most commonly attracted to open wounds and urine- or feces-soaked fur, some species can create an infestation even on unbroken skin. The larvae feed on the host while they slowly grow until they achieve mature stages and finally complete the larvae cycle [59, 60, 62]. The most common flies that cause human disease are *Dermatobia hominis* (also called human botfly) and *Cordylobia anthropophaga* (tumbu fly) [62, 63].

The type of presentation that is seen in patients with myiasis depends both on the fly species involved and where their eggs are laid [60, 64]. Most authors classify human myiasis based on the body area that the parasites end up settling in order to grow, e.g., skin, oral cavity, nose cavity, and eyes [63].

The cutaneous presentation depends both on the type of larvae that is involved and on the anatomical site that has been targeted by the vector:

- Furuncular cutaneous myiasis
- Wound myiasis
- Creeping/migratory cutaneous myiasis

Wound myiasis is most commonly observed in patients with chronic and open wounds from different etiologies, such as skin cancer and diabetic ulcers, but larvae can also penetrate the unbroken skin [65, 66]. Since flies usually thrive in warm

environment and under poor sanitary conditions, people from rural areas are at special risk for the infestation [65, 67]. It also seems that elderly patients, especially those who are mentally disabled, are more affected than young ones, which is probably due to a lower level of attention when flies approach.

Migratory cutaneous myiasis is usually observed in patients who deal with cattle which can be eventually infested by *Hypoderma bovis* and in people who work with horses; in this case, *Gasterophilus intestinalis* is usually involved [60, 61]. This clinical presentation is not frequently seen in clinical practice, but some cases may well be misdiagnosed as cutaneous larva migrans.

The ample variation of prevalence that is noted from country to country is due to differences in latitude that ultimately interferes in the life cycle of the several species of flies [60, 61]. Typically, case reports of myiasis report on patients who live or have recently travelled to tropical global areas, such as Africa and South America [63, 68].

For myiasis to happen, it is essential that a fly exists in the disease chain so that the parasite eggs can ultimately reach human soft tissues [65, 67]. Different species of flies can carry the eggs that will finally evolve into larvae. The type of fly that acts as vector varies considerably from region to region owing to the large variability of environmental factors that can ultimately impact the life cycle of the insects, such as humidity and temperature [60–62].

A case series published by Lachish and colleagues showed that *Dermatobia hominis* was the vector responsible for approximately 80% of cases of cutaneous myiasis [63]; *Cordylobia anthropophaga* was involved in 17% of the cases and caused disease especially in patients who have recently visited Africa [63]. The literature is inconsistent though when it comes to determining the most commonly involved species in cutaneous myiasis, but it seems that *Dermatobia hominis* is the most common causative agent of the furunculoid presentation in Central and South America [63, 64, 69, 70].

The cutaneous infestation usually occurs after a direct contact of the fly with the affected person; nonetheless, fly eggs can also be deposited in fabric and only then reach the human body when they turn into a larval stage [61]. *Dermatobia hominis,* for instance, first lays its eggs on ordinary mosquitoes, and these will then take the eggs to the skin surface of a given person [61]. As opposed, *C. anthropophaga* usually deposits its eggs on fabric and clothes, as well as in soiled blankets and in sand. The larva is capable of living up to 15 days without feeding, until a host is ultimately found [61, 62].

In wound myiasis, eggs are laid in an open cutaneous orifice, such as chronic wounds, necrosis, or ulcers [65]. Larvae can be deposited in any body area and may give rise to complications, especially when the nasal cavity, sinuses, and scalp are affected.

The most common clinical presentation of cutaneous myiasis is furuncular or furunculoid myiasis, named after its similar clinical appearance as a boil (furuncle), caused by *Dermatobia hominis* [62, 68]. Each larva produces a separate lesion, which is clinically recognized as a nonhealing or boil- or furuncle-like lesion, even though multiple larvae can be simultaneously observed at the same body site [62,

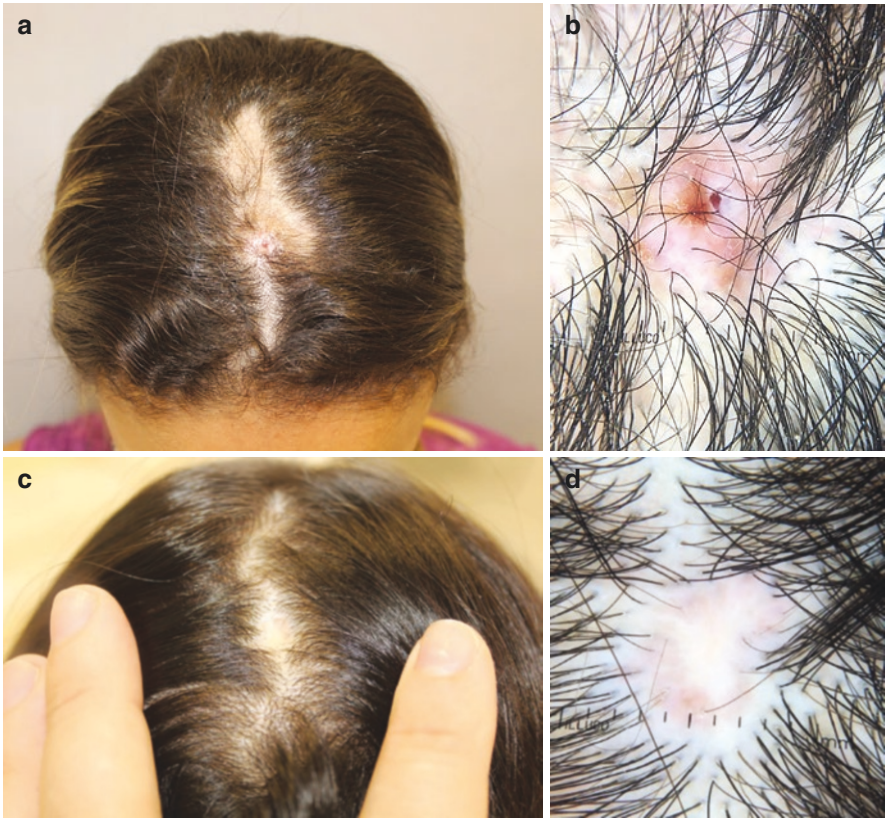


**Fig. 8.9** (**a–d**) Furunculoid myiasis: (**a**, **b**) boil-like lesion with a central punctum, (**c**, **d**) residual scar

63, 66]. The lesion is recognizable as such by discharge from a central punctum (tiny hole) or a small, white structure protruding from the lesion. Healing usually occurs with a scar (Fig. 8.9a–d). Up to 60% of lesions occur on exposed body areas, but it is not mandatory [62]. These lesions oftentimes cause itching sensation that comes along with tenderness on palpation, emission of blood, and purulent discharge, which makes it difficult to be differentiated from simple cutaneous furunculosis and infected epidermal inclusion cysts.

In many cases, myiasis is an accidental diagnosis, being rather a surprise for both the patient and the attending physician.

Table 8.1 lists some symptoms reported by affected individuals on the occasion of their first consultations and the signs observed by the medical team.

The patients' previous history of trips to endemic areas, such as Brazil and other counties of South America, may be of great help to the attending physician when it comes to suspecting of the diagnosis.

**Table 8.1** Clinical signs and symptoms of furuncular scalp myiasis

| Authors | Signs and symptoms |
|---|---|
| Biswas and Mcnerney [60] | Scalp bleeding |
| Kondoh et al. [61] | Bleeding and pain<br>Painful boils, sensation of "something moving inside" |
| Dunphy and Sood [62] | Pruritus, drainage of serosanguinous fluid, intermittent sharp, stabbing episodes of pain |
| Calderaro et al. [64] | Pain, itching, and sensation of movement under the skin |

In 2008, Calderaro and colleagues [64] reported the case of a male Italian patient who had presented for dermatological evaluation owing to the presence of a furunculoid scalp lesion after coming back from a trip to Brazil. The patient reported being stung by insects on the scalp and noticing something mobile protruding from the lesions, resembling larvae. The lesion was surgically accessed, and the larvae were removed.

Since myiasis is not a primary disease of the hair follicles, it is not expected from infected patients to present alopecia. Nevertheless, scalp may well be involved, as reported by several authors [60–62, 66, 69, 70]. It is interesting that hairy areas can be targeted by flies, since dense hair coverage would naturally work as a physical barrier, even though the majority of the authors who have published on scalp myiasis have not mentioned in their papers if the patients were bald or not.

Myiasis has been reported in patients with the diagnosis of scalp malignancies, such as basal cell carcinoma and squamous cell carcinoma [61, 66, 69]. Other scalp conditions have also been associated with local myiasis (Fig. 8.10), as reported by Pereyra-Rodríguez et al. in 2010 [70], when the authors reported a case of a 12-year-old girl with severe scalp larval infestation in lesions of psoriasis.

A dramatic case of scalp myiasis was published by Wollina in 2010 [66]. The author reported on an 89-year-old male patient who was taken to the emergency department with a bleeding large ulcer on his scalp. At the time point, the patient had already had the diagnosis of a squamous cell carcinoma of the scalp for which he had refused surgical treatment. He was mentally healthy and had no social or financial issues, and he was being supported by an ambulatory nursing service. The removal of the wound dressing revealed the presence of more than a hundred maggots of *Lucilia sericata*. This case reinforces the fact that the elderly are at a special risk for cutaneous myiasis but also calls attention to the fact that myiasis can complicate any type of scalp ulcer, even if good healthcare is being provided.

Even though clinical inspection is sufficient to diagnosis wound myiasis, there are several differential diagnoses to be considered in the case of furunculoid myiasis. In regions where myiasis in endemic, in any nonhealing cutaneous furuncular lesion, furuncular myiasis must be considered in the differential diagnosis.

Bacterial furunculosis presents with a prominent surrounding erythema and is centered by a hair follicle orifice, which can be recognized both by the naked eyes and dermoscopy [71]. In case of doubt, a Doppler ultrasound scan can visualize

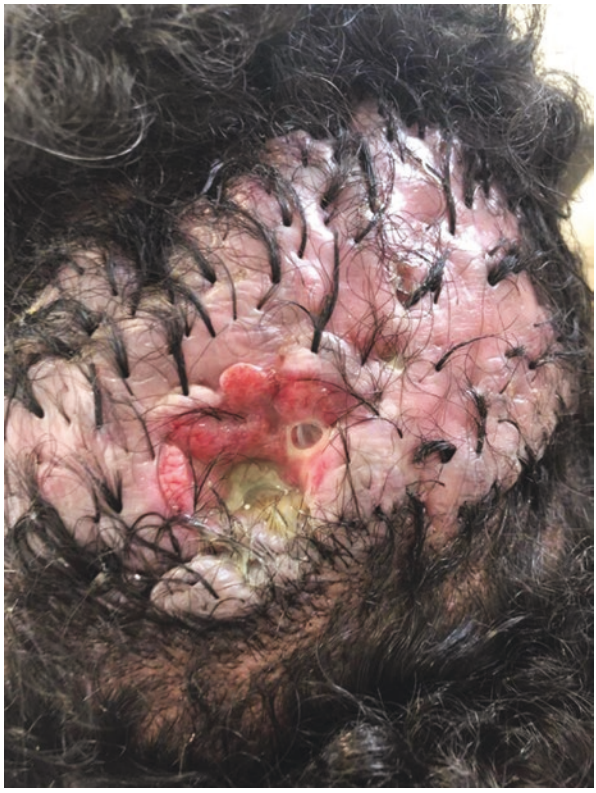

**Fig. 8.10** Furunculoid myiasis on the background of folliculitis decalvans

larval movements within lesions initially thought to be ordinary furuncles [62, 63, 71].

Clinical history is usually enough when it comes to distinguish furuncular myiasis from epidermal inclusion cysts, an exaggerated arthropod bite reaction, and abscesses. In areas where cutaneous leishmaniasis is endemic, it is of ultimate importance to evaluate the patient with extra caution, since leishmaniasis may mimic several cutaneous disorders, including furunculosis [72]. For such cases, complementary diagnostic tools, such as dermoscopy, cutaneous ultrasound, and skin biopsy, may be of help either by showing the presence of the larvae or by demonstrating the presence of *Leishmania* spp. [72, 73].

It is noteworthy that physicians from endemic countries, such as Brazil, usually have the necessary expertise for an immediate clinical diagnosis. Practically speaking, despite the value of several diagnostic tools, the diagnosis of furuncular myiasis is usually solely based on clinical grounds.

Although cutaneous myiasis is considered a self-limiting condition with minimal morbidity in most of patients, treatment is recommended so that relief of pain can be achieved. The great impact on the patients' cosmetic and psychological aspects should also be considered on the decision to treat.

Patients with wound myiasis must have their larvae mechanically removed. Since not all larvae are visible and there is a risk of them to tunnel away, a mixture of 15% chloroform with olive oil has been used in the wound; this mixture is believed to immobilize the larvae and facilitate maggot removal [60, 61].

The literature shows different approaches that have already been proposed to treat furuncular myiasis. After noticing that a breathing hole has been formed in the skin surface, covering it is usually a strategy of success, since it asphyxiates the parasite [68]. This method can be performed with application of petrolatum jelly, which will ultimately oblige the larva to come to the skin surface to breath and then the condition can be more easily managed [68]. Other occluding strategies, such as adhesive tapes and bacon, are also described as effective methods to create localized hypoxia [62, 68] (Fig. 8.11a).

For some patients, removing the larva surgically will be necessary. It must be done under local anesthesia, and even though a late foreign body reaction can occur if parts of the larva remain, surgery is usually curative. For this purpose, the physician must perform a minor incision right across the parasite orifice, and with a slight pressure around the lesion, the larva can be removed with a forceps [68] (Fig. 8.11b–d). Local care after surgery includes the prescription of antiseptic dressings and antibiotics in case of secondary infection.

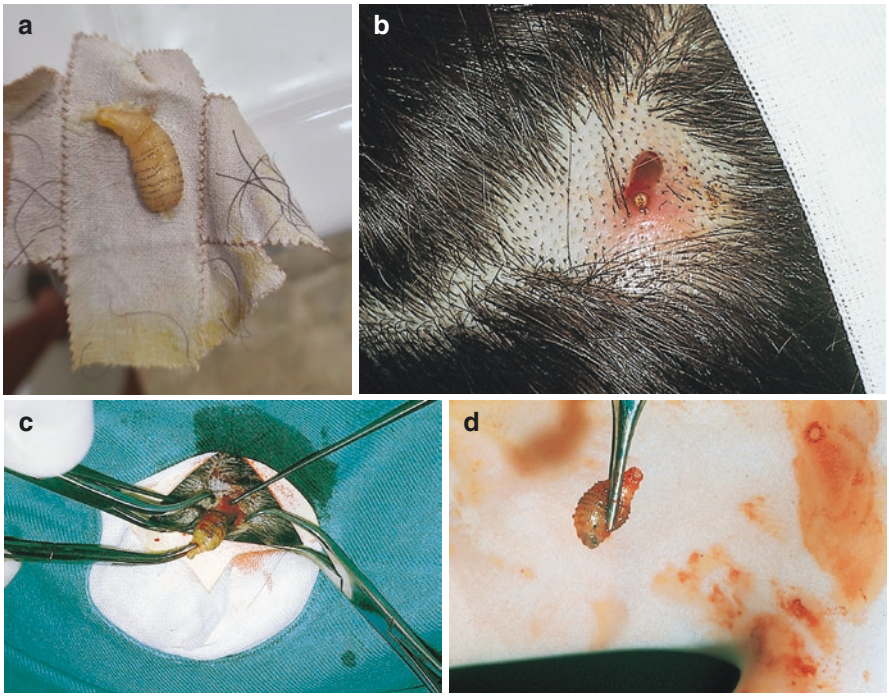


**Fig. 8.11** (**a**–**d**) Treatment of furunculoid myiasis. (**a**) adhesive tape, (**b**–**d**) surgical extraction

**Fig. 8.12** Extracted *Dermatobia hominis*. Notice rows of spines that work as hooks

Finally, patients should be discouraged from managing the lesions on their own, since the larva in furuncular myiasis have several rows of spines that work as hooks (Fig. 8.12) and usually prevent the patient from a successful home extrusion [62, 64].

## 8.6 Cutaneous Larva Migrans

Cutaneous larva migrans, also known as creeping eruption, is a pruritic dermatitis due to the inoculation of helminths larvae in the skin often occurring in children in tropical and subtropical areas. It represents a zoodermatosis caused by the cutaneous penetration usually of parasites from the small intestines of cats and dogs in people who visit beaches or sandy terrains which are polluted with the feces of dogs and cats. Clinically it is characterized by the presence of intensely pruritic erythematous tunnels of linear and serpiginous character. The lesion topography

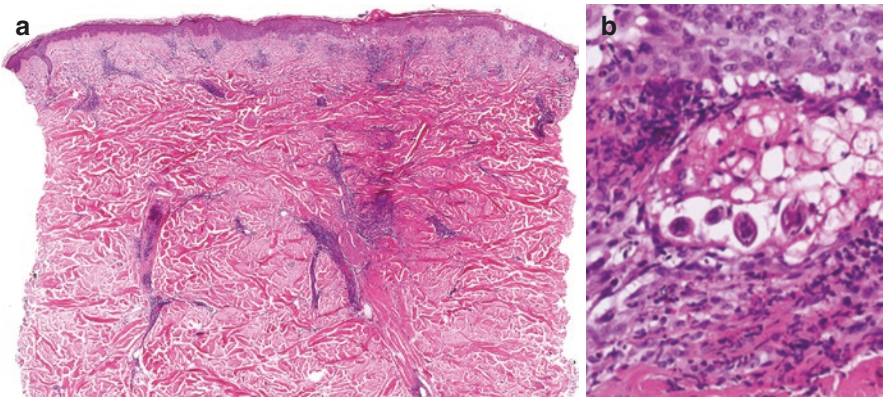


**Fig. 8.13** (**a**, **b**) Cutaneous larva migrans. Histopathology (courtesy Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland)

usually depends on the area which is in wider contact with the ground, like feet, legs, or gluteal regions. Skin biopsy from advancing point of the lesion can show parts of parasite(s), where they typically present as curvilinear eosinophilic larvae within the epidermis (Fig. 8.13a, b).

The main species responsible for cutaneous larva migrans are *Ancylostoma caninum* and *Ancylostoma braziliense*. Among the agents that can also cause the disease are other parasitic larvae of dogs and cats, such as *Uncinaria stenocephala*, *Ancylostoma tubaeforme*, *Gnathostoma spinigerum*, and some strains of *Strongyloides stercoralis*; bovine parasites, *Bunostomum phlebotomum*; rodent parasites, *Strongyloides myopotami*; and wild dogs, *Strongyloides procyonis.* Larvae of *Gasterophilus* and *Hypoderma* flies and ants of *Solenopsis geminata* species may also cause the same clinical manifestations. Another parasitic larva of dogs that deserves emphasis is the species *Toxocara canis*, which on men can cause visceral and ocular *larva migrans*.

Involvement of the scalp with cutaneous larva migrans is an uncommon even but has been reported with the sebaceous gland representing a facilitated route of entry for the parasite [74, 75]. Concomitant typical lesions on other sites may facilitate the diagnosis.

Depending on the number of lesions and their localization, the treatment can be topical or systemic. The drugs of choice are albendazole 400 mg/day for 3 days, ivermectin 200 mcg/kg in a single dose or tiabendazole 25 mg/kg/day, divided into two doses for 5 days. If there are few lesions, the tiabendazole ointment or cream 10% may be used.

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# Delusional Infestation

9

Ralph M. Trüeb

## Contents



It is a common experience among dermatologists that patients often have psychological overlays to their chief complaints. This particularly holds true for complaints related to condition of the hair and scalp. The exact incidence in any particular dermatologic practice most likely depends on the dermatologist's interest; however, even for those dermatologists who are not particularly interested in the psychological aspects of dermatologic disease, some patients have such overt psychopathologic conditions, such as delusion of parasitosis, that even the least psychologically minded dermatologist feels obliged somehow to address the psychological issue. Ideally, this would be accomplished through referral of the patient to a mental health professional. In reality, the majority of psychodermatologic patients are reluctant to be referred to a psychiatrist. Many lack the insight regarding the psychological contribution to their dermatologic complaints. This holds particularly true for the delusional patients.

The dermatologist is often the physician designated by the patient to handle the chief complaint, even if the main disorder is a psychological one. Therefore, it is essential for dermatologists dealing with such patients to expand their clinical acumen and therapeutic armamentarium to effectively handle the psychodermatologic cases in their practice. To accomplish this goal, the following steps are required:

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*Learn to classify and diagnose psychodermatologic disorders*. Because so many different types of conditions lie in between the fields of dermatology and psychiatry, it is paramount to have classification systems that will help clinicians understand what they are dealing with. There are two ways to classify psychocutaneous cases: first, by the category of the dermatologic presentation, e.g., neurotic excoriation, and, second, by the nature of the underlying psychopathologic condition, e.g., depressive disorder, generalized anxiety disorder, or obsessive-compulsive disorder.

*Become familiar with the various therapeutic options available*, both non-pharmacologic and psychopharmacologic.

*Recognize the limits of what can be accomplished in a dermatologic practice*: typically, a dermatologist does not have the time, training, or inclination necessary to administer most non-pharmacologic approaches. If a dermatologist seriously considers the challenge of treating these patients with psychopharmacologic agents, the selection of appropriate agents is dictated by the nature of the underlying psychopathologies that need to be treated. In order to prescribe effectively and safely for these patients, the dermatologist must have a basic understanding of the pharmacology of psychotropic agents.

*Optimize working relationships with psychiatrists*, since dermatologists and psychiatrists tend to have different perspectives when analyzing a clinical situation, different styles of communication, and different approaches to management.

Most psychocutaneous conditions of the hair and scalp can be grouped into the following four categories:

*Psychophysiological disorders*, in which the scalp disorder is exacerbated by emotional factors, e.g., hyperhidrosis, atopic dermatitis, psoriasis, and seborrheic dermatitis of the scalp

*Primary psychiatric disorders*, in which there is no real skin condition, but all symptoms are either self-induced or delusional, e.g., trichotillomania, neurotic excoriations, factitial dermatitis, delusion of parasitosis, or psychogenic pseudo-effluvium

*Cutaneous sensory disorders*, in which the patient has various abnormal sensations of the scalp with no primary dermatologic lesions and no diagnosable internal medical condition responsible for the sensations

*Secondary psychiatric disorders*, in which patients develop emotional problems as a result of the underlying disease, usually as a consequence of disfigurement

The presence of delusion defines psychosis. A delusion is a false idea on which the patient is absolutely fixed. A delusion is deemed to be a basic psychotic phenomenon, in which the objective falseness and impossibility of the delusional content are usually easy to realize. Delusional convictions are not simple misbeliefs: they are constitutions of an abnormal mind that refer to the individual's cognitive experiences of his or her environment – their ego–environment relationship. Delusions are not voluntarily invented by the patients: they are caused by psychotic experiences. From the psychodynamic point of view, a delusional disorder is a special consequence of abnormal self-development. The delusion derives from the patient's desire to be in a safe place, away from the tension caused by the brittleness and contradictoriness of the patient's ego–environment relationship. The subjective certainty of the delusion's content causes its incorrectability: patients consistently keep their convictions, without considering their incompatibility with reality. Neither contrary experiences nor logical arguing can influence them. By definition, delusional patients have no insight, and others cannot talk them out of their belief system.

The type of delusional patient most often seen by the dermatologist is not the schizophrenic, but the patient with monosymptomatic hypochondrial psychosis. Monosymptomatic hypochondrial psychosis is characterized by a delusional ideation held by a patient that revolves around one particular hypochondriacal concern, while with schizophrenia many other mental functions become compromised, besides the presence of delusional ideation.

Delusional of parasitosis represent the most frequent delusional disorder presenting in dermatology. Patients have fixed belief of a usually skin-related invasion or infestation by a number of parasitic species, whose identity has varied over time. Since 2002, an increasing number of patients have complained of unverifiable fibers and filaments in or on the skin, associated with numerous nonspecific Lyme disease-like systemic complaints. This entity has been named Morgellons disease by the patients themselves, although medical evidence for its existence is lacking. Currently the delusional assumption of infestation with Morgellons should be considered as a new type of delusion of parasitosis, however with some sort of inanimate material. Harth et al. have therefore recommended in case of delusion of parasitosis including Morgellons disease the use of the broader term delusional infestation [1].

## 9.1 Delusion of Parasitosis (Ekbom's Disease)

In delusion of parasitosis or Ekbom's disease, there is an unshakable conviction that the skin is infested by parasites. In the older literature, this condition is also described as parasitophobia or acarophobia. However, the terms with phobia attached to them are misnomers and should be omitted, because in classic phobia, patients are aware of the fact that their fearful reactions are both excessive and irrational, while in the case of delusions of parasitosis, the patient is truly convinced of the validity of his or her perceptions.

In dermatologic practice the type of delusional patient most frequently seen is the patient with a delusional ideation that revolves around only one particular hypochondriacal concern. These patients are said to suffer from monosymptomatic hypochondriacal psychosis. These patients are different from other psychotic patients, such as schizophrenics or patients with a major depression, since the latter have many deficits in mental functioning, which is not the case in patients with monosymptomatic hypochondriacal psychosis. Moreover, a delusional disorder appears to run distinct from schizophrenia and mood disorders and does not appear to be a prodrome to either of these conditions.

From a nosologic point of view, delusion of parasitosis is classified as a delusional disorder of the somatic type/with predominantly somatic delusions.

In the medical literature, the typical patient with delusions of parasitosis is reported to be a middle-aged woman, though there seems to be a bimodal distribution of age group. Delusion of parasitosis is frequently encountered in patients in their 20s and 30s of either sex who are at a lower socioeconomic status and who have a marginal existence in society, in work, and in interpersonal relationships.

Patients report cutaneous sensations such as crawling, biting, and stinging, which they relate to their unshakable conviction that their skin is infested by parasites. They often bring in bits of dry skin, debris, and other specimens to try to prove the existence of parasites (Fig. 9.1a). Sometimes secondary injury to the skin (Fig. 9.1b) or infection such as cellulitis may result from excessive scratching or the attempt to remove the imaginary parasites from the skin, also regional reactive lymphadenitis (Fig. 9.1c).

Though the patient with delusions of parasitosis presenting to the dermatologist more frequently suffers from monosymptomatic hypochondriacal psychosis, it must be remembered that the presence of a delusional ideation may be one particular manifestation of a more global psychiatric derangement, such as schizophrenia or major depression.

In fact, in 1951 entomologist Jay Traver published in the *Proceedings of the Entomological Society of Washington* her personal experiences with a mite infestation of her scalp that resisted all treatment and was undetectable to anyone other than herself. However, one must mention that the article made no sense entomologically. The house dust mites (*Dermatophagoides pteronyssinus*) do not parasitize humans. They reside in bedding where they feed on sloughed off skin and represent allergens that may cause rhinoconjunctivitis or asthma or may exacerbate atopic dermatitis. And yet, Traver wrote that she had the highest success in finding live mites on her pillow and scalp. Thus it is likely that she really did find *Dermatophagoides* mites, but the claim that they were parasitizing her is unfounded. Finally, no arthropod could have survived the onslaught of chemicals Traver used on herself on a daily basis, nor would any parasite be able to avoid detection by a dermatologist for that long. *Dermatophagoides* themselves can be easily killed by putting bed sheets in the household dryer for 10 min and are detectable by vacuuming the floor and examining what is collected (Fig. 9.2). A rational person, particularly an entomologist, should never have leaped to the conclusion that the mites were active parasites nor insist so adamantly on the existence of a parasite in the face of

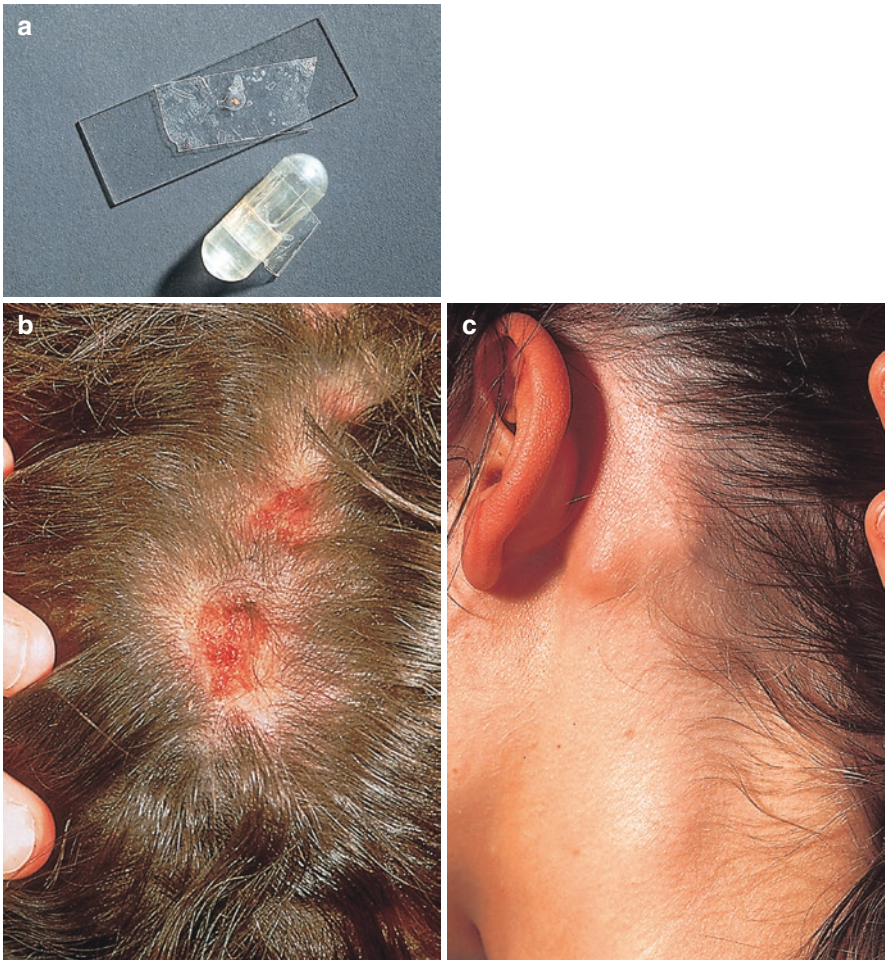


**Fig. 9.1** (**a**–**c**) Delusion of parasitosis: (**a**) specimen provided by patient for examination, (**b**) self-inflicted excoriation of the scalp, (**c**) regional reactive lymphadenitis

repeated failure by professionals to find or exterminate the parasite over the span of decades. The conclusion the scientific community took from the paper, with full awareness of the tragic and dramatic irony of the situation, was that Traver was an entomologist with delusion of parasitosis. The Traver paper is unique in the scientific literature in that its conclusions based on data that were unconsciously fabricated by the author's mind. The paper may have merited retraction on the grounds of error or even scientific misconduct by reason of insanity, but such a retraction raises the issue of discrimination against the mentally ill. Ultimately, this paper raised the question what responsibilities journals have when faced with delusions disguised as science and what right editors have to question the mental sanity of an author [2].

**Fig. 9.2** House dust mite (*Dermatophagoides pteronyssinus*)

Another subset of patients with delusions of parasitosis to consider are those who are substance abusers. Drugs such as cocaine and amphetamine can induce formication and sometimes a delusional state that can be clinically identical to that of idiopathic delusions of parasitosis. Because the induction of formication is so well-known among cocaine users, this phenomenon has been labeled cocaine bugs among substance abusers.

Also, neurologic disorders, such as multiple sclerosis, pernicious anemia, and especially in the elderly brain dysfunction with manifest encephalomalacia due to cerebral arteriosclerosis [3] should be considered in the differential diagnosis.

Trigeminal trophic syndrome results from a prior injury to the sensory distribution of the trigeminal nerve. Patients typically respond to the altered sensation with self-mutilation, most often in the region of the nasal ala; however, three patients with trigeminal trophic syndrome involving the scalp with self-induced ulcerations have been reported. Of these, two developed delusions of parasitosis based on the resulting symptoms of trigeminal trophic. Symptoms such as formication may mimic delusion of parasitosis; however, trigeminal trophic syndrome may be differentiated from delusion of parasitosis by the restriction of symptoms and ulcerations to the distribution of the respective trigeminal nerve [4].

Delusion of parasitosis should always be a diagnosis of exclusion, particularly the presence of inflammatory and pruritic skin disorders or real infestation, such as pediculosis capitis and furunculoid myiasis of the scalp, should not be overlooked.

A case of pseudo-delusory syndrome caused by *Limothrips cerealium* (Fig. 9.3) was reported in a 59-year-old female farmer, who came to observation because of intense itching and sensation of walking insects on the head, with no objective cutaneous signs except lesions due to scratching. After repeated visits, in which negative results of clinical and laboratory tests suggested the diagnosis of delusion of parasitosis, the authors finally isolated on her head some insects, identified by stereomicroscopy as *L. cerealium*. Careful inspection of the house of the patient allowed identification, as possible source of parasites, a wheat field and a deposit of grains

**Fig. 9.3** *Limothrips cerealium*

used for animal feeding. Temporarily removing the patient from her usual environment resulted in complete clinical resolution [5].

Finally, chronic tactile hallucinosis describes those unusual cases in which patients develop chronic tactile sensations without delusions or other definable psychiatric disturbances and without associated medical or neurologic conditions. The condition can be associated with trichoteiromania, i.e., a self-inflicted patch of hair loss that results from the act of rubbing the scalp with fracturing of the hair shafts [6].

A case of delusional parasitosis with trichotillomania has been reported [7].

Trichophobia denotes the plucking of hair on the basis of the delusion of having to pull something out of the hair roots [8].

Since trying to talk a patient out of a delusion is generally counterproductive, the most feasible way to have an impact on delusional ideation is to start the patient with a delusional disorder on an antipsychotic drug.

Traditionally, pimozide has been prescribed [9]. Newer agents include risperidone and olanzapine. The most challenging aspect of managing patients with

delusions of parasitosis is to try to get their cooperation in taking one of these agents. This results from the discrepancy between the patient's belief system and the clinician's understanding of the situation. The first step is to establish a good rapport with the patient. In trying to do so, it is important to recognize that the patient with delusions of parasitosis is expecting the clinician to treat him with respect as a skin patient, not as a psychiatric case. Therefore, the most effective approach is to take the chief complaint seriously, give the patient a good skin examination, and pay attention to whatever specimens are brought in. However, one should not make any comment that may reinforce the patient's delusional ideation.

Once the clinician senses that a reasonable working relationship is established with the patient, psychopharmacological treatment is offered as an empirical therapeutic trial, purposely avoiding any argument about the pathogenesis of the condition or the mechanism of action of the medication. No matter how skillful the clinician is, some delusional patients remain beyond reach. In this situation, the best the physician can do for the patient is simply to take on a supportive role and watch out for any secondary complication such as cellulitis, which may result from skin injury.

Untreated, the condition runs a chronic course. Many patients respond to pimozide, with symptomatic improvement occurring as early as 2 weeks after starting treatment, although several months of treatment may be needed for complete control. Most patients require ongoing maintenance therapy; some achieve remission; in a few, cure does occur. Remission is seldom associated with insight.

## 9.2 Morgellons Disease

Morgellons disease is the informal name of a self-diagnosed, scientifically unsubstantiated skin condition characterized by the presence of multicolored filaments that lie under, are embedded in, or project from the skin.

Individuals afflicted with the disease may have crawling or stinging sensations and, in addition, often experience a variety of systemic manifestations, such as arthralgias, fatigue, and altered cognitive function, all symptoms that are commonly reported by Lyme disease patients.

In light of the previous experience with Morgellons disease patients, a case definition for the condition has been proposed: a somatic Lyme disease-like illness associated with spontaneously appearing, slowly healing, filamentous, ulcerative skin lesions, with the key diagnostic criterion being colored, white, or black filaments (Fig. 9.4a, b) protruding from or embedded in skin. Filaments in Morgellons disease lesions usually require magnification of 50× (as opposed to the magnification of 10× normally used in dermatology) or more to be seen [10].

However, Morgellons disease remains a poorly understood condition, while the general medical consensus is that it is a form of delusional parasitosis in which individuals have some form of skin condition with sores that they believe contain fibers (Fig. 9.5a–d). Its presentation is very similar to delusional parasitosis, with the addition that people with the condition believe there are inanimate objects in

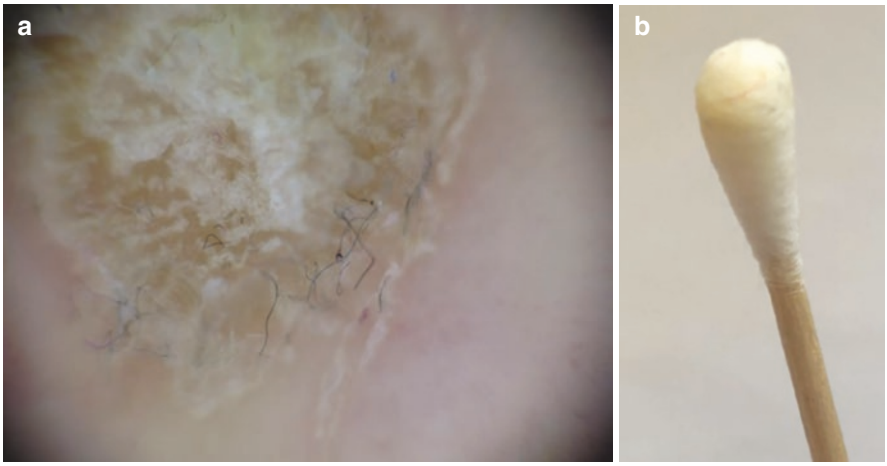


**Fig. 9.4** (**a**, **b**) Morgellons disease: (**a**) black filaments on lesional skin, (**b**) colored filaments on a cotton swab. The fibers, when analyzed, are consistently found to have originated from cotton or other textiles

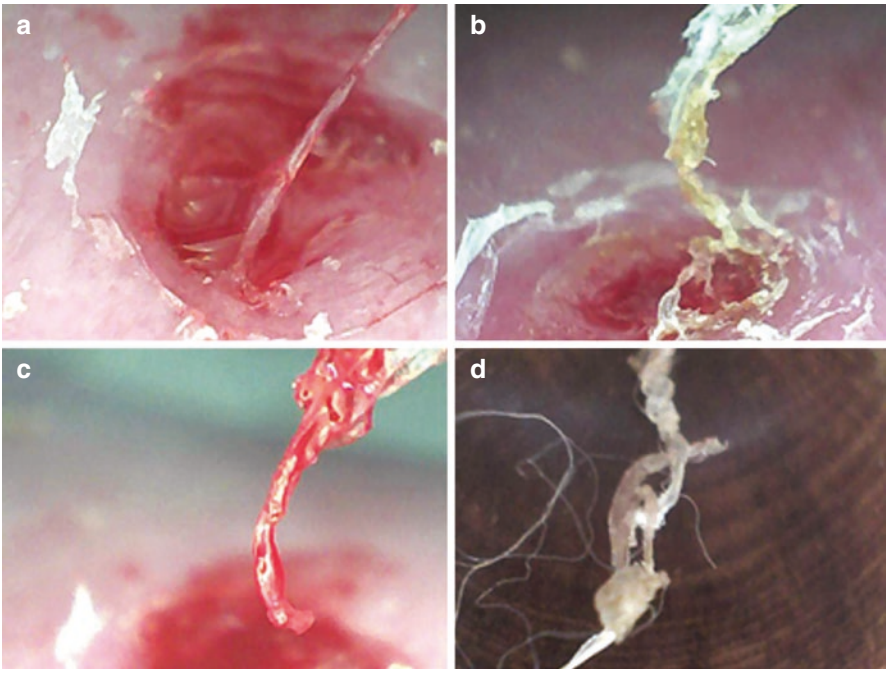


**Fig. 9.5** (**a**–**d**) Morgellons disease: typical (self-inflicted) sores and fibers (of exogenous source)

their skin lesions. An active online community supports the notion that it is an infectious disease, disputes that it is psychological, and proposes an association with Lyme disease. Controversy has resulted with publications largely from a single group of investigators describing findings of spirochetes, keratin, and collagen in skin samples in small numbers of patients. These findings have been contradicted by much larger studies conducted by the CDC, which found skin samples mostly contained cellulose that came from cotton, with no evidence of infection or other causes.

In fact, Morgellons disease may represent a culture-bound syndrome, i.e., a combination of psychiatric and somatic symptoms that are considered to be a recognizable disease only within a specific society or culture, and is as such one of a group of mystery syndromes, such as multiple chemical sensitivity syndrome, amalgam disease, penile retraction syndrome (Koro), and the post-finasteride syndrome [11].

Expressly, the connection of Morgellons with Lyme disease is not surprising, since both have received the respective media attention, particularly in the USA. More broadly, it is an endemic that can be attributed to particular behavioral patterns within a specific culture by suggestion and therefore may also be referred to as a potential behavioral epidemic.

Vila-Rodriguez et al. state that the Internet promotes the spreading and supporting of bizarre disease beliefs since a belief is not considered delusional if it is accepted by other members of an individual's culture or subculture [12].

Sociologist Robert Bartholomew, who has studied the Morgellons phenomenon, states that the World Wide Web has become the incubator for mass delusion and Morgellons disease seems to be a socially transmitted disease over the Internet. According to this hypothesis, people with delusions of parasitosis and other psychological disorders become convinced they have Morgellons after reading internet accounts of others with similar symptoms.

Ultimately, Dermatologist Caroline Koblenzer specifically blames the Morgellons Research Foundation website for misleading people: "Clearly, as more and more of our patients discover this site, there will be an ever greater waste of valuable time and resources on fruitless research into fibers, fluffs, irrelevant bacteria, and innocuous worms and insects" [13].

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# The Hair and Scalp in Systemic Infectious Disease

# 10

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A systemic disease is one that affects a number of organs and tissues or affects the body as a whole. This applies to the infectious diseases as for other conditions. The source of the infection can be any of a number of places throughout the body, where bacteria, fungi, viruses, or parasites enter the body.

In systemic infections the infecting agent or organisms circulate in the bloodstream throughout the body. This is an illness with high risk of morbidity without treatment. It is characterized by an inflammatory state of the entire body, rather than of a single organ or body part. The infection may be viral, bacterial, or other and sometimes is caused by specific bacterial toxins, in the blood or tissues. It presents as an acute illness with systemic symptoms, such as fever, chills, malaise, and body aches.

Since 500 B.C., some scholars have believed that the physical condition of the fingernails can indicate various systemic diseases. Careful examination of the fingernails may provide clues to underlying systemic diseases in the form of transverse linear depressions (Beau's lines) (Fig. 10.1). Beau's lines occur at the same spot of the nail plate in most or all of the person's nails and may be caused by any disease severe enough to disrupt normal nail growth. Knowing that nails grow about 1 mm every 6–10 days, the timing of the disease process may be estimated by measuring the distance from the line to the nail bed.

Hair shedding is yet another symptom of systemic disease. Many factors can lead to a pathologically increased hair loss. Whatever the cause, the follicle tends to behave in a similar way. To grasp the meaning of this generalization requires understanding the varied derangements of the hair cycle underlying hair loss, specifically dystrophic anagen effluvium and telogen effluvium.

The hair follicle is subject to constant turnover in the course of perpetual cycles through phases of proliferation in anagen, involution in catagen, and resting in telogen, with regeneration in the successive hair cycle. Cyclic hair growth activity occurs in a random mosaic pattern, with each follicle possessing its own individual control mechanism over the evolution and triggering of the successive phases, though systemic factors as well as external factors linked to the environment have an influence, such as hormones, cytokines and growth factors, toxins, and deficiencies in nutrients, vitamins, and energy (calories) (Fig. 10.2).

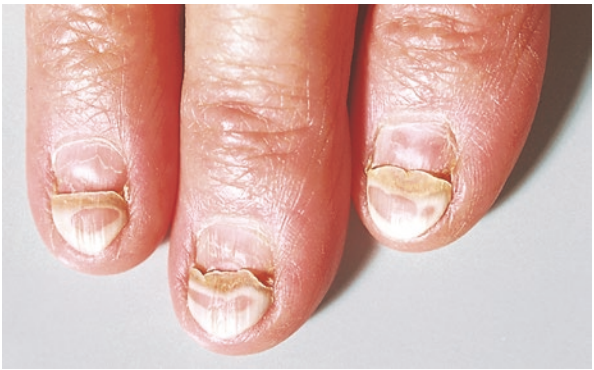

**Fig. 10.1** Beau's lines

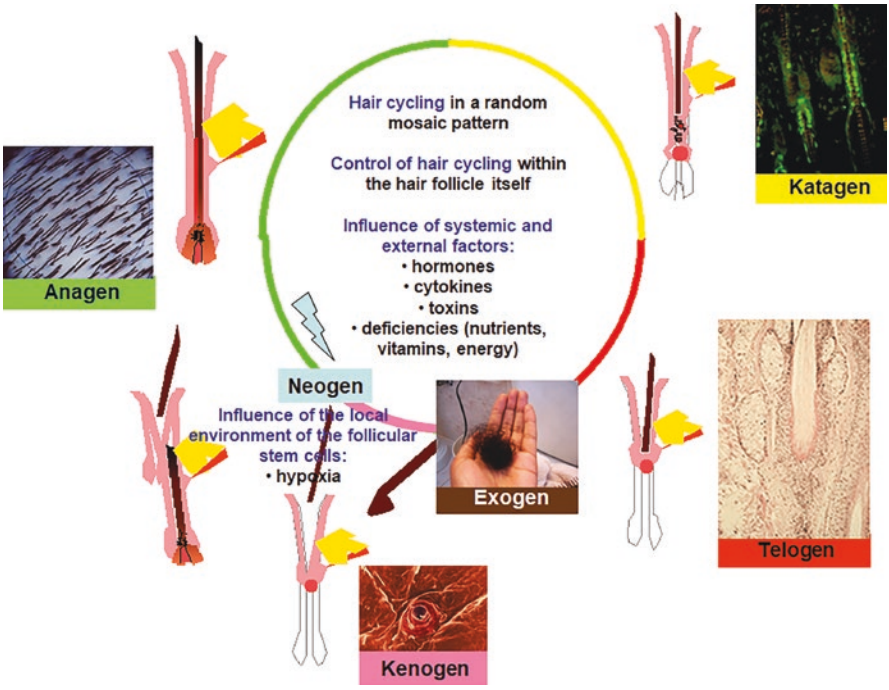


**Fig. 10.2** Hair cycle

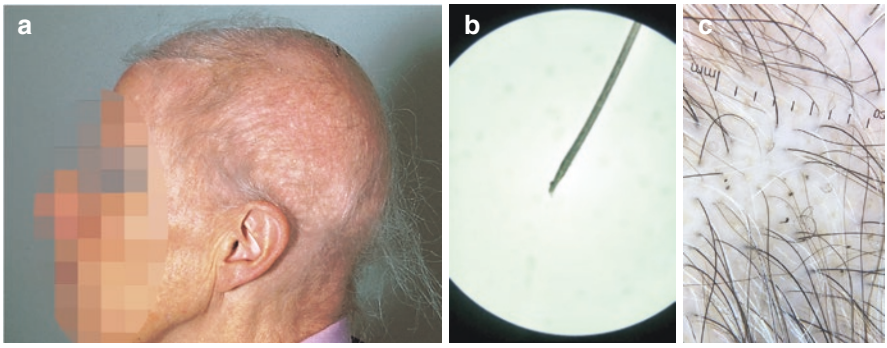


**Fig. 10.3** (**a**–**c**) Dystrophic anagen effluvium: (**a**) loss of >80% of the hair within few weeks of the inciting event; (**b**) light microscopy, dystrophic hair root; (**c**) dermoscopy, broken dystrophic hairs

*Dystrophic anagen effluvium* (Fig. 10.3a–c) is an early onset hair loss that results from the shedding of large numbers of hairs from the anagen phase of growth within few weeks of the inciting event. It is a major characteristic of anagen that the epithelial hair follicle compartment undergoes proliferation, with the hair matrix keratinocytes showing the highest proliferative activity in building up the hair shaft. The

common pathogenesis which unites the different etiologies of dystrophic anagen effluvium is a direct insult to the rapidly dividing bulb matrix cells. Causes are drugs (usually antineoplastic), X-ray, immunologic injury, or environmental exposure to toxins (usually heavy metals or some plant toxins).

*Telogen effluvium* (Fig. 10.4a–e) results from late onset increased shedding of hairs from the telogen phase of the hair cycle and represents by far the commonest cause of hair loss. An increase in the percentage of follicles in telogen >20% leads to increased shedding of hairs in telogen (Fig. 10.4a–c). This can either be due to synchronization phenomena of hair cycling (Fig. 10.4d), with shedding of hairs in the hundreds in telogen effluvium within 3 months of the inciting event, or to a decrease of anagen phase duration in androgenetic alopecia with its sex-typical

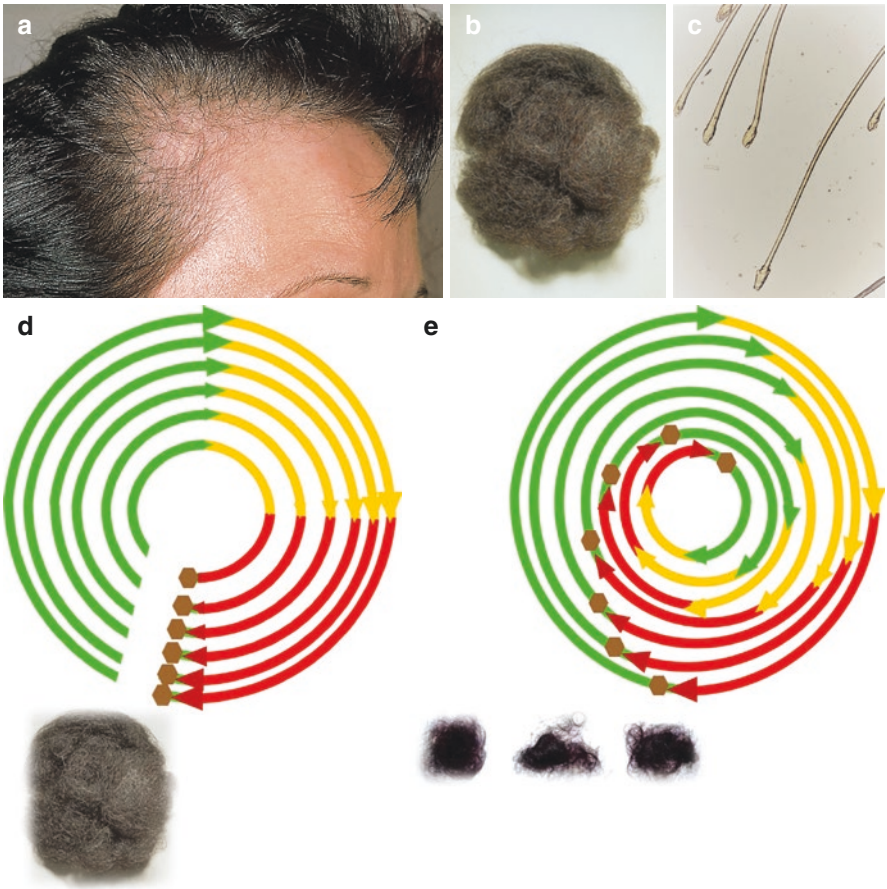


**Fig. 10.4** (**a**–**d**) Telogen effluvium: (**a**) thinning of the temporal area, hair loss is usually <50%; (**b**) hair ball, with synchronous shedding shed hair is usually within the 100 s; (**c**) trichogram, telogen hairs are by definition >20%; (**d**) synchronous shedding of hairs; (**e**) asynchronous shedding of hairs

patterns of alopecia, variable shedding of hair (Fig. 10.4e), and escalating diversity of hair shaft diameters.

While telogen effluvium represents a monomorphic reaction pattern of the hair follicle to a variety of causes, the underlying pathologic dynamics are more diverse. Headington's classification (Table 10.1) [1] represents as yet the single most rational and comprehensive of all proposals so far and has proven its validity, since it covers all clinical types of telogen effluvium, such as postinfectious, post-traumatic, and post-interventional telogen effluvium, postpartum telogen effluvium, shedding phase upon initiation of topical minoxidil treatment, and seasonal hair shedding [2].

Postinfectious hair loss has traditionally been categorized as telogen effluvium, yet, it may present with different pathomechanisms and clinical patterns. Evidence exists that the hair follicle may respond to infection with both shedding patterns, dystrophic anagen effluvium, and telogen effluvium depending on the type and intensity of the insult. Accordingly, the hair may fall out very quickly in clumps or gradually. In systemic infectious disease, the term postinfectious effluvium should be preferred over postfebrile effluvium, since it is not the elevated body temperature causing the hair loss but the underlying immune reaction.

The immune system is understood to be involved in both the regulation of hair follicle cycling, as well as in the pathogenesis of some immune-mediated hair pathologies. Immunomodulatory cytokines not only act as mediators of immunity

**Table 10.1** Functional types of telogen effluvium. From [1]

| |
|---|
| In *immediate anagen release*, follicles that would normally complete a longer cycle by remaining in anagen prematurely enter telogen. It is a very common form of telogen effluvium, typically occurring after periods of physiologic stress including episodes of high fever. In fever, the pyrogens, basically circulating cytokines, drive the hair follicle keratinocytes into apoptosis initiating catagen with following telogen. Because the shedding is dependent on transition from anagen through catagen and telogen with subsequent release of telogen hairs, hair loss occurs 3–4 months after the inciting event |
| In *delayed anagen release*, hair follicles remain in prolonged anagen rather than cycling into telogen. When finally released from anagen, the clinical sign of increased shedding of telogen hair will be found. This type of telogen effluvium underlies postpartum hair loss |
| In *immediate telogen release*, hair follicles normally programmed for release of the club hair after an interval of usually 100 days after the end of anagen are prematurely stimulated to cycle into anagen. There is premature teloptosis. This type of telogen effluvium underlies the shedding of hair upon initiation of therapy with topical minoxidil (shedding phase) |
| In *delayed telogen release*, hair follicles remain in prolonged telogen rather than being shed and recycling into anagen. When finally teloptosis sets in, again the clinical sign of increased shedding of club hairs is observed. This process underlies molting in mammals and probably also seasonal shedding of hairs in humans or mild telogen effluvia following travel from low-daylight to high-daylight conditions |
| Finally, a *short anagen phase* without synchronization phenomena results in a slight but persistent telogen effluvium in association with decreased hair growth length: this may occur in hereditary hypotrichosis, ectodermal dysplasia (tricho-dental syndrome) and as an isolated disorder in otherwise healthy children, as originally described by Barraud-Klenovsek and Trüeb (short anagen hair). Far more frequent is acquired progressive shortening of anagen due to androgenetic alopecia |

and inflammation but also regulate cell proliferation and differentiation and, as such, play a role in hair growth and shedding. Philpott et al. have investigated the effects of ILs and TNF on hair follicle growth in vitro and found these to be potent inhibitors of hair follicle growth in a dose-dependent manner [3]. In addition, IFN-gamma has been shown to be a potent inducer of catagen-like changes in cultured human anagen hair follicles [4].

Since paracetamol/acetaminophen reduces fever by affecting the chemical messengers in an area of the brain that regulates body temperature, it will not have any effect in preventing postinfectious effluvium. In fact, patients on paracetamol may develop postinfectious effluvium without fever. Out of this reason, the term postfebrile effluvium may be misleading.

A careful history and examination of shed hairs will reveal the etiology of most alopecias due to systemic processes [5]. The patient's history and the timing of the illness play an important part in helping to identify the possible source or cause of the infection. Clues to the specific infection can be found in the geographic location of the patient or the patient's exposure to wildlife and animals.

The systemic infectious diseases have been the cause of the great pandemics that have repeatedly ravaged the world from the plaque of Megiddo 1350 B.C., first documented in the Amarna letters EA 244, Biridiya, in which the mayor of Megiddo complains to Pharaoh Amenhotep III of his area being "consumed by death, plague and dust," to the current COVID-19 pandemic. Major pandemics by death toll have been the Black Death 1346–1353 with an estimated death toll of 75–200 million, the Spanish flu 1918–1920 with a death toll of 17–100 million, the Plague of Justinian 541–549 with a death toll of 15–100 million, the HIV/AIDS global epidemic 1981–present with a death toll of 36.3 million (as of 2020), the current COVID-19 pandemic with a death toll of 6–23.6 million (as of March 9 2022), etc.

The World Health Organization (WHO) previously applied a six-stage classification to describe the process by which a novel virus moves from the first few infections in humans through to a pandemic. It starts when mostly animals are infected with a virus and a few cases where animals infect people and then moves to the stage where the virus begins to be transmitted directly between people and ends with the stage when infections in humans from the virus have spread worldwide. In a press conference in 2009 on the influenza pandemic, Dr. Keiji Fukuda, Assistant Director-General ad interim for Health Security and Environment, WHO said "An easy way to think about pandemic ... is to say: a pandemic is a global outbreak." As of February 2020, a WHO spokesperson clarified that "there is no official category for a pandemic."

Historically, measures of pandemic severity were based on the case fatality rate. However, the case fatality rate might not be an adequate measure of pandemic severity during a pandemic response because [6]:

- Deaths may lag several weeks behind cases, making the case fatality rate an underestimate.
- The total number of cases may not be known, making the case fatality rate an overestimate.
- A single-case fatality rate for the entire population may obscure the effect on vulnerable subpopulations, such as children, the elderly, those with chronic conditions, and members of certain racial and ethnic minorities.
- Fatalities alone may not account for the full effects of the pandemic, such as absenteeism or demand for healthcare services.

The basic strategies in the control of an outbreak are containment and mitigation. Containment may be undertaken in the early stages of the outbreak, including contact tracing and isolating infected individuals to stop the disease from spreading to the rest of the population, other public health interventions on infection control, and therapeutic countermeasures such as vaccinations which may be effective if available. When it becomes apparent that it is no longer possible to contain the spread of the disease, management will then move on to the mitigation stage, in which measures are taken to slow the spread of the disease and mitigate its effects on society and the healthcare system.

Ever since Robert Koch and Louis Pasteur established the germ theory of infectious diseases in the 1880s by demonstrating that tuberculosis was of a bacterial origin, and manufacturing vaccines against rabies and cholera, scientist, and the public health officials depending on their technologies have dreamed of defeating the microbes that cause infectious diseases. However, while medical microbiology and its allied disciplines have provided means of understanding the transmission and spread of novel pathogens and making them visible to scientists, all too often these have remained wanting. This is not simply because microbes are constantly mutating and evolving, overtaking our capabilities to keep pace with their shifting genetics and transmission patterns, but it is also because of the propensity of medical researchers to become trapped by particular theories of disease causation, blinding them to the true threats posed by pathogens known or unknown [7].

Finally, so far, every pandemic has given rise to conspiracy theories as to its origins or the authoritative measures to contain or mitigate the extent of contagion. Conspiracy theories typically resist falsification and are reinforced by circular reasoning: both evidence against the conspiracy and an absence of evidence for it are reinterpreted as evidence of its truth, whereby the conspiracy becomes a matter of faith rather than something that can be proven or disproven. Some researchers suggest that conspiracist ideation may be psychopathological [8, 9] and that it is correlated with lower analytical thinking, low intelligence, psychological projection, and paranoia. Ultimately, endorsement of conspiracy theories is influenced by personal willingness to conspire against the mainstream and the authorities [10].

In a press conference on 28 December 2020, WHO officials warned that the current COVID-19 pandemic is "not necessarily the big one" and "the next pandemic may be more severe" and called for preparation. The WHO and the United Nations (UN) advised the world must tackle the cause of pandemics and not just the health and economic symptoms. The October 2020 "Era of pandemics" report by the UN's Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services made the statement that the anthropogenic destruction of biodiversity is paving the way to the pandemic era and could result in as many as 850,000 viruses being transmitted from animals, in particular birds and mammals, to humans. In human history, it is generally zoonoses which have constituted most of the widespread outbreaks, resulting from the domestication of animals. The exponential rise in consumption and trade of commodities such as meat, palm oil, and metals, largely facilitated by developed nations, and a growing human population are the primary drivers of this destruction. According to the chair of the group who produced the report, "there is no great mystery about the cause of the COVID-19 pandemic or any modern pandemic. The same human activities that drive climate change and biodiversity loss also drive pandemic risk through their impacts on our environment." In June 2021, a team of scientists assembled by the Harvard Medical School Center for Health and the Global Environment warned the primary cause of pandemics so far, the anthropogenic destruction of the natural world through such activities including deforestation and hunting, is being ignored by world leaders.

Mechanisms by which systemic infectious diseases, respectively pandemics, may affect the condition of the hair are diverse and may include one or more of the following:

- A direct pathogenic effect of the infectious agent on the hair follicle
- An effect of immune system reaction to the infectious agent on the hair follicle
- A toxic effect of the infectious disease on the hair follicle
- Adverse effects of medications for prevention or treatment of the infection
- Catabolic state during severe infection
- Stress-induced hair loss

## 10.1 Syphilis

In French philosopher Voltaire's (1694–1778) (Fig. 10.5) celebrated satire "Candide, or the Optimist," published in 1759, the protagonist Candide finds a deformed beggar in the street. The beggar is Pangloss, whom he had known from the time at the castle of the baron of Thunder-ten-tronckh in Westphalia, where Pangloss served as the castle's tutor, and from where Candide was chased by the baron for kissing his daughter Cunégonde. Pangloss teaches "metaphysico-theologo-cosmolo-nigology" and believes with Leibnizian optimism that this world is the "best of all possible

**Fig. 10.5** François-Marie Arouet, French Enlightenment writer, known by his nom de plume Voltaire was famous for his wit, criticisms, versatile, and prolific writing. His polemics witheringly satirized intolerance, dogma, and the institutions of his time. His best-known work, *Candide*, ridicules many events, thinkers, and philosophies of his time

worlds." Pangloss explains Candide that the Bulgars attacked the baron's castle and killed the baron, his wife, and his son and raped and murdered Cunégonde. Pangloss explains that syphilis, which he contracted from the maid Paquette, has ravaged his body. Still, he believes that syphilis is necessary in the best of worlds because the line of infection leads back to a man who traveled to the New World with Columbus. If Columbus had not traveled to the New World and brought syphilis back to Europe, then Europeans would also not have enjoyed New World wonders such as chocolate.

The origin of syphilis is disputed [11]. Syphilis was present in the Americas before European contact [12], and it may have been carried from the Americas to Europe by the returning crewmen from Christopher Columbus's voyage to the Americas, or it may have existed in Europe previously but gone unrecognized until shortly after Columbus's return. The timing of the arrival of syphilis in Europe certainly supports the above theory, Columbus having journeyed in 1492. The first written records of an outbreak of syphilis in Europe occurred in 1494 or 1495 in

Naples, Italy, during a French invasion (Italian War of 1494–1498) [13]. Since it was claimed to have been spread by French troops, it was initially called the "French disease" by the people of Naples. The disease reached London in 1497 and was recorded at St Bartholomew's Hospital. In 1530, the pastoral name syphilis (the name of a character) was first used by the Italian physician and poet Girolamo Fracastoro (1476/1478–1553) as the title of his Latin poem in dactylic hexameter Syphilis sive morbus gallicus (Syphilis or The French Disease) describing the ravages of the disease in Italy.

In the sixteenth through nineteenth centuries, syphilis was one of the largest public health burdens in prevalence, symptoms, and disability [14], although records of its true prevalence were generally not kept because of the fearsome and sordid status of sexually transmitted diseases in those centuries. At the time the causative agent was unknown, but it was well-known that it was spread sexually and also often from mother to child (congenital syphilis). Its association with sex, especially sexual promiscuity and prostitution, made it an object of fear and revulsion and a taboo. The magnitude of its morbidity and mortality in those centuries reflected that, unlike today, there was no adequate understanding of its pathogenesis and no truly effective treatments. Mercury compounds and isolation were commonly used, with treatments often worse than the disease [15].

The first effective treatment for syphilis was arsphenamine, discovered by Japanese bacteriologist Sahachiro Hata (1873–1938) in 1909 during a survey of hundreds of newly synthesized organic arsenical compounds led by German physician and scientist Paul Ehrlich (1854–1915). It was manufactured and marketed from 1910 under the trade name Salvarsan by Hoechst AG. This organoarsenic compound was the first modern chemotherapeutic agent.

Danish writer Karen Blixen (1885–1962), most notably known for her memoir "Out of Africa" (publishing year: 1937), an account of her life while living in Kenya, was diagnosed March 1914 having syphilis 2 months after her wedding with Baron Bror von Blixen-Finecke and was treated initially with mercury and later on in Denmark with salvarsan. Years later she received more treatment with mercury, salvarsan, and bismuth, but in fact she was cured already in 1915 and told so by her Danish venereologist Carl Emanuel Flemming Rasch (1861–1938) who regularly followed up on her with the Wassermann test.

During the twentieth century, as both microbiology and pharmacology made substantial progress, syphilis, like other infectious diseases, became more of a manageable inconvenience than a daunting and disfiguring horror, at least in the developed countries among those who could afford to pay for timely diagnosis and treatment. Penicillin was discovered in 1928, and effectiveness of treatment with penicillin was confirmed in trials in 1943 [15] and remains the mainstay of syphilis treatment until today.

Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum*. The signs and symptoms of syphilis vary depending in which of the four stages it presents (primary, secondary, latent, and tertiary). Syphilis has been known as the great imitator as it may cause symptoms similar to many other diseases. "He who knows syphilis knows medicine" said Sir William Osler (1849–1919) at the

turn of the twentieth century. So common was syphilis in those days that all physicians were attuned to its various clinical presentations. Indeed, the nineteenth century witnessed the development of an entire medical subspecialty, syphilology, devoted to the study of the great imitator, *Treponema pallidum*.

The primary stage classically presents with a firm, painless, non-itchy skin ulceration usually between 1 cm and 2 cm in diameter (primary chancre). On histopathology, primary syphilis demonstrates an acanthotic epidermis which erodes with time to become ulcerated. Under the ulcer bed, there is typically a dense lymphocytic response, numerous plasma cells, and endothelial swelling (Fig. 10.6a). There are typically numerous organisms which may be exhibited with a variety of techniques including immunohistochemistry directed against *Treponema pallidum*.

In secondary syphilis, a symmetrical, reddish-pink, non-itchy rash occurs on the trunk and extremities, typically including the palms and soles (Fig. 10.6b–d), as well as flat, broad, whitish lesions on mucous membranes (condyloma latum). All of these lesions harbor bacteria and are infectious. Other symptoms may include fever, sore throat, malaise, and alopecia. Secondary syphilis exhibits considerable histopathologic variability and may be easily misinterpreted. The epidermis is often involved and shows a psoriasiform hyperplasia with superficial neutrophils (Fig. 10.6e). There is also a lichenoid tissue reaction, epidermal apoptosis, and exocytosis of neutrophils (Fig.10.6f). The dermis shows a superficial and deep chronic infiltrate which may resemble the changes of primary syphilis. There are numerous plasma cells in about 1/3 of cases and often endothelial swelling. Necrotic keratinocytes are one of the characteristics of secondary syphilis. The combination of plasma cells, irregular acanthosis, elongated rete ridges, and endothelial swelling should increase the likelihood of syphilis. In this instance, various special stains may be applied for detection of the pathogenic microorganism. The specific immunohistochemical stain for *Treponema pallidum* is highly specific and sensitive and reveals the organisms to be delicate and spiral-shaped. Silver impregnation techniques such as Warthin-Starry highlight the organisms.

Infection of the visual system (ocular syphilis) or auditory system (otosyphilis) can occur at any stage of syphilis but is commonly identified during the early stages and can present with or without additional central nervous system (CNS) involvement. Ocular syphilis often presents as panuveitis but can involve structures in both the anterior and posterior segment of the eye, including conjunctivitis, anterior uveitis, posterior interstitial keratitis, optic neuropathy, and retinal vasculitis. Ocular syphilis can result in permanent vision loss. Otosyphilis typically presents with cochleovestibular symptoms, including tinnitus, vertigo, and sensorineural hearing loss. Hearing loss can be unilateral or bilateral, have a sudden onset, and progress rapidly. Otosyphilis can result in permanent hearing loss.

Latent syphilis develops after secondary syphilis and is defined as having serologic proof of infection without symptoms of disease. The latent phase of syphilis can last many years after which, without treatment, approximately 15–40% of people can develop tertiary syphilis.

Tertiary syphilis may occur approximately 3–15 years after the initial infection and may be divided into three different forms: gummatous syphilis, late

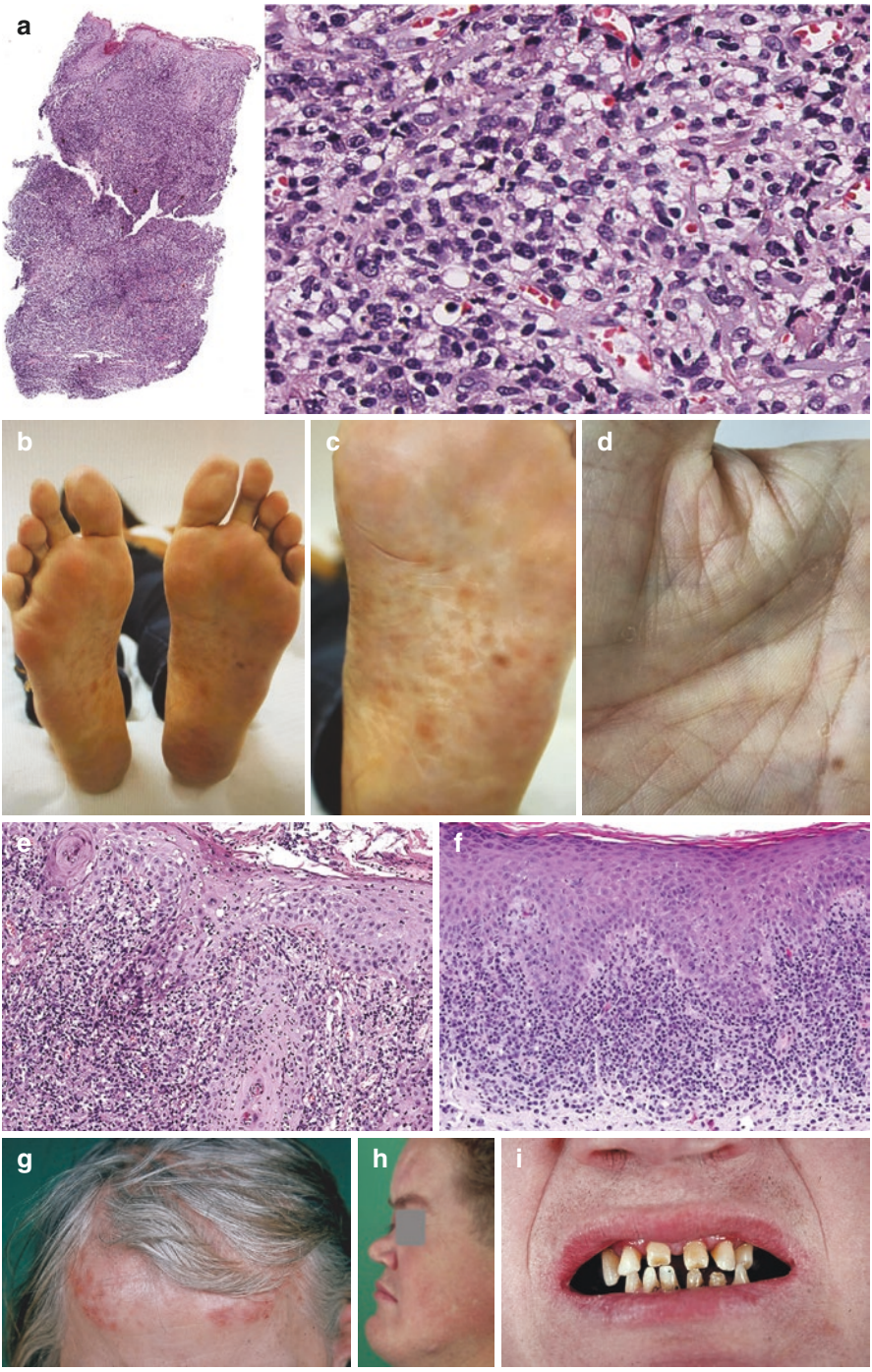
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**Fig. 10.6** (**a**–**i**) Syphilis: (**a**) histopathology. Primary syphilis. Ulceration, plasma cell- and histiocyte-rich infiltrates (courtesy Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland), (**b**–**d**) Secondary syphilis of the soles and palm. (**e**, **f**) Histopathology. Secondary syphilis: (**e**) plasma cell and histiocyte-rich infiltrates, vacuolization in the junctional zone, exocytosis of neutrophils, (**f**) lichenoid pattern, plasma cells, occasionally histiocyte-rich (courtesy Prof. Werner Kempf, kempf und pfaltz histologische diagnostik, Zurich, Switzerland) (**g**) Tertiary syphilis. Tubero-serpiginous syphilid of the forehead. (**h**, **i**) Congenital syphilis: (**h**) saddle nose deformity, (**i**) Hutchinson's teeth

neurosyphilis (meningovascular syphilis, general paresis, or tabes dorsalis), and cardiovascular syphilis (syphilitic aortitis). Individuals with tertiary syphilis are not infectious. Gummatous syphilis usually occurs 1–46 years after the initial infection, with an average of 15 years. It is characterized by the formation of soft, tumor-like nodes of inflammation which may vary considerably in size. They typically affect the skin, bone, and liver but can occur anywhere, including the brain and heart, leading to a variety of potential problems such as neurological disorders or heart valve disease.

Gummatous syphilis is caused by a reaction to spirochaete bacteria in the tissue. Gummas have a firm, necrotic center surrounded by inflamed tissue, which forms an amorphous mass. The center may become partly hyalinized. These central regions begin to necrotize through coagulative necrosis, though they also retain some of the structural characteristics of previously normal tissues, allowing a distinction from the granulomas of tuberculosis where caseous necrosis obliterates pre-existing anatomical structures. With time, gummas eventually undergo fibrous degeneration, leaving behind an irregular scar or a round fibrous nodule. The formation of gummata is rare in developed countries but common in areas that lack adequate medical treatment. Skin gummas are nodular or nodular ulcerative lesions, with an arciform pattern (Fig. 10.6g).

Congenital syphilis is syphilis present in utero and at birth and occurs when a child is born to a mother with syphilis. Untreated early syphilis infections results in a high risk of poor pregnancy outcomes, including saddle nose (collapse of the bony part of nose) (Fig. 10.6h), lower extremity abnormalities, miscarriages, premature births, stillbirths, or death in newborns. Some infants with congenital syphilis have symptoms at birth, but many develop symptoms later. Often these babies will develop syphilitic rhinitis, the mucus from which is laden with the *T. pallidum* bacterium, and therefore highly infectious. If a baby with congenital syphilis is not treated early, damage to the bones, teeth, eyes, ears, and brain can occur. Centrally notched, widely spaced peg-shaped upper central incisors known as Hutchinson's teeth (Fig. 10.6i) are characteristic of congenital syphilis.

Syphilitic alopecia is an uncommon manifestation of secondary syphilis, occurring in only 4% of patients. It can present in a diffuse pattern, a moth-eaten pattern, or a combination of both (Fig. 10.7a–h). It can also affect the eyebrows, eyelashes [16], beard and has also been reported on the legs [17]. The most important differential diagnosis is the reticular type of alopecia areata. The histopathological features include follicular plugging, a sparse, perivascular and perifollicular

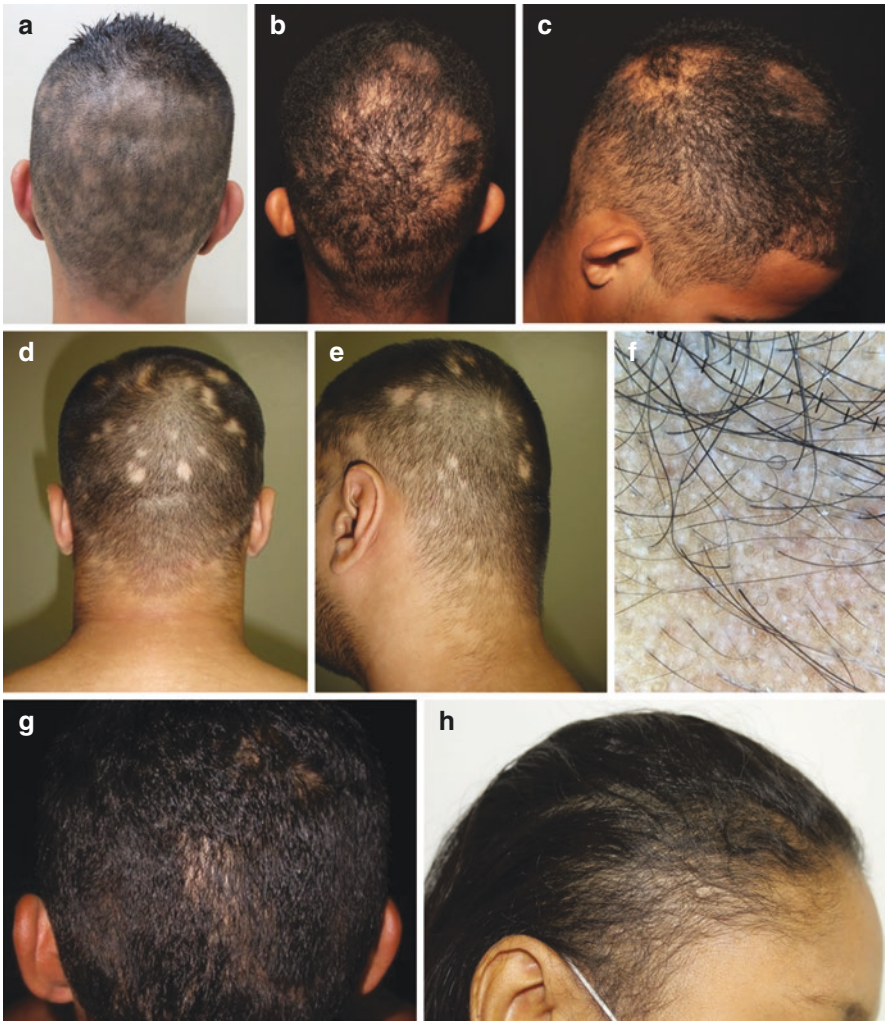


**Fig. 10.7** (**a**–**h**) Syphilitic alopecia (courtesy of Prof. Dayvison Freitas Evandro Chagas National Institute of Infectiology, Oswaldo Cruz Foundation, Brazil (**a**), Prof. Fábio Francesconi, Federal University of Amazonas, Brazil (**b**, **c**), and Prof. Sinesio Talhari, Department of Infectious Diseases, Amazonas Foundation of Tropical Medicine, Brazil (**d**, **e**))

lymphocytic infiltrate, telogenization, and follicle-oriented melanin clumping [18]. Immunohistochemical staining for syphilis may reveal spirochete microorganisms in the follicular epithelium of the hair root sheath [19] and papillary dermis, confirming the diagnosis of secondary syphilis [20].

Syphilitic alopecia has been reported in association with ocular syphilis [20–22].

Cutaneous tertiary syphilitic gumma affecting the scalp has been reported [23], though it seems to represent a rare event from the paucity of respective reports.

Syphilis is difficult to diagnose clinically during early infection. Confirmation is either via direct visual inspection using dark field microscopy or serologic testing. The latter is commonly used, as it is easier to perform. The diagnostic tests are unable to distinguish between the stages of the disease.

Dark field microscopy of serous fluid produced from a chancre may be used to make an immediate diagnosis by visualization of spirochaete bacteria. Clinics do not always have the respective equipment or experienced staff members, and testing must be done within 10 min of acquiring the sample. Two other sets of tests can be carried out on a sample from the chancre: direct fluorescent antibody (DFA) and polymerase chain reaction (PCR). DFA uses antibodies tagged with fluorescein, which attach to specific *T. pallidum* proteins, while PCR uses techniques to detect the presence of specific *T. pallidum* genes. These tests are not as time-sensitive, as they do not require living bacteria to make the diagnosis [24].

The serologic tests are divided into non-treponemal and treponemal tests. Non-treponemal tests are used initially and include the venereal disease research laboratory (VDRL) and the rapid plasma reagin (RPR) tests. False positives on the non-treponemal tests can occur with some viral infections, lymphoma, tuberculosis, malaria, endocarditis, connective tissue disease, and pregnancy.

For this reason, confirmation is required with a treponemal test, such as the treponemal pallidum particle agglutination (TP-PA) or the fluorescent treponemal-antibody absorption (FTA-ABS) test. Treponemal antibody tests usually become positive 2–5 weeks after the initial infection. The majority of patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of adequate treatment or disease activity. Treponemal antibody titers do not predict treatment response and therefore should not be used for this purpose.

Diagnosis of neurosyphilis depends on a combination of cerebrospinal fluid (CSF) tests, e.g., CSF cell count, protein, or reactive CSF-VDRL, in the presence of reactive serologic test (non-treponemal and treponemal) results and neurologic signs and symptoms. Neurosyphilis is diagnosed by finding high numbers of leukocytes, predominately lymphocytes, and high protein levels in the CSF in the setting of a known syphilis infection. CSF-VDRL is highly specific but insensitive. For a person with neurologic signs or symptoms, a reactive CSF-VDRL in the absence of blood contamination is considered diagnostic of neurosyphilis. When CSF-VDRL is negative despite clinical signs of neurosyphilis, reactive serologic tests results, lymphocytic pleocytosis, or protein, neurosyphilis should be considered. In that instance, additional evaluation by using FTA-ABS or TP-PA testing on CSF might be warranted. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Neurosyphilis is highly unlikely with a negative CSF FTA-ABS or TP-PA test, especially among persons with nonspecific neurologic signs and symptoms.

Serologic cure can be measured when the non-treponemal titers decline by a factor of 4 or more within 6–12 months in early syphilis or 12–24 months in late syphilis [25].

The treatment of syphilis by stage and by circumstance according to the Centers for Disease Control Prevention (CDC) recommendations is summarized in Table 10.2.

All persons who have primary and secondary syphilis should be tested for HIV at the time of diagnosis and treatment. Those persons whose HIV test results are negative should be offered HIV pre-exposure prophylaxis (PrEP) with emtricitabine plus tenofovir [26]. In geographic areas in which HIV prevalence is high, persons who have primary or secondary syphilis should be offered PrEP and retested for HIV in 3 months if the initial HIV test result was negative.

Persons who have syphilis and symptoms or signs indicating neurologic disease, such as cranial nerve dysfunction, meningitis, stroke, or altered mental state, should have an evaluation that includes CSF analysis.

**Table 10.2** Treatment of syphilis

| Stage and circumstance of infection | | Treatment recommendations | Penicillin allergy |
|---|---|---|---|
| Primary syphilis | | Benzathine penicillin G 2.4 million units IM in a single dose<br>Among infants and children benzathine penicillin G 50,000 units/kg body weight IM, up to the adult dose of 2.4 million units in a single dose | Doxycycline (100 mg orally two times/day for 14 days) |
| Secondary syphilis | | | |
| Latent syphilis | Early (<2 years) | Benzathine penicillin G 2.4 million units IM in a single dose | Doxycycline (100 mg orally two times/day for 14 days) |
| | Late (>2 years) or of unknown duration | Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units IM each at 1-week intervals | Doxycycline (100 mg orally two times/day) for 28 days |
| Tertiary syphilis with normal CFS examination | | Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units IM each at 1-week intervals | Any person allergic to penicillin should be treated in consultation with an infectious disease specialist |
| Neurosyphilis, ocular syphilis, otosyphilis | | Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 h or continuous infusion for 10–14 days<br>*or*<br>Procaine penicillin G 2.4 million units IM once daily plus probenecid 500 mg orally four times/day, both for 10–14 days | Ceftriaxone 1–2 g daily either IM or IV for 10–14 days |

**Table 10.2** (continued)

| | | | |
|---|---|---|---|
| Syphilis among persons with HIV infection | Primary and secondary syphilis | Benzathine penicillin G, 2.4 million units IM in a single dose | Persons with HIV infection who are allergic to penicillin and have primary or secondary syphilis should be managed according to the recommendations for persons without HIV who are allergic to penicillin |
| | Early latent syphilis | Benzathine penicillin G, 2.4 million units IM in a single dose | |
| | Late latent syphilis or latent syphilis of unknown duration | Benzathine penicillin G, 7.2 million units total, administered as three doses of 2.4 million units IM at 1-week intervals | |
| | All persons with HIV and syphilis co-infection should receive a neurologic, ocular, and otic examination | Persons with HIV infection and neurosyphilis should be treated according to the recommendations for persons with neurosyphilis and without HIV infection | |
| Syphilis during pregnancy | | Pregnant women should be treated with the recommended penicillin regimen for their stage of infection. Certain evidence indicates that additional therapy is beneficial for pregnant women to prevent congenital syphilis. For women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin G 2.4 million units IM can be administered 1 week after the initial dose | No proven alternatives to penicillin are available for treatment of syphilis during pregnancy |
| Congenital syphilis | | Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose by IV every 12 h during the first 7 days of life and every 8 h thereafter for a total of 10 days<br>*or*<br>Procaine penicillin G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days | Neonates who require treatment for congenital syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should be desensitized and then treated with penicillin G |

Persons with syphilis who have symptoms or signs of ocular syphilis, such as uveitis, iritis, neuroretinitis, or optic neuritis, should have a thorough cranial nerve examination and ocular slit-lamp and ophthalmologic examinations. CSF evaluation is not always needed for persons with ocular syphilis if no evidence of cranial nerves 2, 3, 4, 5, and 6 dysfunction or other evidence of neurologic disease exists.

If symptoms and signs of otic syphilis are present, then an otologic examination is needed. Treatment should be guided by the results of these evaluations.

Clinical and serologic evaluation should be performed at 6 and 12 months after treatment.

Failure of non-treponemal test titers to decrease fourfold within 12 months after therapy for primary or secondary syphilis (inadequate serologic response) might be indicative of treatment failure. However, clinical trial data have demonstrated that 10–20% of persons with primary and secondary syphilis treated with the recommended therapy will not achieve the fourfold decrease in non-treponemal titer within 12 months after treatment.

For retreatment, weekly injections of benzathine penicillin G 2.4 million units intramuscularly for 3 weeks are recommended, unless CSF examination indicates that neurosyphilis is present.

## 10.2 Human Immunodeficiency Virus

Human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV), a retrovirus.

Following initial infection, an individual may not notice any symptoms or may experience a brief period of influenza-like illness. Typically, this is followed by a prolonged incubation period with no symptoms. If the infection progresses, it interferes more with the immune system, increasing the risk of developing common infections such as tuberculosis, as well as other opportunistic infections, and tumors which are otherwise rare in people who have normal immune function. These late symptoms of infection are referred to as acquired immunodeficiency syndrome (AIDS). This stage is often also associated with unintended weight loss.

HIV is spread primarily by unprotected sex, including anal and vaginal sex, contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding.

Accordingly, the methods of prevention include safe sex, needle exchange programs, treating those who are infected, as well as both pre- and postexposure prophylaxis. Disease in a baby can often be prevented by giving both the mother and child antiretroviral medication.

While there is no broadly available cure or vaccine, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy. Treatment is recommended as soon as the diagnosis is made. Without treatment, the average survival time after infection is 11 years.

Between the time that AIDS was identified in the early 1980s and 2020, the disease has caused an estimated 36 million deaths worldwide. Accordingly, HIV/AIDS is considered a pandemic.

HIV/AIDS has had a large impact on society, both as an illness and as a source of discrimination. AIDS stigma exists around the world in a variety of ways, including ostracism, rejection, discrimination and avoidance of HIV-infected people, compulsory HIV testing without prior consent or protection of confidentiality, violence against HIV-infected individuals or people who are perceived to be infected with HIV, and the quarantine of HIV-infected individuals. Stigma-related violence or the fear of violence prevents many people from seeking HIV testing, returning for their results, or securing treatment, possibly turning what could be a manageable chronic illness into a death sentence and perpetuating the spread of HIV.

AIDS stigma has been divided into the following three categories:

- *Instrumental AIDS stigma*—a reflection of the fear and apprehension that are likely to be associated with any deadly and transmissible illness
- *Symbolic AIDS stigma*—the use of HIV/AIDS to express attitudes toward the social groups or lifestyles perceived to be associated with the disease
- *Courtesy AIDS stigma*—stigmatization of people connected to the issue of HIV/AIDS or HIV-positive people

Often, AIDS stigma is expressed in conjunction with one or more other stigmas, particularly those associated with homosexuality, bisexuality, promiscuity, prostitution, and intravenous drug use. In many developed countries, there is an association between AIDS and homosexuality or bisexuality, and this association is correlated with higher levels of sexual prejudice, such as anti-homosexual or anti-bisexual attitudes. There is also a perceived association between AIDS and all male-male sexual behavior, including sex between uninfected men. However, the dominant mode of spread worldwide for HIV remains heterosexual transmission [27].

Finally, There are many misconceptions about HIV and AIDS. Three misconceptions are that AIDS can spread through casual contact, that sexual intercourse with a virgin will cure AIDS, and that HIV can infect only gay men and drug users. In 2014, some among the British public wrongly thought one could get HIV from kissing (16%), sharing a glass (5%), spitting (16%), a public toilet seat (4%), and coughing or sneezing (5%). Other misconceptions are that any act of anal intercourse between two uninfected gay men can lead to HIV infection and that open discussion of HIV and homosexuality in schools will lead to increased rates of AIDS.

A small group of individuals continue to dispute the connection between HIV and AIDS [28], the existence of HIV itself, or the validity of HIV testing and treatment methods [29] These claims, known as AIDS denialism, have been scrutinized and rejected by the scientific community. Ultimately, discredited conspiracy theories have held that HIV was created by scientists, either inadvertently or deliberately. Operation INFEKTION was a worldwide Soviet active measures operation to

spread the claim that the United States had created HIV/AIDS. Surveys show that a significant number of people believed—and continue to believe—in such claims.

HIV/AIDS is diagnosed via laboratory testing and staged based on the presence of certain signs or symptoms.

Most people infected with HIV develop specific antibodies within 3–12 weeks after the initial infection. Diagnosis of primary HIV before seroconversion is done by measuring HIV-RNA or p24 antigen. Positive results obtained by antibody or PCR testing are confirmed either by a different antibody or by PCR.

Two main clinical staging systems are used to classify HIV and HIV-related disease for surveillance purposes: the WHO disease staging system for HIV infection and disease and the CDC classification system for HIV infection [30]. The latter is more frequently adopted in developed countries, while the former is suited to the resource-restricted conditions encountered in developing countries, where it can also be used to help guide clinical management, since the WHO disease staging system for HIV infection does not require laboratory testing.

The WHO system uses the following categories:

- *Primary HIV infection*: May be either asymptomatic or associated with acute retroviral syndrome.
- *Stage I*: HIV infection is asymptomatic with a CD4+ T-cell count (also known as CD4 count) greater than 500 per microliter (μL or cubic mm) of blood [27]. May include generalized lymph node enlargement.
- *Stage II*: Mild symptoms, which may include minor mucocutaneous manifestations and recurrent upper respiratory tract infections. A CD4 count of less than 500/μL.
- *Stage III*: Advanced symptoms, which may include unexplained chronic diarrhea for longer than a month, severe bacterial infections including tuberculosis of the lung, and a CD4 count of less than 350/μL.
- *Stage IV or AIDS*: severe symptoms, which include toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi, or lungs, and Kaposi's sarcoma. A CD4 count of less than 200/μL.

The US Center for Disease Control and Prevention classifies HIV infections based on CD4 count and clinical symptoms and describes the infection in five groups. In those greater than 6 years of age, it is:

- *Stage 0*: the time between a negative or indeterminate HIV test followed less than 180 days by a positive test
- *Stage 1*: CD4 count ≥500 cells/μL and no AIDS-defining conditions
- *Stage 2*: CD4 count 200–500 cells/μL and no AIDS-defining conditions
- *Stage 3*: CD4 count ≤200 cells/μL or AIDS-defining conditions
- *Unknown*: if insufficient information is available to make any of the above classifications

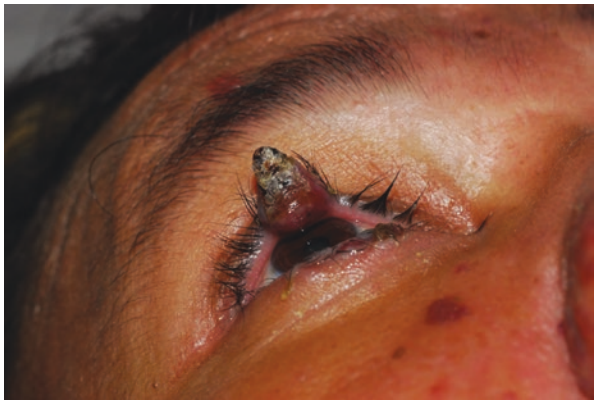

**Fig. 10.8** Kaposi sarcoma in patient with AIDS (courtesy: Prof. Fábio Francesconi, Federal University of Amazonas, Brazil)

The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia, cachexia in the form of HIV wasting syndrome, and esophageal candidiasis.

Opportunistic infections may be caused by bacteria, viruses, fungi, and parasites that are normally controlled by the immune system. Which infections occur depends partly on what organisms are common in the person's environment.

People with AIDS have an increased risk of developing various viral-induced cancers, including Kaposi's sarcoma (Fig. 10.8), Burkitt's lymphoma, primary central nervous system lymphoma, and cervical cancer.

For surveillance purposes, the AIDS diagnosis still stands even if, after treatment, the CD4+ T-cell count rises to above 200 per μL of blood or other AIDS-defining illnesses are cured.

Approximately 90% of HIV-infected patients develop some type of skin disease. Cutaneous manifestations associated to HIV infection can be classified as primary or HIV-related and secondary mucocutaneous signs of HIV infection. Secondary complications, such as opportunistic infections and skin tumors, are directly correlated with a decline in the CD4+ cell counts.

Many dermatological conditions have been described in HIV-infected patients, either in the context of an uncontrolled HIV infection or in the situation of highly active antiretroviral therapy (HAART). Among these, hair loss is reportedly common in patients with HIV-1 infection. Possible causes include chronic HIV-1 infection itself, recurrent secondary infections, nutritional deficiencies, immunologic and endocrine dysregulation, and exposure to multiple drugs.

The most frequently skin conditions related to HIV infection are divided in infectious (candidiasis, dermatophyte infection, *Staphylococcus aureus* infection, syphilis, cryptococcosis, histoplasmosis, herpes simplex virus, varicella-zoster virus, human papillomavirus, epidermodysplasia verruciformis-like phenotype, molluscum contagiosum, mycobacterium cutaneous infection, bacillary angiomatosis), infestation (scabies), neoplasms, inflammatory conditions (seborrheic dermatitis, HIV-related pruritus, eosinophilic folliculitis, atopic dermatitis), drug reactions, itch, xerosis, photosensitivity, lipoatrophy, psoriasis, and the immune reconstitution inflammatory syndrome (IRIS).

The scalp is a warm and moist region due to its higher follicular density and sebum production. This humidity contributes to a favorable environment for the development of bacteria and fungi. Faria et al. [31] studied scalp postmortem samples of 28 women aged between 18 and 46 year-old, 14 diagnosed with AIDS and 14 without AIDS. The scalp samples were subjected to histologic processing and were cut for histochemistry and immunohistochemistry procedures. No scalp diseases were found in the group without AIDS. In the AIDS group, there was a decrease in the number of total hair follicles and a significant increase in the number of telogen hair follicles. Two patients with AIDS presented scalp lesions of seborrheic dermatitis and disseminated erythematosquamous lesions. The authors demonstrated that there was a reduction in the epidermis thickness, number of layers, and cell diameters in the scalp of patients with AIDS. The authors believe that these observations may be a cause of a decrease regenerative capacity of the scalp that favors opportunistic infection.

The observation of an increased frequency of telogen effluvium was also by Smith et al. [32], who described presence of apoptotic or necrotic keratinocytes seen within the outer root sheath and dystrophy of hairs as putative markers for hair loss in patients with HIV infection. They observed variation in the diameter of the hairs sometimes associated to longitudinal ridging, indentations of the hairs, and twisting of the hair shafts. Other features were abnormality in the transverse cuticular scales and loss of cohesion. Also, a variable mononuclear inflammatory infiltrate was seen surrounding and within the basaloid cells of the follicle in telogen phase. This inflammation is possibly related to seborrheic dermatitis of psoriasis that is commonly seen in these patients. The authors also observed the presence of trichoschisis or fracture of the hair shaft. The presence of trichoschisis has been associated to cysteine deficiency and may suggest an alteration in the amino acids metabolism and oxidative stress.

In another, case-control study conducted to investigate the occurrence of apoptosis of follicular stem cells at the bulge in diffuse alopecia of HIV-1 infection, the investigators applied a double-staining procedure to transverse scalp sections from 15 HIV-1-infected patients and 12 controls, with the monoclonal antibody anticytokeratin 19 as stem cell marker and TUNEL technique to identify apoptosis. Eighty percent of cases and 25% of controls presented at least one double-stained follicle. The proportion of positive follicles per section was 48% (±7%) for cases and 26% (±13%) for controls. The study demonstrated that diffuse alopecia related to HIV-1 infection represents a hair cycle disturbance, and that part of the follicular stem cell population become apoptotic in a higher proportion than normal subjects. No cytotoxic folliculitis was found. Owing to its cell cycle interaction and caspase induction capacities, HIV-1 viral protein R was proposed as a possible follicular stem cell apoptosis inductor [33].

To review the literature evaluating antiretroviral-related alopecia and to provide guidance on the differential diagnosis and management of this condition, a literature search was performed using PubMed, MEDLINE, Embase, International Pharmaceutical Abstracts (IPA), Cumulative Index to Nursing and Allied Health (CINAHL), and the Cochrane database (through May 2014). Relevant conference

abstracts and product monographs were reviewed. Search terms included antiretroviral, individual antiretroviral classes and names, highly active antiretroviral therapy, HIV, AIDS, alopecia, hair, hair loss, and drug. The study selection and data extraction encompassed English language studies and case reports. A total of 16 articles and 1 conference abstract were retrieved, with a total of 46 patients with hair loss. The protease inhibitor class, in particular indinavir, was most commonly reported to cause hair loss, followed by the NRTI, lamivudine. The majority of cases presented with alopecia of the scalp alone, with a median time of onset of 2.5 months. Management involved discontinuing the drug in most cases, with at least partial reversal in half the cases. In conclusion, discontinuation of the suspected agent is the optimal management of antiretroviral-induced alopecia, and hair regrowth should occur within 1–3 months. Management may also include replacing the offending medication with an antiretroviral less likely to cause hair loss. It is essential to rule out other causes of alopecia with a complete patient history, including characterization of the hair loss and assessment of the patient's medical history, medication use, and family history of alopecia [34].

Alopecia (areata) universalis, either alone [35–39] or with concomitant vitiligo (Fig. 10.9) [40], has been reported in association with HIV infection or the with the immune reconstitution inflammatory syndrome (IRIS), a condition representing the occurrence of a new or latent disorder observed 3–6 months after the start of HAART [41]. Also, a case observation of remission of long-standing alopecia universalis after human immunodeficiency virus infection has been reported [42], giving rise to speculations on the pathogenesis of alopecia universalis in these patients in relation to immune dysfunction with HIV infection.

Sons et al. reported a case of HIV-associated generalized syphilitic alopecia mimicking alopecia universals [43]. The patient presented with neurosyphilis and had a dramatic improvement of both the hair loss and the neurosyphilis following 14 days of intravenous benzyl penicillin treatment. Presence of treponemal spirochetes in the hair follicles suggests direct involvement in alopecia.

Sadick reported the so far largest study on the incidence of trichocutaneous disorders in 500 patients infected with HIV-1 in a large university-based setting [44]. The majority of hair disorders in the study population occurred with helper T-cell numbers of less than 150/mm3. Seborrheic dermatitis and psoriasis were most commonly noted followed by disorders of cell growth cycle regulation and trichokeratinization, i.e., telogen effluvium, acquired loose anagen hair, and straightening of hair in blacks (straight hair sign) (Fig. 10.10). The classification of AIDS-related hair disorders (AIDS trichopathy) based on the observations of Sadick is summarized in Table 10.3.

However, straightening of the hair is not pathognomonic for HIV infection. This phenomenon has been attributed to a variety of factors, including caloric and protein malnutrition, as well as deficiencies in minerals that affect hair growth, such as copper, zinc, and selenium. In addition, endocrine factors, such as decreased androgen levels and increased estradiol levels, are seen in patients with liver disease associated with alcoholism and late-stage HIV disease, and they are thought to play a role in abnormal hair development [45]. While in malnourished and hypoproteinemic

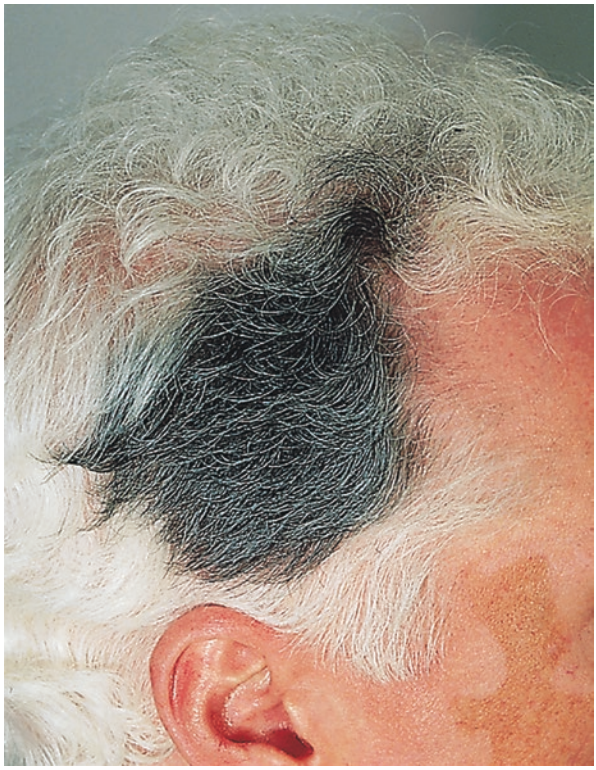

**Fig. 10.9** Poliosis from alopecia areata and vitiligo in patient with AIDS

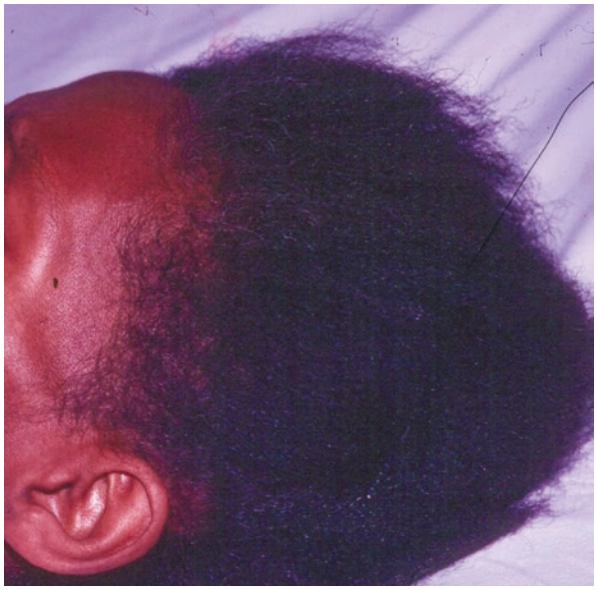

**Fig. 10.10** Straight hair sign in black patient with AIDS (courtesy Prof. Sinesio Talhari, Department of Infectious Diseases, Amazonas Foundation of Tropical Medicine, Brazil)

**Table 10.3** Classification of AIDS trichopathy

| |
|---|
| **Disorders affecting the hair** |
| Telogen effluvium |
| Acquired loose anagen hair |
| Premature graying |
| Eyelash trichomegaly |
| Hairy pinnae |
| Brittle hair syndrome |
| Alopecia areata |
| Straight hair sign |
| **Disorders affecting the scalp and hair** |
| *Infectious etiologies secondarily noted in AIDS patients* |
| Bacterial |
| Staphylococcal furunculosis |
| Syphilis |
| Fungal |
| Dermatophytes |
| Scopulariopsis |
| Cryptococcosis |
| Zygomycete infection |
| Aspergillosis |
| Viral |
| Molluscum contagiosum |
| Infestations |
| Papular *Demodex folliculorum* |
| Norwegian scabies |
| *Inflammatory disorders* |
| Seborrheic dermatitis |
| Psoriasis |
| Necrotizing folliculitis |
| Vascular hypersensitivity alopecia |
| *Neoplastic disease* |
| Lymphoma |
| Kaposi's sarcoma |
| *Miscellaneous* |
| Nodular prurigo |
| Vitiligo |

states, African hair straightens in an uncomplimentary manner, in certain diseases African hair changes to a rather desirable silky wavy texture, similar to the hair of the African neonatal child, namely, AIDS, rheumatoid arthritis, systemic lupus erythematosus, pulmonary tuberculosis with cachexia, and Behcet's disease [46].

Eyelash trichomegaly (Fig. 10.11) is increased length, curling, pigmentation, or thickness of eyelashes. Various causes include congenital syndromes (Oliver-McFarlane syndrome), acquired conditions (ocular diseases), and drugs (prostaglandin analogues, interferon alpha, epidermal growth factor inhibitors). In HIV, trichomegaly has been observed to occur in association with late-stage disease. Eyelash length has been shown to normalize as patients respond to antiretroviral therapy [47]. The onset of eyelash trichomegaly in relation to the chronology of

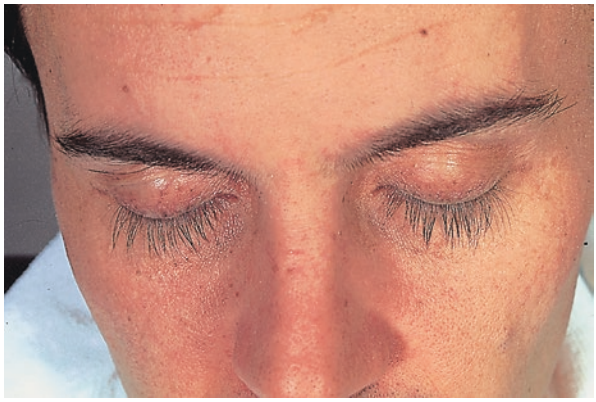

**Fig. 10.11** Acquired eyelash trichomegaly in patient with AIDS

medical events is an important point for delineating a specific etiology. Although usually benign, the condition can lead to psychological disturbances and can result in corneal abrasions. The main treatment of eyelash hypertrichosis involves regular trimming of the eyelashes if they cause symptoms.

Hair pinnae (auricular hypertrichosis) (Fig. 10.12) is a usually genetic condition expressed as long and strong hairs growing from the helix of the pinna. The condition is primarily restricted to older men. According to the available literature, hypertrichosis pinnae auris is a Y-linked character and particularly frequent in the male population of southern India. Tosti et al. [48] reported acquired hairy pinnae in a patient infected with HIV-1.

Patients with AIDS may present with atypical lesions of molluscum contagiosum. Molluscum contagiosum is a benign skin tumor caused by a parapoxvirus. The typical lesions are usually smooth, dome-shaped, umbilicated flesh-colored papules, and approximately 10–20% of patients with symptomatic HIV or AIDS have molluscum contagiosum lesions [49]. Atypical presentations of molluscum contagiosum are represented as abscess or nodular lesions, some of them with central crusts. Those lesions are larger than the typical ones and must be distinguished from basal cell carcinoma, cutaneous cryptococcosis, histoplasmosis, keratoacanthoma, and sporotrichosis. Transmissions routes include skin contact and sexual contacts. The transmission by fomite contact is controversial. Immunocompromised hosts exhibit lesions on the face and intertriginous areas. The lesions tend to regress with highly active antiretroviral therapy and immune reconstitution. Mackowiak [50] described a patient with giant lesions of the face and scalp due to molluscum contagiosum, treated with topical 3% cidofovir. Other possible treatments such as podophyllin, tretinoin, cryotherapy, and mechanical curettage may be successful.

Eosinophilic folliculitis (Fig. 10.13a) is a chronic pruritic type of folliculitis of unknown pathogenesis that is common in HIV-infected patients. It was originally described by Ofuji et al. in 1970, and it was later associated with HIV infection as a separate entity. Theories of follicular hypersensitivity reaction or autoimmune reaction to sebum components have been proposed. The condition presents with increased serum IgE levels and peripheral leukocytosis with eosinophilia [51].

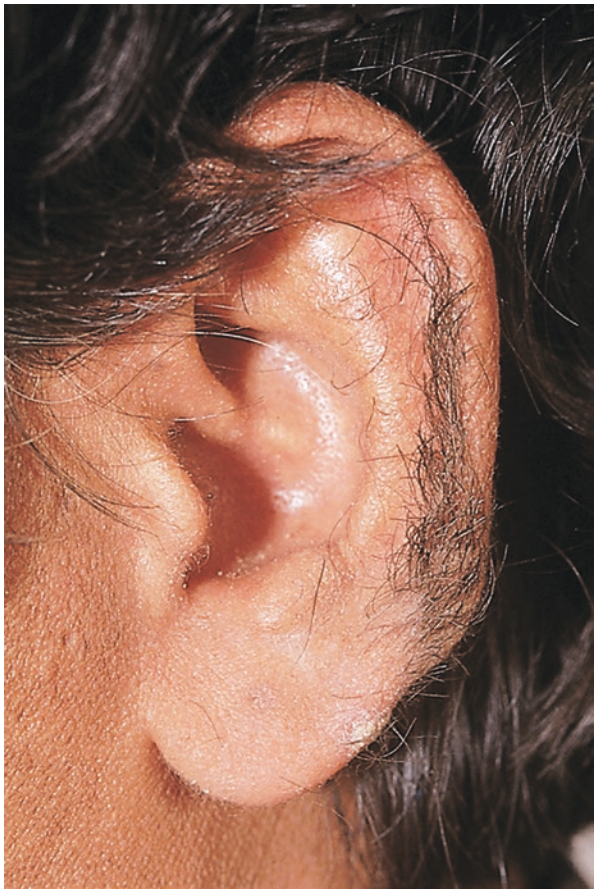

**Fig. 10.12** Hairy pinnae

Patients affected with eosinophilic pustular folliculitis complain of chronic pruritus associated with deep excoriations. Clinically the lesions are follicular urticarial papules with some pinpoint vesicles or pustules in the shoulders, trunk, upper arms, neck, and forehead. It is most common in HIV-infected individuals with low CD4 count. Up to 50% of patients have peripheral eosinophilia [52]. Differential diagnosis is between other types of folliculitis, scabies, drug rashes, and eczema. A skin biopsy taken from an unexcoriated fresh lesion is usually recommended. Scrapings for scabies should also be performed. Histopathology shows a folliculocentric inflammatory infiltrated composed by lymphocytes and eosinophils with marked sebaceous lysis (Fig. 10.13b). Possible treatments are topical steroids, antihistamines, ultraviolet B phototherapy, dapsone, prednisolone, and isotretinoin. Highly antiretroviral therapy may decrease the intensity of the symptoms.

Seborrheic dermatitis is a common skin disease in HIV-infected patients, and the severity of the disease is related to immunosuppression level. Thus, it can be used as a marker for disease progression. It affects the scalp and other seborrheic areas of the body such as the face, chest, back, axillae, and groin. The affected areas show

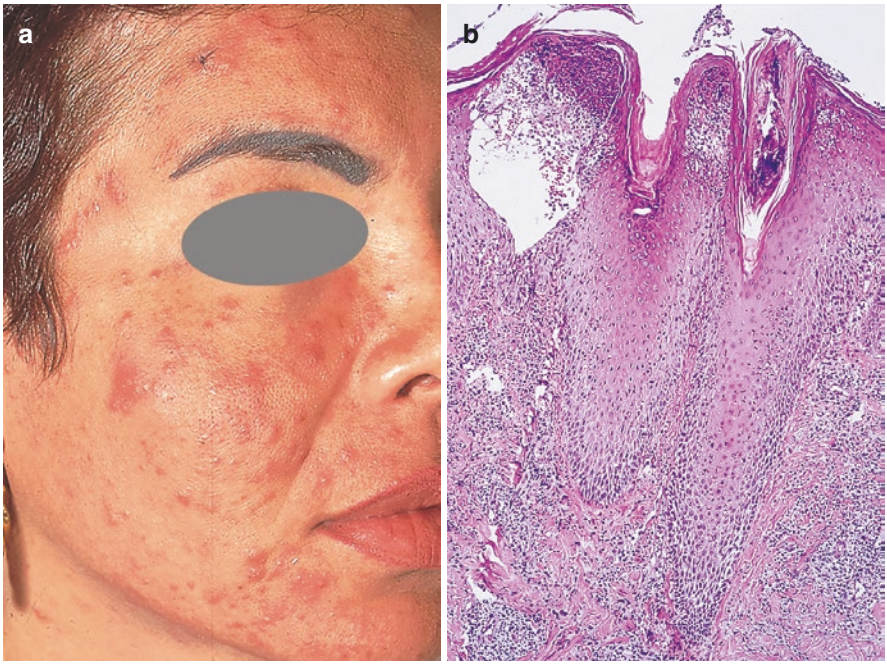


**Fig. 10.13** (**a**, **b**) (**a**) Eosinophilic pustular folliculitis, (**b**) histopathology

erythema and scaling lesions sometimes associated to itching [53]. Yeast of the genus *Malassezia* has long been implicated as a main factor related to the condition. These seem to elicit a nonspecific immune response triggered by the invasion of the stratum corneum by the microorganism with further release of lipases that act on the sebum forming free fatty acid. The presence of those free fatty acids seems to trigger a cascade of inflammation that causes hyperproliferation of the stratum corneum and disruption of the skin barrier. A high lipid environment acts increasing the population of *Malassezia* perpetuating the inflammation [54]. Men are more likely to have their heads colonized by *Malassezia* species than women. The clinical symptom of scalp seborrheic dermatitis is an itchy scaling scalp, greasy rash, sometimes associated with the complaint of hair shedding and hair thinning. Scaling is often concurrent with an oily complexion. On the face, seborrheic dermatitis affects the eyebrows, nasolabial fold, and cheeks. Scaling and redness are specially perceived when men grow beard and moustaches. In HIV patients the rash is sometimes crusty and oozing, possibly due to the higher colonization of *Staphylococcus epidermidis* [55]. Histologically, the lesions of SD of the scalp taken from AIDS patients show widespread parakeratosis, keratocystic necrosis, leukoexocytosis, and superficial perivascular infiltrate of plasma cells.

Treatment of scalp seborrheic dermatitis consists primarily of antifungal shampoos such as ketoconazole 2%, selenium sulfide, zinc pyrithione 1–2.5%, ciclopirox 1% shampoos, and coal tar-containing shampoos [56]. Shampoos can be used daily

or, at least, three times a week, for several weeks until remission is achieved and once a week for maintenance. The shampoo must stay on the scalp for 3–5 min before rinsing. Depending on the severity of scalp inflammation and itching symptoms, topical corticosteroids can be used for a short period of time. Clobetasol 0.05% shampoo is an option for moderate to severe cases, twice weekly, alternating with an antifungal shampoo. There is no loss of effect reported with long-term use of antifungal shampoos.

Finally, unusual *Microsporum canis* infections of the scalp and nails in adult HIV patients have been reported. In adult men, tinea capitis is infrequent; moreover *Microsporum* spp. nail infections are extremely rare. In most cases *Microsporum canis* scalp infection is usually easy to treat with antifungal agents. The authors describe two HIV-infected men with an unusual *M. canis* infection. Both patients had tinea capitis, presenting as alopecia in one and as scaling of the scalp in the other. One patient also had tinea unguium caused by *M. canis*. Ketoconazole was ineffective in both patients, terbinafine was tried in one patient without benefit, and, finally, itraconazole was effective, but treatment took many months, and only one patient was cured [57].

The hair changes associated with HIV infection and AIDS may seem of subordinate significance, and yet they do not only have cosmetic and psychological consequences but may also be markers for more serious disease or complications.

## 10.3 HTLV-1

HTLV-1 (human T-cell lymphotropic virus type 1) is a human retrovirus of the family Retroviridae, genus *Deltaretrovirus*, associated with malignancy. The virus integrates into T helper (CD4+) lymphocytes. The main diseases caused by HTLV-1 are myelopathy/tropical spastic paraparesis, adult T-cell leukemia/lymphoma, and a peculiar infective dermatitis.

The virus infects individuals worldwide, with approximately five to ten million people infected, and Brazil is considered to be a highly endemic area [58]. Other endemic regions are Japan, Caribbean, South and Central America, equatorial Africa, and Iran [59]. A study in Brazil evaluated 193 infected subjects and 76% had some type of skin disease [60].

The human T-cell lymphotropic virus type 1-associated infective dermatitis (HAID) is a chronic exudative eczematous eruption that is the prime cutaneous manifestation of HTLV-1. It was first described in Jamaica in 1966 as a peculiar pattern of relapsing infected eczema [61]. It is most prevalent in the pediatric population, but it can also present in adults [62]. Recognizing the infection may lead to the adoption of preventive measurements to avoid propagation of the infection [63].

Uveitis, thyroiditis, arthritis, and polymyositis have also been associated to the virus [60].

HTLV-1 is an RNA retrovirus with tropism for CD4+ T lymphocytes that replicates via reverse transcriptase. Surrounding cells are infected by cell-to-cell contact aided by an extracellular biofilm-like structure. Once the infection is stablished,

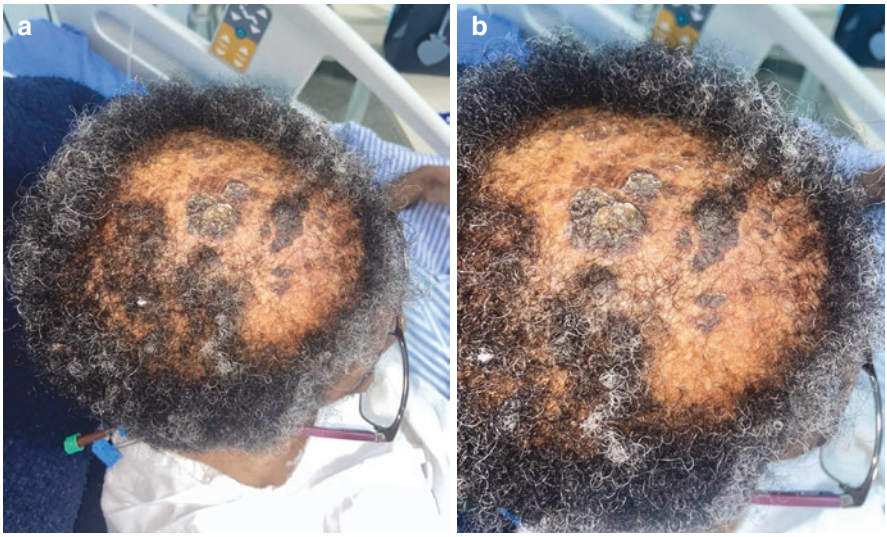


**Fig. 10.14** (**a**, **b**) Human T-cell lymphotropic virus type 1-associated infective dermatitis of the scalp

there is the generation of pro-inflammatory cytokines and triggering of a cytotoxic cell response causing the lysis of infected cells. HAID is characterized by a Th-1 immune response with increased levels of TNF-α, IL-6, and IFN-γ [63]. A study by Setoyama et al. showed that HTLV-1 DNA is also present in the epithelial lining of sweat ducts and vascular spaces, demonstrating that the virus not only infect lymphocytes [64].

In adults, HTLV-1 is mainly transmitted through sexual contact followed by blood transfusion and use of contaminated material. In children, the main rout of transmission is vertical, from mother to child via breast milk, and it is more likely to occur after 6 months of age as the protective maternal antibodies in the child decline. There is a positive correlation between the duration of breastfeeding and proviral load in breast feed [59, 65].

Classically, HAID eruption is a chronic exudative eczematous rash with crusting that involves the scalp (Fig. 10.14a, b), paranasal folds, eyelid (blepharoconjunctivitis), ears and retroauricular areas, neck, axillae, and groin. Some severe cases show generalized papular eruption and follicular papules. Secondary infection by *Staphylococcus aureus* and beta-hemolytic Streptococci is often present. The lesions may be fetid, pruritic, and painful. The clinical features are very similar to what is found in seborrheic dermatitis and atopic dermatitis. Nasal discharge is often seen in infants and is one of the major criteria that may help to differentiate HAID from atopic dermatitis and seborrheic dermatitis. As described by in the first publication about HAIDS, skin lesions in children begin around the nostrils and/or ears and rapidly spread to the rest of the face, to the scalp, and around the neck. Of notice is the description of Sweet in Jamaican patients of a pattern of diffusely

**Table 10.4** Diagnostic criteria of infectious dermatitis

| |
|---|
| *Major criteria* |
| 1. Eczema in two or more areas: scalp, armpits, groin, ear, retroauricular region, eyelid margins, perinasal area, neck |
| 2. Chronic rhinorrhea without other signs of rhinitis and/or crusted lesions in nasal vestibule (nostril) |
| 3. Chronic relapsing dermatitis with prompt response to antibiotic therapy but with relapse on withdrawal of treatment |
| 4. Onset in early childhood |
| 5. Seropositive to HTLV-1 |
| *Minor criteria* |
| 1. Positive cultures for *Staphylococcus aureus* and/or *Streptococcus β* (skin or nares) |
| 2. Generalized lymphadenopathy with dermatopathic lymphadenitis |
| 3. Anemia |
| 4. Elevated erythrocyte sedimentation rate |
| 5. Hypergammaglobulinemia IgD and IgE |
| 6. Increased CD4 and CD8 and CD4/CD8 ratio |

Four major criteria are needed to establish the diagnosis. The presence of items 1, 2, and 5 among major criteria are mandatory

disseminated eczema in children and young adults, strikingly follicular in distribution on extensor surfaces in spite of the minimal development of body hair, resembling an itchy patchy keratosis pilaris [61].Other cutaneous manifestations of HTLV-1 include crusted scabies, xerosis, acquired ichthyosis, and extensive dermatophytic infections [63]. Uncommon adulthood skin lesions are intertriginous inframammary eczematous lesions, lichenification, hyperchromia and desquamation of the ankles and malleolar region [66].

The diagnostic criteria of infected dermatitis are listed in Table 10.4. Opposed to HIV, HTLV-1 may remain silence during many years, and only 10% will present clinical manifestations, being infective dermatitis one of the earliest ones, mainly in children. In adults, the most common clinical symptoms are tropical spastic paraparesis (TSP) and adult T-cell leukemia-lymphoma. Souza et al., analyzed 12 patients with adulthood HAIDS and 42 patients with juvenile HAIDS. Scalp involvement was present in 100% of the patients. Some of them complained of hair loss, and two presented small areas of alopecia [66].

The histopathology of HTLV-1 associated infective dermatitis is nonspecific and similar to what is observed in atopic dermatitis. Histopathology features are of a chronic dermatitis with spongiosis and perivascular lymphocytic infiltration predominantly of CD8+ T cells. Other features include hyperkeratosis, parakeratosis, and basal cell vacuolization. Histological findings may resemble psoriasis and cutaneous T-cell lymphoma with subcorneal collection of neutrophils resembling Munro microabscesses, epidermal collection of lymphocytes resembling Pautrier microabscesses, plasma cells, and eosinophils. Some cases may present epidermotropism without atypical lymphocytes. Affected lymph nodes present a dermatopathic lymphadenitis. Clinicopathological aspects of adulthood and juvenile HAIDS are similar and the same major diagnosis criteria can be applied for both forms [66].

HTLV-1 infection is detected by ELISA and confirmed by Western blot [66].

Differential diagnosis includes chronic erythematous and eczematous skin diseases such as atopic dermatitis, psoriasis, seborrheic dermatitis, allergic contact dermatitis, and mycosis fungoides.

For treatment, antibiotics such as cephalexin, amoxicillin with clavulanate and SMX-TMP are good options, but relapse is common after withdrawal of the treatment. Topical treatment may include mupirocin and, sometimes, hydrocortisone.

## 10.4 Dengue Fever

Dengue fever is a mosquito-borne tropical disease caused by the dengue virus. The dengue fever virus is an RNA virus of the family *Flaviviridae*, genus *Flavivirus*. Other members of the same genus include yellow fever virus, West Nile virus, Zika virus, St. Louis encephalitis virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kyasanur forest disease virus, and Omsk hemorrhagic fever virus. Most are transmitted by arthropods (mosquitos or ticks) and are therefore also referred to as arboviruses (arthropod-borne viruses) [67]. With up to 100 million cases annually, dengue fever is today's most important arboviral disease. Dengue fever is endemic in many parts of Southeast Asia, the Indian subcontinent, Oceania, and the Americas. The disease mainly affects the local population but occasionally also visitors from non-endemic areas.

The virus is primarily transmitted by *Aedes* mosquitos, particularly *Aedes aegypti.* These mosquitos usually live between the latitudes of 35° north and 35° south below an elevation of 1000 m. They typically bite during the early morning and in the evening, but they may bite and hence spread infection at any time of day. An infection can be acquired via a single bite. A female mosquito that takes a blood meal from a person infected with dengue, during the initial 2- to 10-day febrile period, becomes itself infected with the virus in the cells lining its gut. About 8–10 days later, the virus spreads to other tissues including the mosquito's salivary glands and is subsequently released into its saliva. The virus seems to have no detrimental effect on the mosquito, which remains infected for life. *Aedes aegypti* is particularly involved, as it prefers to lay its eggs in artificial water containers, to live in close proximity to humans, and to feed on people rather than other vertebrates.

When a mosquito carrying dengue virus bites a person, the virus enters the skin together with the mosquito's saliva. It binds to and enters white blood cells and reproduces inside the cells while they move throughout the body. The white blood cells respond by producing several signaling proteins, such as cytokines and interferons, which are responsible for many of the symptoms, such as the fever, the flu-like symptoms, and the severe pains. In severe infection, the virus production inside the body is greatly increased, and many more organs (such as the liver and the bone marrow) can be affected. Fluid from the bloodstream leaks through the wall of small blood vessels into body cavities due to capillary permeability. As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs. Furthermore, dysfunction of the bone marrow due to infection of the stromal cells leads to reduced numbers of platelets,

which are necessary for effective blood clotting; this increases the risk of bleeding, the other major complication of dengue fever [68].

Once inside the skin, dengue virus binds to Langerhans cells. The virus enters the cells through binding between viral proteins and membrane proteins on the Langerhans cell, specifically the C-type lectins called DC-SIGN, mannose receptor, and CLEC5A [69] DC-SIGN, a nonspecific receptor for foreign material on dendritic cells, seems to be the main point of entry [70]. The dendritic cell moves to the nearest lymph node. Meanwhile, the virus genome is translated in membrane-bound vesicles on the cell's endoplasmic reticulum, where the cell's protein synthesis apparatus produces new viral proteins that replicate the viral RNA and begin to form viral particles. Immature virus particles are transported to the Golgi apparatus, the part of the cell where some of the proteins receive necessary sugar chains (glycoproteins). The now mature new viruses are released by exocytosis. They are then able to enter other white blood cells, such as monocytes and macrophages. The initial reaction of infected cells is to produce interferon, a cytokine that raises many defenses against viral infection through the innate immune system by augmenting the production of a large group of proteins mediated by the JAK-STAT pathway. Other processes of interest include infected cells that become necrotic, which affect both coagulation and fibrinolysis and low platelets in the blood, also a factor in normal clotting.

Nevertheless, people infected with dengue virus are asymptomatic in 80% or have only mild symptoms, such as an uncomplicated fever, while others (5%) suffer of more severe illness that in a small proportion may be life-threatening [71]. The incubation period ranges from 3 to 14 days, but most often it is 4 to 7 days.

The characteristic symptoms of dengue are sudden-onset fever; headache, typically located behind the eyes; muscle and joint pains; and a rash. An alternative name for dengue, "breakbone fever," comes from the associated muscle and joint pains [72]. The course of infection is divided into three phases: febrile, critical, and recovery.

The febrile phase involves high fever, potentially over 40 °C, and is associated with generalized pain and a headache; this usually lasts 2–7 days. Nausea and vomiting may also occur. A rash occurs in 50–80% of those with symptoms in the first or second day of symptoms as flushed skin or later in the course of illness (days 4–7) as a measles-like rash. A rash described as "islands of white in a sea of red" has also been observed. Some petechiae can appear at this point, as may some mild bleeding from the mucous membranes of the mouth and nose. The fever itself is classically biphasic or saddleback in nature, breaking and then returning for 1 or 2 days.

In some people, the disease proceeds to a critical phase as fever resolves. During this period, there is leakage of plasma from the blood vessels, typically lasting 1–2 days. This may result in fluid accumulation in the chest and abdominal cavity as well as depletion of fluid from the circulation and decreased blood supply to vital organs. There may also be organ dysfunction and severe bleeding, typically from the gastrointestinal tract. In a small proportion of cases (5%), the disease develops into a more severe dengue hemorrhagic fever, resulting in bleeding, low levels of blood platelets, and blood plasma leakage or into dengue shock syndrome, where

dangerously low blood pressure occurs [73]. This critical phase, while rare, occurs relatively more commonly in children and young adults [74]. Other risk factors for severe disease include female sex, high body mass index, and viral load. Elderly people are also at higher risk of a poor outcome [75].

The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream. This usually lasts 2–3 days. The improvement is often striking and can be accompanied with severe itching and a slow heart rate. Another rash may occur with either a maculopapular or a vasculitic appearance, which is followed by peeling of the skin. During this stage, a fluid overload state may occur. If it affects the brain, besides inflammation of the brain by the virus, it may cause a reduced level of consciousness or seizures in 0.5–6% of severe cases.

A pregnant woman who develops dengue is at higher risk of miscarriage, low birth weight, and premature birth [76]. Vertical transmission (from mother to child) during pregnancy or at birth has been reported [77].

Veraldi et al. reported telogen effluvium as first clinical presentation of Dengue [78].

In a clinical analysis of 250 cases of dengue fever-like patients during the 1987–1988 epidemic at Kaohsiung City, southern Taiwan, hair loss was noted in 45% of patients [79].

In another study of clinical data on 26 cases with serological confirmed dengue fever diagnosed in Norway in 1991–1996, postinfectious complications were common, and 4 weeks after the acute illness, hair loss was again reported in 45% of cases, besides mental depression in 50% and asthenia in 100%. The majority of patients (81%) were infected in Asia [80].

Persistence of dengue symptoms is known, but it has been little studied. In a prospective study of patients with persistent symptoms of dengue in Brazil, symptoms that persisted for more than 14 days were observed in 61 (54.0%) patients, and six (6.2%) of them had symptoms for 6 months or more. Of these, the authors found hair loss in 36.1% [81].

Finally, Hitani et al. reported on a Japanese traveler to Indonesia who developed long-lasting depression accompanied by alopecia after the classic symptoms of dengue fever such as fever, arthralgia, and maculopapular rash had resolved [82].

On the occasion of the epidemic of the dengue virus infection in Taiwan in 2014 and 2015, Wei et al. observed an abnormally high frequency of increased scalp hair shedding in infected individuals that they believed that they could not explain by telogen effluvium. Therefore, the authors explored the mechanism of hair loss caused by dengue virus infection. Since, human hair follicle dermal papilla cells (HFDPCs) are essential for hair follicle morphogenesis and cycling, the investigators established an in vitro dengue virus infection model in HFDPCs. On immunofluorescence analysis, HFDPCs that were susceptible to dengue virus infection responded to type 1 interferon treatment, and the cells showed antibody-dependent enhancement effect. The expression of the pro-inflammatory cytokines, interleukin-6, and tumor necrosis factor-alpha revealed an inflammatory response in dengue virus-infected HFDPCs. In particular, dengue virus infection impaired cell viability, and it activated caspase-associated cell death signaling in HFDPCs. The authors concluded that direct

infection with dengue virus causes inflammation and cell death in HFDPCs, which is involved in the mechanisms of hair loss after dengue virus infection [83]. In addition, the investigators found that long-term infection with dengue virus downregulated the expression of hair growth regulatory factors, such as Rip1, Wnt1, and Wnt4, providing the evidence that long-term infection with dengue virus in dermal fibroblasts and dermal papilla cells may be involved with the prolonged dengue virus infection-mediated hair loss of post-dengue fatigue syndrome [84].

However, direct evidence for viral replication in the human hair of a dengue victim is as yet outstanding.

There are no specific antiviral drugs for dengue. Treatment depends on the symptoms, and maintaining a proper fluid balance is particularly important. In those with severe dengue care should be provided in an area where there is access to an intensive care unit.

## 10.5 Chikungunya

Chikungunya is an infection caused by the chikungunya virus. The virus is a member of the genus *Alphavirus*, and family Togaviridae. Because it is transmitted by arthropods, namely, mosquitoes, it can also be referred to as an arbovirus.

Chikungunya is related to mosquitoes, their environments, and human behavior. The adaptation of mosquitoes to the changing climate of North Africa around 5000 years ago made them seek out environments where humans stored water. Human habitation and the mosquitoes' environments were then very closely connected. During periods of epidemics, humans are the reservoir of the virus. Because high amounts of virus are present in the blood in the beginning of acute infection, the virus can be spread from a viremic human to a mosquito and back to a human.

Three genotypes of this virus have been described, each with a distinct genotype and antigenic character: West African, East/Central/South African, and Asian genotypes [85]. The Asian lineage originated in 1952 and has subsequently split into two lineages: India (Indian Ocean Lineage) and Southeast Asian clades. During the years 2014 and 2015, the Region of the Americas underwent a devastating epidemic of chikungunya virus (CHIKV) of the Asian genotype, resulting in millions of affected individuals. Phylogenetic investigations have shown that there are two strains in Brazil, the Asian and East/Central/South African types and that the Asian strain arrived in the Caribbean most likely from Oceania in about March 2013 [86]. Global warming is one of the leading causes behind the range of movement of mosquitoes. Current decades have experienced a major change with the emergence of new viral infections worldwide [87].

In vitro, chikungunya virus is able to replicate in human epithelial and endothelial cells, primary fibroblasts, and monocyte-derived macrophages. Viral replication is highly cytopathic but susceptible to type 1 and type 2 interferon [88]. In vivo, in studies using living cells, chikungunya virus appears to replicate in fibroblasts, skeletal muscle progenitor cells, and myofibers [89–91]. The type 1 interferon response seems to play an important role in the host's response to chikungunya infection.

Upon infection with chikungunya, the host's fibroblasts produce type 1 alpha and beta interferon (IFN-α and IFN-β) [92]. In the chronic phase, it is suggested that viral persistence, lack of clearance of the antigen, or both contribute to joint pain. The inflammation response during both the acute and chronic phase of the disease results in part from interactions between the virus and monocytes and macrophages [93]. Chikungunya virus disease is associated with elevated serum levels of specific cytokines and chemokines that have been linked to more severe acute disease: interleukin-6 (IL-6), IL-1β, RANTES, monocyte chemoattractant protein 1 (MCP-1), monokine induced by gamma interferon (MIG), and interferon gamma-induced protein 10 (IP-10).

Around 85% of individual infected with the virus experience symptoms, typically beginning with a sudden high fever above 39 °C that is soon followed by severe muscle and joint pain. Pain usually affects multiple joints in the arms and legs and is symmetric. This first set of symptoms, called the acute phase of chikungunya, lasts around a week, after which most symptoms resolve spontaneously. However, occasionally the joint pain may last for months or years, termed the post-acute phase for symptoms lasting 3 weeks to 3 months, and the chronic stage for symptoms lasting longer than 3 months. The word "chikungunya" is believed to have been derived from a description in the Makonde language, meaning "that which bends up," of the contorted posture of people affected with the severe joint pain and arthritic symptoms associated with this disease [94].

The mucocutaneous manifestations of chikungunya disease were found more in males than females. Generalized erythematous maculopapular rash (53.5%) was the most common finding. Genital pustular rash with aphthae (4.4%), oral and intertriginous aphthae, red lunula, subungual hemorrhage, localized erythema of the ear pinnae, erythema, swelling, and eczematous changes over the pre-existing scars and striae (scar phenomenon) were other interesting findings. Various patterns of pigmentation (37.5%) were observed, including striking nose pigmentation in a large number of patients. There was flare-up of existing dermatoses like psoriasis [95].

In a case series of 67 patients with chikungunya fever, diffuse hair loss was observed in 20.9% [96].

The effect of chikungunya fever on pregnancy outcomes and its consequences for infants born to infected mothers at the peak of the epidemic wave in Latin America have been reviewed. Chikungunya represented a substantial risk for neonates born to symptomatic parturients during the chikungunya outbreak in the Americas region, with important clinical and public health implications. The observed vertical transmission rate ranged between 27.7% and 48.29%. The incidence of congenital disease was unrelated to the use of cesarean section or natural delivery. The case fatality rate at the only center that reported deaths was 5.3%. The most common clinical manifestations included fever, irritability, rash, hyperalgesia syndrome, diffuse limb edema, meningoencephalitis, and bullous dermatitis. Severe complications included meningoencephalitis, myocarditis, seizures, and acute respiratory failure. Leukocytosis with neutrophilia and normal or increased platelets was a common finding, and in those with signs of meningeal involvement, moderate lymphocytic pleocytosis with normal glucose and protein levels was typical [97].

The diagnosis of chikungunya is based on clinical, epidemiological, and laboratory findings. Laboratory criteria include a decreased lymphocyte count consistent with viremia. However, a definitive laboratory diagnosis can be accomplished through viral isolation, RT-PCR, or serological diagnosis, with the most important differential diagnoses being other mosquito-borne diseases, such as dengue or malaria. After the detection of Zika virus in Brazil in April 2015, it is now thought some chikungunya and dengue cases could in fact have been Zika virus cases or coinfections. Serological diagnosis uses an ELISA assay to measure chikungunya-specific IgM levels in the blood serum. Virus isolation provides the most definitive diagnosis but takes 1–2 weeks for completion and must be carried out in biosafety level III laboratories.

No specific treatment for chikungunya is available. Supportive care is the mainstay, and symptomatic treatment of fever and joint swelling includes the use of nonsteroidal anti-inflammatory drugs such as naproxen and nonaspirin analgesics such as paracetamol (acetaminophen) and fluids [98]. The likelihood of prolonged symptoms or chronic joint pain is increased with increased age and prior rheumatological disease [99, 100].

Because no approved vaccine exists, the most effective means of prevention are protection against contact with the disease-carrying mosquitoes and controlling mosquito populations by limiting their habitat [98].

## 10.6 Zika

Zika fever, also known as Zika virus disease or simply Zika, is an infectious disease caused by the Zika virus. Zika virus is a member of the virus family *Flaviviridae*. Zika virus shares a genus with the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. The virus was first isolated in Africa in 1947 [101]. Since the 1950s, it has been known to occur within a narrow equatorial belt from Africa to Asia. From 2007 to 2016, the virus spread eastward, across the Pacific Ocean to the Americas, leading to the 2015–2016 Zika virus epidemic. This led the World Health Organization to declare it a Public Health Emergency of International Concern in February 2016.

Most cases are asymptomatic or present with usually mild symptoms that can resemble dengue fever. Symptoms may include fever, red eyes, joint pain, headache, and a maculopapular rash. Symptoms generally last less than 7 days. It has not caused any reported deaths during the initial infection.

However, mother-to-child transmission during pregnancy can cause birth defects in the offspring. The full range of birth defects caused by infection during pregnancy is not known, but they appear to be common, with large-scale abnormalities seen in up to 42% of live births [102, 103]. The most common observed associations have been abnormalities with brain and eye development such as microcephaly and chorioretinal scarring. These abnormalities can lead to intellectual problems, seizures, vision problems, hearing problems, problems feeding, and slow development [104]. Zika virus infection is also a trigger of Guillain-Barré syndrome, neuropathy, and myelitis, particularly in adults and older children.

So far, no particular hair issues have been reported in association with Zika virus infection, whether in the social media or in the medical research literature.

Zika fever is mainly spread via the bite of daytime-active *Aedes* mosquitoes, such as *A. aegypti* and *Aedes albopictus* [105]. Zika virus replicates in the mosquito's midgut epithelial cells and then its salivary gland cells. After 5–10 days, the virus can be found in the mosquito's saliva. If the mosquito's saliva is inoculated into human skin, the virus can infect epidermal keratinocytes, skin fibroblasts in the skin, and the Langerhans cells. The pathogenesis of the virus is hypothesized to continue with a spread to lymph nodes and the bloodstream [106]. The viral protein numbered NS4A can lead to small head size (microcephaly) because it disrupts brain growth by hijacking a pathway which regulates growth of new neurons.

The virus can also be sexually transmitted and potentially spread by blood transfusions [107].

The recent increase in cases of microcephaly and other neurological disorders potentially associated with Zika virus infection has prompted an increase in demand for laboratory testing to detect Zika virus infection. Groups prioritized for diagnostic testing should be symptomatic individuals and asymptomatic pregnant women with possible exposure to Zika virus. Arthralgias and flu-like symptoms are common, although the majority (about 80%) of infected patients remain asymptomatic. Because of the nonspecific morbilliform morphology, travel history is important, and the differential diagnosis should also include dengue and chikungunya virus.

Diagnosis is by testing the blood, urine, or saliva for the presence of the virus's RNA when the person is sick or the blood for antibodies after symptoms are present more than a week. Testing via ELISA and PCR can be done within the first 7 days, or testing based on Zika-specific IgM antibodies and plaque-reduction neutralization tests can be done 4 or more days after disease onset.

Travel to an area where Zika is present is the main risk factor for the virus. Avoiding mosquito bites is a key aspect of Zika virus prevention. Unlike the malaria-carrying mosquitoes, *Aedes* is most active during the day. Barrier methods of prevention, such as mosquito nets, are less effective. The mosquitoes can survive in both indoor and outdoor environments. To increase protection, people are advised to:

- Use insect repellent. Insect repellents should contain one of the following: DEET (>10% concentration), picaridin, IR3535, oil of lemon eucalyptus (i.e., para-menthane-diol).
- Insect repellent is most effective when applied: after applying sunscreen, onto clothes as well as the body, for example, clothes treated with permethrin, under clothing. Always check the instructions for the particular brand of repellent or sunscreen for guidance on use.
- Wear long-sleeved garments and long pants.
- Place mosquito nets over beds (in some cases).
- Use window and door screens.
- Avoid areas with standing water, by emptying tanks or choosing to camp away from lakes or ponds.

A person who is infected with Zika should do everything possible to avoid being bitten by a mosquito for 3 weeks after symptoms appear, because the mosquito can pass the virus to the next person. This includes people who have returned from a trip with the disease. The person must also be careful to avoid unprotected sex, as this, too, can pass on the virus. The CDC recommend using condoms during and after traveling to regions affected by the virus.

A person who has had the Zika virus is normally protected and unlikely to have it again.

## 10.7 COVID-19

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by infection with a strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [108]. SARS-CoV-2 is a virus of the species severe acute respiratory syndrome-related coronavirus (SARSr-CoV), related to the SARS-CoV-1 virus that caused the 2002–2004 SARS outbreak [109]. It is of zoonotic origins and has close genetic similarity to bat coronaviruses, suggesting it emerged from a bat-borne virus [110, 111]. Research is ongoing as to whether SARS-CoV-2 came directly from bats or indirectly through any intermediate hosts.

The first known case was identified in Wuhan, China, in December 2019.The disease has since spread worldwide, leading to an ongoing pandemic. During the initial outbreak in Wuhan, the virus and disease were commonly referred to as "coronavirus" and "Wuhan coronavirus," with the disease sometimes called "Wuhan pneumonia" [112, 113]. In the past, many diseases have been named after geographical locations, such as the Spanish flu, Middle East respiratory syndrome, and Zika virus. However, in January 2020, the World Health Organization (WHO) recommended 2019-nCoV and 2019-nCoV acute respiratory disease as interim names for the virus and disease per 2015 guidance and international guidelines against using geographical locations or groups of people in disease and virus names to prevent social stigmatization. The official names COVID-19 and SARS-CoV-2 were issued by the WHO on 11 February 2020.

The virus primarily spreads between people through close contact and via aerosols and respiratory droplets that are exhaled when talking, breathing, or otherwise exhaling, as well as those produced from coughs or sneezes. It enters human cells by binding to angiotensin-converting enzyme 2 (ACE2), a membrane protein that regulates the renin-angiotensin system [114, 115] and is most abundant on the surface of type 2 alveolar cells of the lungs [116]. The virus uses a special surface glycoprotein called a "spike" to connect to the ACE2 receptor and enter the host cell [117].

The effect of the virus on ACE2 cell surfaces leads to leukocytic infiltration, increased blood vessel permeability, alveolar wall permeability, as well as decreased secretion of lung surfactants. These effects cause the majority of the respiratory symptoms.

However, the aggravation of local inflammation causes a cytokine storm eventually leading to a systemic inflammatory response syndrome. Although SARS-CoV-2 has a tropism for ACE2-expressing epithelial cells of the respiratory tract, people with severe COVID-19 have symptoms of systemic hyperinflammation. Clinical laboratory findings of elevated IL-2, IL-7, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP 1 alpha), and tumor necrosis factor (TNF-α) indicative of cytokine release syndrome (CRS) suggest an underlying immunopathology [118].

The severity of the inflammation can be attributed to the severity of what is known as the cytokine storm [119]. Levels of interleukin-1B, interferon gamma, interferon-inducible protein 10, and monocyte chemoattractant protein 1 were all associated with COVID-19 disease severity. Treatment has been proposed to combat the cytokine storm as it remains to be one of the leading causes of morbidity and mortality in COVID-19 disease [120].

A cytokine storm is due to an acute hyperinflammatory response that is responsible for clinical illness in an array of diseases, but in COVID-19, it is related to worse prognosis and increased fatality. The storm causes acute respiratory distress syndrome, blood-clotting events such as strokes, myocardial infarction, encephalitis, acute kidney injury, and vasculitis. The production of IL-1, IL-2, IL-6, TNF-alpha, and interferon gamma, all crucial components of normal immune responses, inadvertently become the causes of a cytokine storm. The cells of the central nervous system, microglia, neurons, and astrocytes, are also involved in the release of pro-inflammatory cytokines affecting the nervous system, and effects of cytokine storms toward the CNS are not uncommon [121].

After the initial outbreak of COVID-19, misinformation and disinformation regarding the origin, scale, prevention, treatment, and other aspects of the disease rapidly spread online.

Oppositely, international research on vaccines and medicines in COVID-19 is underway by government organizations, academic groups, and industry researchers [122, 123]. There has been a great deal of COVID-19 research, involving accelerated research processes and publishing shortcuts to meet the global demand [124]. As of December 2020, hundreds of clinical trials have been undertaken, with research happening on every continent [125].

Repurposed antiviral drugs make up most of the research into COVID-19 treatments. Other candidates in trials include vasodilators, corticosteroids, immune therapies, lipoic acid, bevacizumab, and recombinant angiotensin-converting enzyme 2. In March 2020, the WHO initiated the Solidarity trial to assess the treatment effects of some promising drugs: an experimental drug called remdesivir, antimalarial drugs chloroquine and hydroxychloroquine, two anti-HIV drugs, lopinavir/ritonavir, and interferon-beta. In November 2020, the US Food and Drug Administration (FDA) issued an emergency use authorization for the investigational monoclonal antibody therapy with bamlanivimab and etesevimab.

However, violations of medical ethics have also been committed. A clinical trial with the anti-androgen proxalutamide as an experimental drug as a cure for

COVID-19 in Brazil "disrespected almost the entire protocol" and may have contributed to the deaths of as many as 200 people, said the National Health Council, which oversees clinical research in Brazil. Some of those people were not adequately informed of the risks they were undertaking in the trial, and some did not know that they were taking part in one, it said. To test proxalutamide's possible use against COVID-19, the initiator of the study, an endocrinologist and clinical director for Applied Biology, oversaw its prescription to a man exhibiting severe COVID-19 symptoms. The report, which stated that after 24 h the patient showed "marked improvement of symptoms and markers of disease severity," was published in BMJ Case Reports on 26 February 2021 [126]. In February 2021, the principal investigator oversaw the drug's administration to 645 patients with COVID-19 at nine hospitals in Brazil's Amazonas region as it was hit with a severe wave of infections. Altogether, 317 patients received proxalutamide and 328 a placebo. The treatment was prescribed by doctors as if it were an established medical treatment, although it was approved only for clinical studies. The number of people given the drug was also larger than the number approved for the trial. The trial, which was reported on the preprint server medRxiv7 and not peer-reviewed, found that the 14-day recovery rate was 81.4% with proxalutamide and 35.7% with placebo (recovery ratio 2.28 (95% confidence interval (CI) 1.95 to 2.66); $P < 0.001$). At 28 days the all-cause mortality rate was reported to be 11.0% with proxalutamide and 49.4% with placebo (hazard ratio 0.16 (0.11 to 0.24)). Around 200 people died in the trial, mostly in the control group. "The reported results would be a miracle—if they were true," said epidemiologist Jesem Orellana who closely followed the effects of the gamma variant of COVID-19 on the Amazon region at Brazil's leading public health institute, Fiocruz. "Everything about this trial is suspicious and anything but clinical and randomised." If the published results were true, the trial should have been stopped and unblinded to ensure better treatment of the control group. If they were not, 200 people were subjected to die in research that has no scientific value at all. The consent form given to patients omitted key sections that guarantee the rights of research participants and explain the trial, said the National Health Council. "In the entire history of the National Health Council, there has never been such disrespect for ethical standards and research participants in the country," it said in a statement. Arthur Caplan, head of New York University's Division of Medical Ethics, told the British Medical Journal that if the alleged practices were true, the trial would be "an ethical cesspool of violations, from consent and design to overoptimistic reporting of results and hiding deaths." Ultimately, the publication of the respective study outcomes [127] was retracted [128].

Falsified results have been dangerous during the COVID-19 pandemic, Caplan said, as they have encouraged the popular use of unproven and sometimes dangerous drugs based on false claims [129].

Indeed, the novel viral pandemic COVID-19 has sparked uncertainties and controversies worldwide as to its origin, epidemiology, and natural course. In this situation, the medical disciplines have strived to contribute to a better understanding of the disease, some with a sound and sober approach, and the best available evidence gained from the scientific method of observation and statistics and others with a

propensity for publicity and sensationalism, further igniting the emotional overtones associated with the pandemic. Since the outbreak of the COVID-19 pandemic, scholars have explored the bioethics, normative economics, and political theories of healthcare policies related to the public health crisis [130].

### 10.7.1 Androgenetic Alopecia in COVID-19

The study of the cutaneous manifestations of COVID-19 has evolved with the hope that they may be useful as markers for the disease, for prognostication, and for further insights into the pathogenesis of the disease manifestations [131]. With regard to the hair, clinicopathological correlations have so far remained hypothetic.

A group of investigators originally hypothesized an association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectiveness and the androgen pathway, which presumably results in an androgen-mediated SARS-CoV-2 vulnerability explaining the disproportioned mortality rate of males from COVID-19 [132]. Since then, the same league of authors has provided within half a year a total number of eight scientific publications aiming at corroborating their hypothesis of an association of male androgenetic alopecia with more severe symptoms of COVID-19 [133–139], with the corresponding reverberation in the public media. In fact, Science Integrity Digest (www.scienceintegritydigest.com) drew attention to the practice of some groups of authors cranking up the number of papers on their resumes. In one of the journals indicted in this practice, allegedly, the Editor-in-Chief and associates, many from the editorial board with invited co-authorships of reputed dermatologists involved in hair, publish dozens of papers, frequently in form of letters to the editor, on COVID-19, with some peer reviews taking less than 24 h, and then cite themselves in other publications. Finally, despite the dermatologic nature of the respective journal and the corresponding background of the authors, some of these papers have nothing to do with dermatology [140]. Ultimately, they pressed ahead with the proposition of the eponym the "Gabrin sign" to visually identify patients at higher risk of COVID-19 based on the presence of androgenetic alopecia, since Dr. Frank Gabrin was the first American emergency room doctor to die from COVID-19 and also had androgenetic alopecia [139]. And yet, their respective studies have been scrutinized by others with regard to the accuracy and validity of the statistics and have not been found to be conclusive [141, 142]. We do not support establishing the "Gabrin sign" as an eponym, before the observation as it relates to its proposed eponym is confirmed by at least one other party of investigators. Moreover, Dr. Frank Gabrin is rather to be remembered for his selfless and courageous personality [143] during his service at the front lines of the pandemic than for the stigma of his alopecia [144]. Even though we value the use of eponyms in dermatologic nomenclature for the background knowledge they convey, we do so solely under the terms of conclusive evidence and absence of a derogative connotation [145] (Fig. 10.15).

Based on their speculations, the respective group of investigators further suggested that anti-androgen treatment could have a therapeutic benefit, while others

**Fig. 10.15** Satire. Some authors consider male androgenetic alopecia to be a prognostic factor for severe COVID-19 with respiratory distress in men ([139], comment in [144])

caution against the uncritical use of these agents, as they may disrupt androgen metabolism in the lungs which could in fact aggravate respiratory disease [146]. Ultimately, others [147] did not find a postulated protective effect of androgen deprivation therapy in a study of patients aged >70 years with metastatic prostate cancer, as others did not, and in fact discouraged compassionate use of drugs that suppress pituitary gonadotropin secretion or inhibit androgen synthesis or androgen receptor in an attempt to decrease SARS-CoV-2 infection risk or to alleviate the course of COVID-19 [148].

Moreover, alternative molecular mechanisms for sex bias differences in COVID-19 mortality have been postulated [149], specifically gender-based differences in the host immune response to coronaviruses which have just begun to be unraveled, such as loss-of-function variants of X-chromosomal TLR7 associated with impaired type 1 and type 2 IFN responses [150].

With reference to the original work on androgenetic alopecia and COVID-19 severity, a group of Brazilian investigators [151] aimed at evaluating the hair condition in relation to COVID-19 based on a questionnaire-based population survey. The authors analyzed demographics, comorbidities, hair color, amount of hair in relation to COVID-19 status, and severity outcomes. Obviously, they found that the prevalence of grey hair and baldness correlated with age, and, as expected, that disease severity was associated with age and particular comorbidities of the

participants. Sex, age, ethnicity, comorbidities, and their complex interdependencies in relation to COVID-19 call for a multivariate regression analysis, which the authors do not provide to support their claim that besides androgenetic alopecia, as formerly proposed, grey hair may represent yet another independent risk factor for disease severity.

In the past, various dermatologic conditions have been investigated as cutaneous markers for elevated mortality risk. Among these have been those related to cardiovascular disease, such as the horizontal ear lobe crease, high breast hair density, precocious greying, and alopecia. Despite an impressive number of data on this topic, on close assessment, many of the studies also proved to be marred by methodical errors [152].

### 10.7.2 Post-COVID-19 Effluvium

So far, only postinfectious effluvium (Fig. 10.16a–c) has been reliably observed in a causal association with COVID-19 severity. Originally, only single-case reports of either dystrophic anagen or telogen effluvium in association with COVID-19 exist, though the alleged anagen effluvium was neither confirmed by means of light microscopic examination of a hair pull nor of a hair pluck (trichogram) [153]. In the reported case of telogen effluvium, a trichogram was consistent with the diagnosis

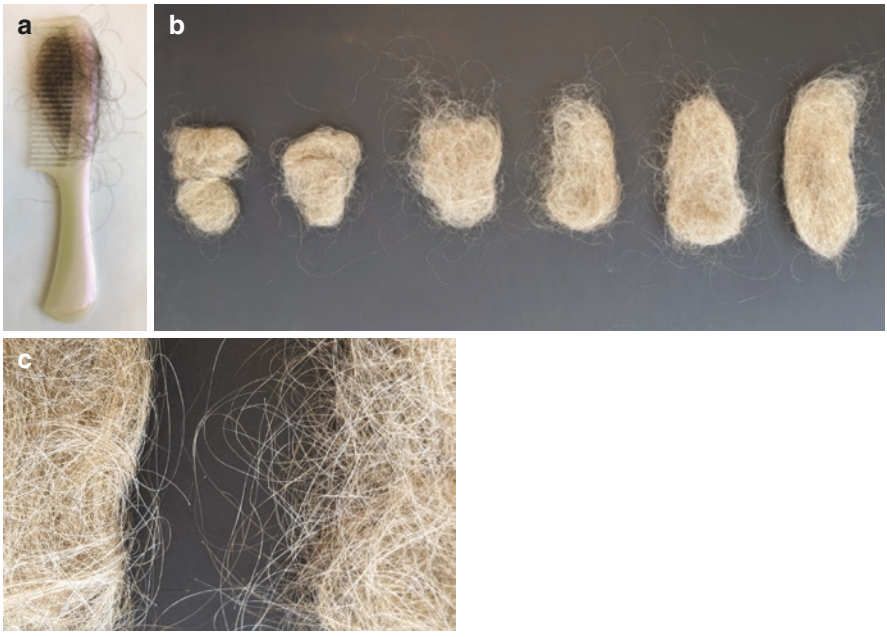


**Fig. 10.16** (**a–c**) Post-COVID-19 effluvium: (**a**) comb with shed hairs, (**b**) balls of daily shed hairs, (**c**) consisting of telogen hairs

[154]. We published our observations on ten patients with confirmed SARS-CoV-2 infection seen in the ambulatory setting of a hair consultation clinic. The onset and acuity of hair loss following COVID-19 depended on the clinical severity of the disease and fever. There was complete recovery of hair within 3–6 months (Fig. 10.17a–c). We did not identify any risk pattern for severity relating to the pre-existing condition of the hair, specifically alopecia or grey hair. All patients had pre-existent androgenetic alopecia and recovered from COVID-19 within 1 day to 3 weeks (mean: 10 + 6 days SD) [155]. On the basis of our observations, we attributed the hair loss to the multisystemic inflammatory and febrile disease process and did not find an association of presence of androgenetic alopecia with disease severity.

As yet, evidence has not been provided for a pathogenic inflammatory reaction at the level of the hair follicle, for COVID-19-associated microthrombotic lesions in the scalp vasculature, or for a direct infection of the hair follicle with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulting in inflammation and cell death, as has been demonstrated in dengue hemorrhagic fever [83, 84].

Moreover, considering the rich anastomosis of the scalp vasculature, it is not likely that scalp microthrombi should affect the hair, and if so, this would result in scalp ulceration from avascular necrosis as exemplified in the case of ulcerating temporal arteritis with blindness [156].

Trichodynia has been alleged to be associated with COVID-19 [157]. In our experience, this is neither the case, nor is the respective terminology appropriate for the condition of a symptomatic scalp in a febrile illness. Trichodynia refers to the painful sensation of the scalp related to the complaint of hair loss. Originally suggested to be distinguishing for telogen effluvium and related to hair loss activity and follicular inflammation, further studies have found trichodynia to be common in androgenetic alopecia as well and coexisting with psychopathologic findings. The respective studies failed to demonstrate correlations between trichodynia and quantifiable hair loss activity and histopathologic evidence for follicular inflammation. A symptomatic scalp is a frequent condition in various specific dermatological conditions of the scalp. By definition of exclusion, we are not dealing with trichodynia in these cases [158].

Finally, other authors have related a worsening of telogen effluvium in women during the pandemic to the impact of the psychosocial stress inflicted by the national quarantine imposed on the people by the government [159]. The respective reiterations in the social media have been melodramatic and out of proportion. In fact, it is a common experience among dermatologists that many of their patients have psychological overlays to their chief complaints. Psychophysiological disorders is the term used for psychocutaneous cases in which a particular dermatologic condition is exacerbated by emotional stress. Typical examples are hyperhidrosis, atopic dermatitis, psoriasis, and seborrheic dermatitis. In each, one comes across two types of patients: those who experience a close chronologic association between stressful experiences and exacerbation of their dermatologic condition and those for whom the emotional state seems not to influence the natural course of their disease. These two groups are referred to as “stress responders” and “non-stress responders,” respectively. The relative proportion of stress responders versus non-stress

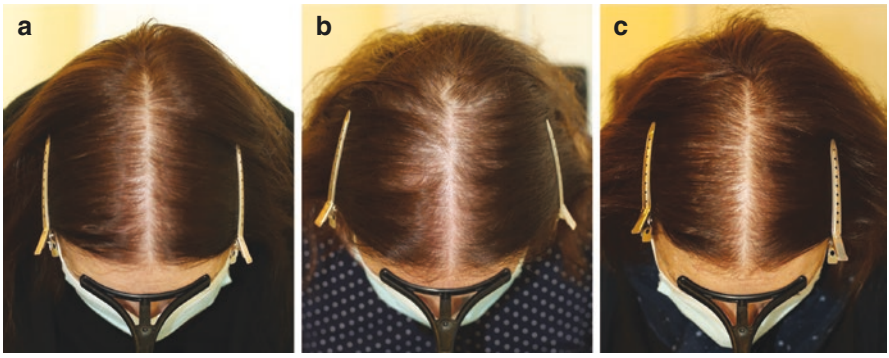


**Fig. 10.17** (**a**–**c**) Post-COVID-19 effluvium: (**b**) hair loss within 3 months and (**c**) recovery within 6 months

responders varies among the different psychophysiological conditions. A study involving a large number of subjects from the Harvard healthcare system in Boston, Massachusetts, determined the proportion with emotional trigger to be 100% for hyperhidrosis, 70% for atopic dermatitis, 62% for psoriasis, and 41% for seborrheic dermatitis [160]. The respective figures have so far not been established for telogen effluvium, notwithstanding the evidence of perceived stress inhibiting hair growth in murine stress models in vivo [161]. Ultimately, the presence of emotional stress is not indisputable proof of its having incited the patient's hair loss. The relationship may also be the inverse. The differential diagnosis of overvalued ideas is particularly challenging, since there is a considerable overlap between hair loss and psychological issues. Patients with hair loss have lower self-confidence, higher depression scores, greater introversion, as well as higher neuroticism [162].

In conclusion, further in-depth studies are warranted to establish whether the COVID-19-associated hair loss is due exclusively to the systemic inflammation with fever or whether the inflammation and/or SARS-CoV-2 may also target the hair follicle, especially in case of early onset hair loss in clumps. So far, the subject of psychogenic hair loss has been more mystifying than enlightening and a popular object of dramatization in the social media.

### 10.7.3 Long COVID-19

Long COVID is a condition characterized by long-term health problems persisting or appearing after the typical recovery period of COVID-19. Although studies into long COVID are under way, as of May 2022, there is no consensus on the definition of the term.

The most commonly reported symptoms of long COVID are fatigue and memory problems [163]. Many other symptoms have also been reported, including malaise, headaches, shortness of breath, anosmia (loss of smell), parosmia (distorted smell), muscle weakness, low-grade fever, and cognitive dysfunction. Overall, it is considered by default to be a diagnosis of exclusion [164].

It can be difficult to determine whether an individual's set of ongoing symptoms represents a normal, prolonged convalescence, or extended long COVID. One rule of thumb is that long COVID represents symptoms that have been present for longer than 2 months, though there is no reason to believe that this choice of cutoff is specific to infection with the SARS-CoV-2 virus [165].

The World Health Organization (WHO) established a clinical case definition [166]: post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include, but are not limited to, fatigue, shortness of breath, and cognitive dysfunction and generally have an impact on everyday functioning. Symptoms might be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms might also fluctuate or relapse over time.

The (National Institutes of Health) NIH listed long COVID symptoms of fatigue, shortness of breath, brain fog, sleep disorders, intermittent fevers, gastrointestinal symptoms, anxiety, and depression.

It is currently unknown why most people recover fully within 2–3 weeks and others experience symptoms for weeks or months longer [167]. The exact processes that cause long COVID remain uncertain, and a number of mechanisms have been suggested. In October 2020, a review by the United Kingdom's National Institute for Health and Care Research hypothesized that ongoing long COVID symptoms may be due to four syndromes [168]:

- Permanent damage to the lungs and heart
- Post-intensive care syndrome
- Post-viral fatigue, sometimes regarded as the same as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
- Continuing COVID-19 symptoms

Other situations that might cause new and ongoing symptoms to include are [167, 169–172]:

- The virus being present for a longer time than usual, due to an ineffective immune response
- Reinfection (e.g., with another strain of the virus)
- Damage caused by inflammation and a strong immune response to the infection
- Post-traumatic stress or other mental sequelae, especially in people who had previously experienced anxiety, depression, insomnia, or other mental health problems
- Inhibited oxygen exchange as a result of persistent circulating blood plasma microclots
- Development of various autoantibodies after infection

A March 2021 review article cited the following pathophysiological processes as the predominant causes of long COVID [173]:

- Direct toxicity in virus-infected tissue, especially the lungs
- Ongoing inflammation due to postinfection immune system dysregulation
- Vascular injury and ischemia caused by virus induced hypercoagulability and thrombotic events
- Impaired regulation of the renin-angiotensin system related to the effect of SARS-CoV-2 on ACE2-containing tissue

One study provides some observational evidence of compositional alterations of gut microbiome in patients with long-term complications of COVID-19. The authors propose that further studies should investigate whether microbiota modulation can facilitate timely recovery from post-acute COVID-19 syndrome. Moreover, the investigators propose that microbiome-based profiling might be used as a tool in early risk stratification for occurrence of post-acute COVID-19 syndrome [174].

Several risk factors have been found for long COVID:

- Gender—Women are more likely to develop long COVID than men [163]. Some research suggests this is due primarily to hormonal differences [175], while other research points to other factors, including chromosomal genetics, sex-dependent differences in immune system behavior; non-biological factors may also be relevant [165].
- Age, with older people more at risk [163, 176].
- Obesity [163].
- Asthma [163].
- Depression or anxiety [176].
- Post-traumatic stress [177].
- The number of symptoms during acute COVID [163].

Xenon magnetic resonance imaging (MRI) is being used to study long COVID, because it provides patients and physicians with explanations for previously unexplained observations. Xenon MRI can measure gas exchange and provide information on how much air is taken up by a patient's bloodstream, which is being researched in long-haul COVID patients [178]. Xenon MRI can quantify three components of lung function: ventilation, barrier tissue uptake and gas exchange. Xenon-129 is soluble in pulmonary tissue, which allows the evaluation of lung functions such as perfusion and gas exchange (an advantage over helium). Ventilation measures how the air is distributed in the lung and can provide the locations of potentially compromised lung areas if no xenon reaches those areas. Barrier tissue uptake and gas exchange measure how much air diffuses across the

alveolar-capillary membrane. Xenon MRI helps determine how well air is taken in by the lungs, absorbed into lung tissue, and taken up by the blood.

As of May 2022, there are no established pharmaceutical treatments for long COVID. There are however trials in progress for possible treatments [179]. Management of long COVID depends on symptoms, with current guidelines recommending multidisciplinary rehabilitation to improve symptoms and quality of life. Rest, planning, and prioritizing are advised for people with fatigue. People who suffer from post-exertional system exacerbation may benefit from activity management with pacing [180]. Patients should be routinely screened for mental health conditions, such as post-traumatic stress, which has been associated with fatigue severity [177].

It is of note that some people experiencing long COVID have formed groups on social media sites. In many of these groups, individuals express frustration and their sense that their problems have been dismissed by medical professionals, a situation reminiscent of the post-finasteride syndrome.

In a systematic review and meta-analysis of long-term effects of COVID-19 [181], the investigators identified more than 50 conditions that persisted, sequelae, and other medical complications with a minimum of 100 patients. For effects reported in two or more studies, meta-analyses using a random-effects model were performed using the MetaXL software to estimate the pooled prevalence with 95% CI. PRISMA guidelines were followed. A total of 18,251 publications were identified, of which 15 met the inclusion criteria. The prevalence of 55 long-term effects was estimated, 21 meta-analyses were performed, and 47,910 patients were included (age 17–87 years). The included studies defined long-COVID as ranging from 14 to 110 days post-viral infection. It was estimated that 80% of the infected patients with SARS-CoV-2 developed one or more long-term symptoms. The five most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%).

Limitations of this systematic review and meta-analyses include the small sample size for some outcomes, making it difficult to generalize these results to the general population, the variation in the definition of some outcomes and markers, and the possibility of bias. For example, several studies that used a self-reported questionnaire could result in reporting bias. In addition, the studies were very heterogeneous, mainly due to the follow-up time references and the mixture of patients who had moderate and severe COVID-19.

Hair, in particular, could be considered as telogen effluvium, defined by diffuse hair loss after an important systemic stressor or infection. In a total sample size of 658, 178 cases of hair loss were identified in 2 studies [182, 183]. It is usually a self-limiting condition that lasts approximately 3 months following febrile COVID-19 infection [155]. As such, the WHO clinical case definition of post-COVID fails to take the pathodynamic chronology of telogen effluvium into consideration, which occurs 3 months following the inciting event to last for further 3 months until recovery. In case of persistent alopecia, untreated androgenetic alopecia is to be taken into consideration and treated accordingly, typically with minoxidil. Nevertheless, COVID-19 induced hair loss in general may cause emotional

distress, though HRQoL has been observed to be quite passable, as most patients who had a professional activity before the infection went back to work [182]. Usually, patient education and reassurance are sufficient.

### 10.7.4 Post-COVID-19 Vaccination Effluvium

Since the COVID-19 pandemic has developed to become a global emergency, it became clear that a vaccine would be necessary to control the situation, and several vaccines have become available, including the mRNA vaccines from Moderna, Pfizer, and Astra Zeneca [184]. With time, a number of adverse events have become apparent in association with the vaccines. Several case series and registry reviews have documented COVID-19 vaccine-related adverse events since the vaccines have come into widespread use. McMahon et al. reported a registry-based study of 414 cases of cutaneous reactions after Moderna and Pfizer COVID-19 vaccination. These included local reactions, urticarial and morbilliform eruptions, and less commonly pernio/chilblains, cosmetic filler reactions, herpes zoster, herpes simplex flares, and pityriasis rosea-like rashes [185]. Reactions related to the hair have originally not been reported.

We observed 16 patients who developed a similar pattern of postfebrile hair loss following the vaccine as following febrile COVID-19. Again, the onset and acuity of the hair shedding were associated with the severity of the vaccination reaction and fever. All patients had a reduced density of hair and a positive hair pull test. One patient, in whom a trichogram was performed, showed a mixed telogen and dystrophic anagen effluvium.

Again, many factors can lead to a pathologically increased hair loss. Whatever the cause, the follicle tends to behave in a similar way. Dystrophic anagen effluvium is an early onset hair loss that results from the shedding of large numbers of hairs from the anagen phase of growth. It is a major characteristic of anagen that the epithelial hair follicle compartment undergoes proliferation, with the hair matrix keratinocytes showing the highest proliferative activity in building up the hair shaft. The common pathogenesis which unites the different etiologies of dystrophic anagen effluvium is a direct insult to the rapidly dividing bulb matrix cells. Telogen effluvium results from late onset increased shedding of hairs from the telogen phase of the hair cycle and represents by far the commonest cause of hair loss. An increase in the percentage of follicles in telogen >20% leads to increased shedding of hairs in telogen. This can either be due to synchronization phenomena of hair cycling, with shedding of hairs in the hundreds in telogen effluvium, or to a decrease of anagen phase duration in androgenetic alopecia with its sex-typical patterns of alopecia, variable shedding of hair, and increasing diversity of hair shaft diameters.

Postfebrile effluvium has traditionally been categorized as telogen effluvium, yet, it may present with different pathomechanisms and clinical patterns. Evidence exists that the hair follicle may respond to infection with both shedding patterns, dystrophic anagen effluvium, and telogen effluvium depending on the type and

intensity of the insult. Accordingly, the hair may fall out very quickly in clumps or gradually.

The immune system is understood to be involved in both the regulation of hair follicle cycling, as well as in the pathogenesis of some immune-mediated hair pathologies. Immunomodulatory cytokines not only act as mediators of immunity and inflammation but also regulate cell proliferation and differentiation and, as such, play a role in hair growth and shedding. Philpott et al. have investigated the effects of ILs and TNF on hair follicle growth in vitro and found these to be potent inhibitors of hair follicle growth in a dose-dependent manner [3]. In addition, IFN-gamma has been shown to be a potent inducer of catagen-like changes in cultured human anagen hair follicles [4].

The cytokine profiles generated by COVID-19 vaccination, particularly in those with severe vaccine reactions with fever, are yet to be established. However, the observation and analogies of postfebrile effluvium following COVID-19 vaccination are in favor of COVID-19-related effluvium being due to the systemic inflammatory reaction rather than to a direct infection of the hair follicle with SARS-CoV-2, as has been shown in dengue hemorrhagic fever [83].

### 10.7.5 Alopecia Areata

Two further putative cutaneous adverse events following COVID-19 vaccination have been recurrence of alopecia areata [186–188] and new-onset vitiligo [189, 190].

Alopecia areata is characterized by patchy hair loss, while vitiligo is caused by the destruction of melanocytes resulting in the appearance of white patches on any part of the body. The immune cell populations (T cells) and cytokines (interferon-γ) that drive each disease are similar, and alopecia areata and vitiligo share some genetic risk factors, suggesting a common immune pathogenesis [191].

The vaccines have in common the property of inducing the immune system with antibodies production and T helper cell 1 (Th1) activation and release of pro-inflammatory cytokines. Thus, at least in genetically predisposed individuals, the interaction between the vaccines and the immune system may enhance other autoimmune mechanisms.

While a billion of individuals have so far been vaccinated for COVID-19, the respective authors argued that the temporal association and a lack of a more plausible explanation seem to indicate that the vaccine may have been at least contributory, despite the paucity of respective case reports. Given the potent immune response produced by the vaccine, one can speculate whether other inadvertent reactions of a vaccinated individual's immune system may occur.

We observed five female patients between 39 and 56 years old (median age of 45.2) with a history of alopecia totalis or widespread alopecia areata with total hair regrowth and stable remission under subcutaneous methotrexate or intralesional triamcinolone acetonide during the months preceding the vaccination. Rapid and widespread hair loss occurred 1–8 weeks after BNT162b2 vaccine (Pfizer) or mRNA-1273 vaccine (Moderna), in two cases total loss of hair in terms of alopecia

universalis and subuniversalis, was observed (Fig. 10.18a–c). Interestingly, a third booster vaccination of either Pfizer or Moderna vaccine led to an earlier onset or to an aggravation of the recurrence in four cases within 1–8 weeks. Also, we observed an otherwise healthy 53-year-old male patient who presented with new-onset sharply demarcated white macular patches distributed symmetrically on the distal portion of his fingers (Fig. 10.19) 4 weeks after receiving the second dose of

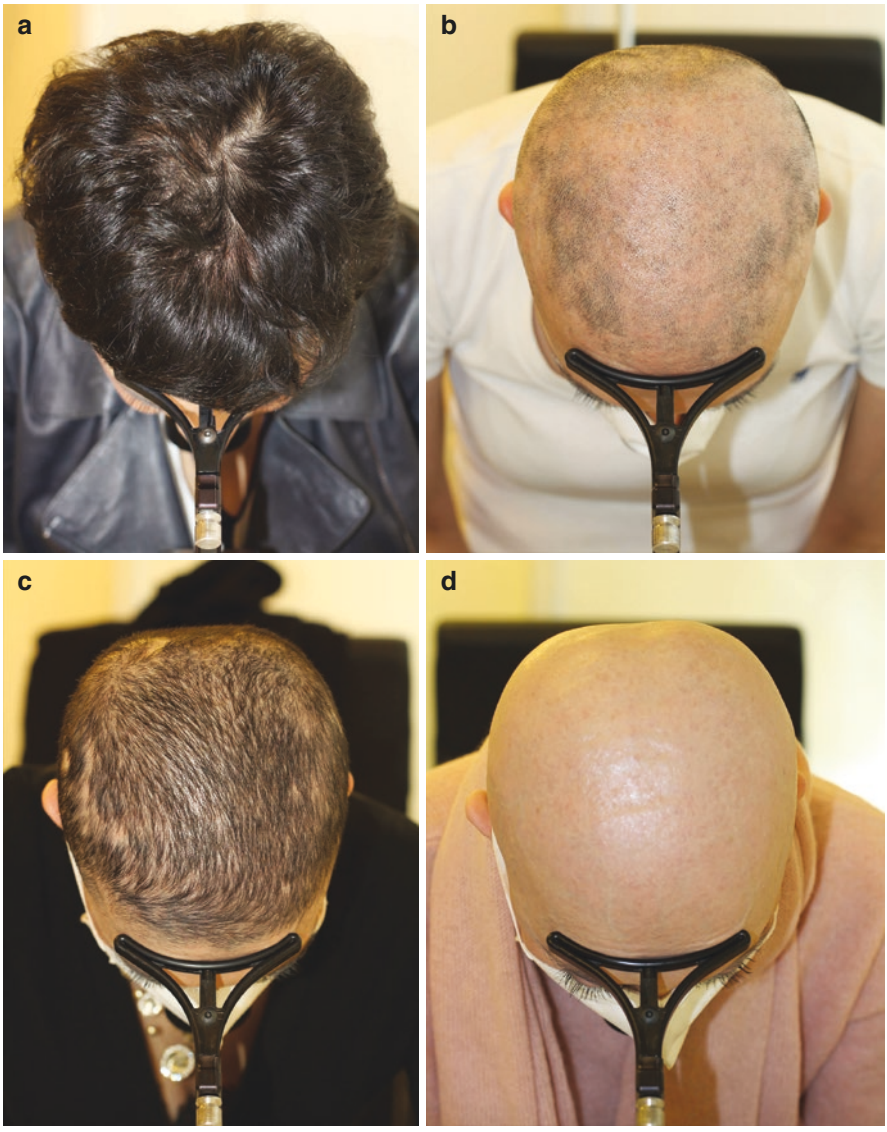


**Fig. 10.18** (**a**–**d**) Recurrence of alopecia areata (**a**) before and (**b**) after the first and (**c**) before and (**d**) after the second COVID-19 vaccination

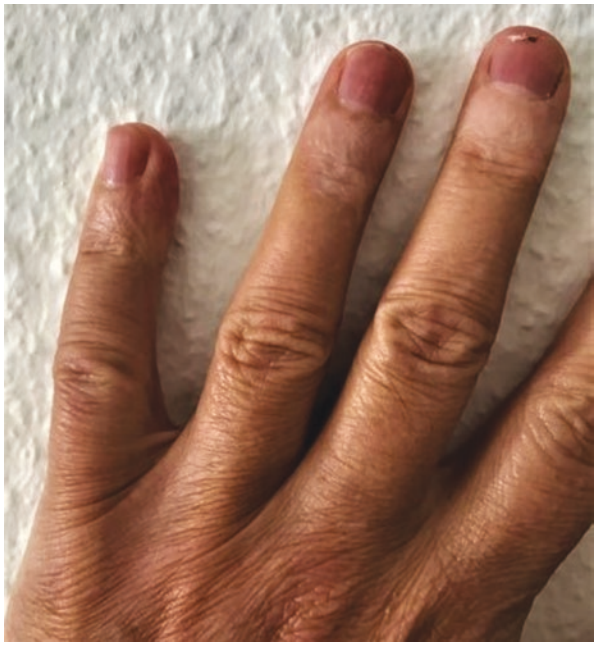

**Fig. 10.19** Vitiligo associated with COVID-19 vaccination

mRNA-1273 (Moderna) COVID-19 vaccine. The lesions were consistent with vitiligo, and Wood's light examination typically highlighted the areas of depigmentation. There were no further vitiligo lesions seen at other body sites, and there was no personal or family history of vitiligo and of exposures for chemical-induced vitiligo, other pigmentary disorders, or autoimmune disease. The patient was diagnosed with new-onset acral vitiligo in temporal association with COVID-19 vaccination.

While some AEs of COVID-19 vaccines are temporary and not life-threatening, such as the local reactions and cutaneous eruptions, as formerly reported, others may be more problematic. Vitiligo is a potentially disfiguring and alopecia totalis particularly distressing skin disorder, and both are difficult to treat. Certainly, the small number of cases is not sufficient to draw any conclusion. However, new-onset vitiligo following COVID-19 vaccine may be underreported due to negligence. Whether recurrence of alopecia areata and new-onset vitiligo occurred fortuitously or in causal relationship with the vaccine remains to be further elucidated in respective large-scale studies.

Whereas some authors consider that the risks of the vaccination are far outweighed by the benefits conferred, both to the vaccinated individual and to society at large [186, 190], we believe that it lies in the responsibility of the physician to remain alert and counsel patients regarding the spectrum of possible immune-mediated vaccine-related adverse events. Admittedly, immune-mediated side effects remain a rare event; thus the benefits of COVID-19 vaccines may outweigh the risk of disease flares in a patient population. However, the individual at hand should be informed and assisted in weighing the risks of alopecia areata and vitiligo against

the risk of COVID-19 infection from exposition or comorbidity for decision making. Ultimately, experts have pointed out that the specific risks of the immune response produced by the COVID-19 vaccine should be disclosed not only to the research subjects being recruited for vaccine trials but also in patients after vaccine approval, in order to meet the medical ethics standard of patient comprehension for informed consent [192].

## 10.8 Impact of Climate Change on the Communicable Diseases

Climate change is one of the defining issues for human well-being in the twenty-first century. As several dermatological diseases have a high sensitivity to climate and ecologic change, dermatologists will have an increasingly important role in public health affairs [193].

Anthropogenic global climate change is a well-documented phenomenon that has led to average global temperatures climbing to approximately 1 °C above preindustrial (1850–1900) levels, with even higher regional deviations in some areas and significantly increased average warming in densely populated urban centers. In 2018, the United Nations Intergovernmental Panel on Climate Change set a threshold of 1.5 °C of average warming (above the preindustrial baseline), beyond which our planet will become significantly less hospitable to human life. However, adverse human health impacts are already occurring.

Climate change, exemplified by higher average global temperatures resulting in more frequent extreme weather events, has the potential to significantly impact human migration patterns and health. The consequences of environmental catastrophes further destabilize regions with pre-existing states of conflict due to social, political, and/or economic unrest. Migrants may carry diseases from their place of origin to their destinations and once there may be susceptible to diseases in which they had not been previously exposed to. Skin diseases are among the most commonly observed health conditions observed in migrant populations. Skin diseases associated with human migration fall into three major categories: (a) communicable diseases, (b) noncommunicable diseases, and (c) environmentally mediated diseases [194].

Climate variables directly influence the survival and reproduction of infectious microorganisms, their vectors, and their animal reservoirs. Due to sustained warmer temperatures at higher latitudes, climate change has expanded the geographic range of certain pathogenic microbes. More frequent climate change-related extreme weather events create circumstances where existing infectious microorganisms flourish and novel infections emerge. Climate instability is linked to increased human migration, which disrupts healthcare infrastructure as well as the habitats of microbes, vectors, and animal reservoirs and leads to widespread poverty and overcrowding.

Several representative climate-sensitive infectious diseases were identified in each of the following categories: vector-borne infectious diseases, infectious

diseases associated with extreme weather events, and infectious diseases linked to human migration [195].

Although globalization, travel, and trade are also important to changing disease and vector patterns, climate change creates favorable habitats and expanded access to immunologically naïve hosts. Endemic North American illnesses such as Lyme disease, leishmaniasis, and dimorphic fungal infections have recently expanded the geographic areas of risk. Chikungunya and dengue are now reported within the southern United States, with Zika on the horizon [196].

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# Diagnostic Techniques

# 11

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## Contents



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Diagnosis is the identification of the nature and cause of a certain phenomenon. Diagnosis is used in many different disciplines, with variations in the use of logic, analytics, and experience, to determine cause and effect.

Medical diagnosis is the process of determining which disease or condition explains a person's symptoms and signs. It is most often referred to as diagnosis with the medical context being implicit. The information required for diagnosis is typically collected from a history and physical examination of the person seeking medical care. Often, one or more diagnostic procedures, such as medical tests, are also done during the process.

Diagnosis is often challenging, because many signs and symptoms are nonspecific. For example, erythema, by itself, is a sign of many disorders and thus does not tell the healthcare professional what is wrong. Therefore, differential diagnosis in which several possible explanations are compared and contrasted must be performed. This involves the correlation of various pieces of information followed by the recognition and differentiation of patterns. In a pattern recognition method, the provider uses experience to recognize a pattern of clinical characteristics. It is mainly based on certain symptoms or signs being associated with certain diseases or conditions, not necessarily involving the more cognitive processing involved in a differential diagnosis. Occasionally the process is made easy by a sign or symptom or a group of several that are pathognomonic.

A diagnosis, in the sense of diagnostic procedure, can be regarded as an attempt at classification of an individual's condition into separate and distinct categories that allow medical decisions about treatment and prognosis to be made.

A diagnostic test is any kind of medical test performed to aid in the diagnosis or detection of disease and to provide prognostic information on people with established disease.

The term "diagnostic criteria" designates the specific combination of signs and symptoms and test results that the clinician uses to attempt to determine the correct diagnosis.

A medical algorithm is any computation, formula, statistical survey, nomogram, or look-up table, useful in healthcare. Medical algorithms include decision tree approaches to healthcare treatment and also less clear-cut tools aimed at reducing or defining uncertainty. The intended purpose of medical algorithms is to improve and standardize decisions made in the delivery of medical care. Medical algorithms assist in standardizing selection and application of treatment regimens. However, algorithms are based on a typical patient with a typical condition. Clinical algorithms may be useful for the average diagnosis and treatment, but they fail when a doctor needs to think outside of their boxes, when symptoms are vague, multiple, or confusing, and when test results are inconclusive. Doctors who turn down their own thinking on the authority of classification schemes and algorithms have a statistic way of looking at people. But statistics embody averages, not individuals. Ultimately, computations obtained from medical algorithms should be compared with, and tempered by, clinical knowledge and physician judgment.

For a diagnostic workup in infectious diseases, access to the following diagnostic tools and facilities are required:

- Patient history (hair specific, general, psychosocial)
- Clinical examination (scalp, complete skin, nails, mucous membranes)
- Dermoscopy
- Microscopic examination (light, polarization, and scanning electron microscopy)
- Hair pluck (trichogram)
- Scalp biopsy
- Histopathology, including immunofluorescence
- Wood lamp examination
- Mycology, including KOH preparation and fungal cultures
- Other microbiological services, including PCR
- Blood test facilities (phlebotomy and laboratory services: CRP, CBC, VDRL, TPHA, Quantiferon-Tbc test, others)
- Imaging
- Access to non-dermatological clinical disciplines

## 11.1 Patient History

History taking is of paramount importance in assessing infectious disease. By careful and systematic questioning, it is possible to assess the factors pertinent to differential diagnosis and particular lines for further investigation.

In the course of history taking, it is advisable never to accept anything for true, neither from the patient nor from the referring physician, which is not clearly recognizable as such, that is to say, carefully to avoid precipitancy and prejudice, and to comprise nothing more in one's judgment than what is presented to the mind so clearly and distinctly as to exclude all ground of doubt.

William Osler (Canadian physician, 1849–1919) said "If you listen to the patient, he is telling you the diagnosis." How a doctor asks questions is key to patient activation and engagement. The way a doctor poses his questions, structures the patient's answers, and at the same time gives the patient the feeling that the doctor is really interested in hearing what he has to say.

The six components of a patient history are:

- Chief concern
- History of present illness
- Past medical history
- Family history
- Sociocultural history
- Review of systems

Specific components relevant to infectious diseases require particular attention. In general, these aspects focus on two areas:

1. An exposure history that may identify microorganisms with which the patient may have come into contact
2. Host-specific factors that may predispose to the development of an infection

Although the social history taken by physicians is often limited to inquiries about a patient's alcohol and tobacco use, a complete social history can offer a number of clues to the underlying diagnosis. Knowing whether the patient has any high-risk behaviors, such as unsafe sexual behaviors, and IV drug use, potential hobby-associated exposures, such as avid gardening with possible *Sporothrix schenckii* exposure, animal exposure, such as increased risk for *Microsporum canis* or *Trichophyton mentagrophytes* infection, and tick-borne diseases, or occupational exposures, such as increased risk for *Mycobacterium tuberculosis* exposure in funeral service workers, can facilitate diagnosis. Finally, attention should be paid to both international and domestic travels. Domestic travel may have exposed patients to pathogens that are not normally found in their local environment and therefore may not routinely be considered in the differential diagnosis. Beyond simply identifying locations that a patient may have visited, the physician needs to delve deeper to learn what kinds of activities and behaviors the patient engaged in during travel, such as the types of food and sources of water consumed, freshwater swimming, animal exposures, and whether the patient had the necessary immunizations and/or took the necessary prophylactic medications prior to travel.

Because many opportunistic infections affect only immunocompromised patients, it is of vital importance to determine the immune status of the patient. Defects in the immune system may be due to malnutrition, an underlying disease, such as malignancy and HIV infection; a medication, particularly glucocorticosteroids and immunosuppressives; a treatment modality, such as splenectomy, chemotherapy, or total body irradiation; or a primary immunodeficiency condition.

Many infections are caused by members of the indigenous microbiota. These infections typically occur when these microbes escape their normal habitat and enter a new one. Thus, maintenance of epithelial barriers is one of the most important mechanisms in protection against infection. However, hospitalization of patients is often associated with breaches of these barriers, such as placement of IV lines, surgical drains, or tubes that allow microorganisms to localize in sites to which they normally would not have access. Accordingly, knowing what lines, tubes, and drains are in place is helpful in ascertaining what body sites might be infected.

Finally, knowledge about a patient's previous infections, with the associated microbial susceptibility profiles, is very helpful in determining possible etiologic agents. Specifically, knowing whether a patient has a history of infection with drug-resistant organisms, such as methicillin-resistant *Staphylococcus aureus*, or may

have been exposed to drug-resistant microbes during a recent stay in a hospital, nursing home, or long-term acute-care facility may alter the choice of empirical antibiotics.

## 11.2 Clinical Examination

The skin and hair are gratifying for diagnosis. One has but to look, and recognize, since everything to be named is in full view. Looking would seem to be the simplest of diagnostic skills, and yet its simplicity lures one into neglect. To reach the level of artistry, looking must be a skillful active undertaking. The skill comes in making sense out of what is seen, and it comes in the quest for the underlying cause, once the disorder has been named. The first look is best made without prejudices of former diagnoses and without bias of laboratory data. In many instances a specific diagnosis is made in a fraction of a second if it is a simple matter of recognition. The informed look is the one most practiced by dermatologists; it comes from knowledge, experience, and visual memory. Where the diagnosis doesn't come from a glance, the diagnostic tests come in, i.e., the dermatological techniques of examination, and the laboratory evaluation.

The fact that many infections have cutaneous manifestations gives the skin examination particular importance in the evaluation of patients. Pattern recognition relies both on the specificity of a particular disease pattern and on the diagnostic skill of the physician. It relies on symptoms and signs compared to previous patterns or cases and on the memory of known patterns.

Spot diagnosis arises from an unconscious recognition of a particular nonverbal pattern, usually visual. The spot diagnosis is almost instantaneous, relies on previous nonverbal experience of the condition, and does not require further history from the patient to trigger the possible diagnosis. Many consider a spot diagnosis as basically pattern recognition. The main determinant in the use of spot diagnosis is clinical experience with a given condition.

Red flags are specific symptoms or signs that may be volunteered by the patient or may need to be elicited in the history or examination to rule out a serious condition, for example, checking for neck stiffness in a patient with headache to rule out meningitis. If the symptom or sign cannot be ruled out, it triggers action, which can range from a more detailed physical examination to hospital referral.

Probabilistic reasoning is the specific use of symptoms, signs, or diagnostic tests to rule in or rule out a diagnosis. Probabilistic reasoning requires knowing the degree to which a positive or negative result of a test adjusts the probability of a given disease [1].

## 11.3 Dermoscopy

The naked eye is right for the global look, but for close inspection, the additional use of a magnifying glass is practiced. The handheld, single-lens magnifier is the simplest and least expensive, most commonly used by dermatologists, usually at a

magnification of 3× to 4×. Although the pathologist lives in a world magnified 100 to 1000 times, the clinician doesn't benefit from a highly magnified view of the patient, lest he performs dermoscopy (10×) and is knowledgeable of the clinicopathologic correlations.

Dermoscopy is a noninvasive diagnostic tool that permits recognition of morphologic structures not visible to the naked eye. Dermatologists involved in the management of and scalp disorders have discovered dermoscopy to also be useful in their daily clinical practice. Scalp dermoscopy is not only helpful for the diagnosis of hair and scalp disorders, but it can also give clues about the disease stage and progression.

Some experts suggest that the use of dermoscopy in the clinical evaluation of hair and scalp disorders improves diagnostic capability beyond simple clinical inspection and reveals novel features of disease, which may extend our clinical and pathogenetic understanding. Therefore, dermoscopy of hair and scalp is gaining popularity in daily clinic practice as a valuable tool in differential diagnosis of hair and scalp disorders. This method allows viewing of the hair and scalp at high magnifications using a simple handheld dermatoscope (Heine Delta 20®, DermoGenius®, DermLite II PRO HR®, or DermLite DL3® (Fig. 11.1a) can be used, with alcohol as the interface solution.

Using dermoscopy, signature patterns are seen in a range of scalp and hair conditions. Some predominate in certain diseases; others can even help make a diagnosis in clinically uncertain cases.

Dermoscopic findings in specific infectious diseases of the hair and scalp have been comma hairs and corkscrew hairs in tinea capitis [2] (Fig. 11.1b). Dermoscopy has proven useful to identify parasitism of hair of the beard in tinea barbae, just as it has proven useful in the diagnosis of tinea capitis [3].

Dermoscopy of the moth-eaten areas in syphilitic alopecia showed that alopecia is mainly due to a reduction in the number of terminal hairs [4] (Fig. 11.1c).

In pediculosis capitis, either the lice (Fig. 11.1d) or nits (Fig. 11.1e) are easily visualized through the dermoscope, and empty cases can reliably be differentiated from nymph-containing viable eggs [5].

In children, important dermoscopic structures seen in infectious and inflammatory skin conditions and hair disorders, such as scabies, pediculosis, phthiriasis, molluscum contagiosum, tinea nigra, and verrucae are well-characterized dermoscopically by delta-shaped structures, ovoid-shaped nits, the crab louse, red corona, brown strands or spicules, and multiple densely packed papilla with a central black dot surrounded by a whitish halo (Fig. 11.1f), respectively [6].

Dermoscopy may support the recognition of folliculitis etiology. In an observational study on 240 patients with folliculitis determined on the basis of clinical and dermoscopic assessments, dermoscopic images of the most representative lesions were acquired for each patient, and etiology was determined on the basis of cytologic examination, culture, and histologic examination. Dermoscopic images were evaluated according to predefined diagnostic criteria by a dermatologist who was blinded to the clinical findings. Of the 240 folliculitis lesions examined, 90% were of infectious and 10% of noninfectious origin. Infectious folliculitis was caused by


**Fig. 11.1** (**a**–**g**) Dermoscopy: (**a**) different models of hand held dermoscopes; (**b**) dermoscopy of tinea capitis, comma hairs and corkscrew hairs; (**c**) of syphilitic alopecia, reduction in the number of terminal hairs, (**d**, **e**) of pediculosis capitis, (**d**) the louse (**e**) and nits; (**f**) of a wart; and of (**g**) folliculitis decalvans, hair tufting, follicular pustule, and capillary loops

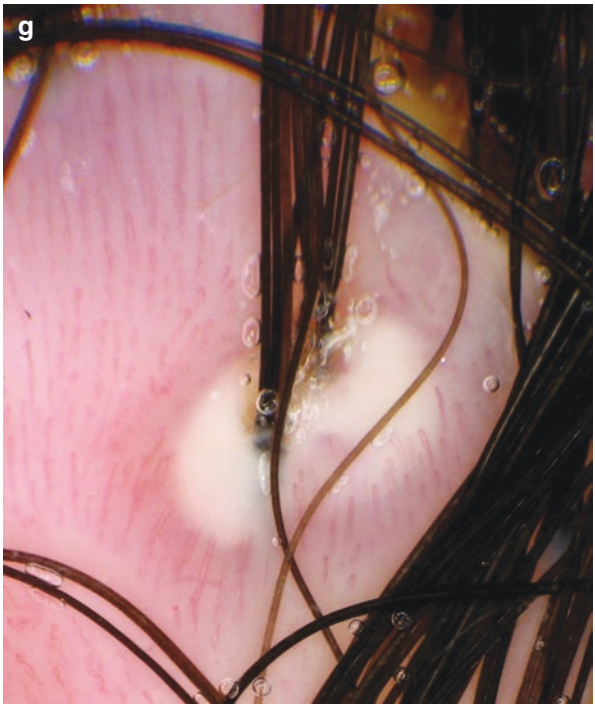


**Fig. 11.1** (continued)

parasites ($n$ = 71), fungi ($n$ = 81), bacteria ($n$ = 57), or seven viruses ($n$ = 7). The overall accuracy of dermoscopy was 73.7%. Dermoscopy showed good diagnostic accuracy for *Demodex* (88.1%), scabietic (89.7%), and dermatophytic folliculitis (100%), as well as for pseudofolliculitis (92.8%) [7].

Dermoscopic features of folliculitis decalvans are severe scaling and crusting, pronounced hair tufting, follicular pustules, and numerous coiled capillary loops (Fig. 11.1g) [8]. Based on dermoscopic findings, ultimately a trichoscopy activity scale for folliculitis decalvans has been proposed, though short of correlations with histopathological or microbiological studies [9].

In summary, as a diagnostic procedure, dermoscopy remains to be understood as representing an integral part of a more comprehensive dermatological examination. Moreover, dermoscopy of the hair and scalp also represents an integral part of surface or epiluminescence microscopy of the skin, given that an important portion of respective signature patterns relates to the condition of the scalp skin rather than to the hair, and as such should retain its original designation as dermoscopy versus the sectarian term trichoscopy. Finally, it would be unwise to choose shortcuts and replace time-tested examination techniques with a higher sensitivity and specificity with dermoscopy, specifically the hair pluck in telogen effluvium, the light microscopic hair shaft analysis in the disorders of the hair shaft, the microbiological studies in the pustulofollicular and granulomatous diseases of the scalp, the scalp biopsy

for histopathological examination, histochemical and microbiological studies in the scarring alopecias, and serologic testing in syphilis, HIV, and other systemic infectious diseases [10].

## 11.4 Microscopic Examination

Microscopy is the technical field of using microscopes to view objects and areas of objects that cannot be seen with the naked eye. There are three well-known branches of microscopy: optical, electron, and scanning probe microscopy.

Optical or light microscopy involves passing visible light transmitted through or reflected from the sample through a single lens or multiple lenses to allow a magnified view of the sample. The resulting image can be detected directly by the eye, imaged on a photographic plate, or captured digitally. The single lens with its attachments, or the system of lenses and imaging equipment, along with the appropriate lighting equipment, sample stage, and support, makes up the basic light microscope.

Live cells in particular generally lack sufficient contrast to be studied successfully, since the internal structures of the cell are colorless and transparent. The most common way to increase contrast is to stain the structures with selective dyes, but this involves fixing the sample. Staining may introduce artifacts, which are apparent structural details that are caused by the processing of the specimen and are thus not features of the specimen (FDS).

To improve specimen contrast or highlight structures in a sample, special techniques must be used:

*Bright-field microscopy* is the simplest of all the light microscopy techniques. Sample illumination is via transmitted white light illuminated from below and observed from above. Limitations include low contrast of most biological samples and low apparent resolution due to the blur of out-of-focus material. The simplicity of the technique and the minimal sample preparation required are significant advantages.

*Dark-field microscopy* is a technique for improving the contrast of unstained, transparent specimens. Dark-field illumination uses a carefully aligned light source to minimize the quantity of directly transmitted unscattered light entering the image plane, collecting only the light scattered by the sample. Dark field can dramatically improve image contrast, particularly of transparent objects, while requiring little equipment setup or sample preparation. However, the technique suffers from low light intensity in the final image of many biological samples and continues to be affected by low apparent resolution. Since 1909, examinations of unstained and unfixed preparations by dark-field microscopy have been able to show with complete certainty the presence of infection caused by spirochetes, even before the appearance of the serologic tests. Dark-field microscopy allows visualization of live treponemes obtained from a variety of cutaneous or mucous membrane lesions. In primary syphilis, the chancre teems with treponemes that can be seen with dark-field microscopy. A positive dark-field result is an almost

certain diagnosis of primary, secondary, or early congenital syphilis. Of note, the mouth harbors normal nonpathogenic treponemes that are indistinguishable microscopically from *Treponema pallidum*. Therefore, oral specimens cannot be used for dark-field microscopy because of the possibility of false-positive test results.

*Polarized light microscopy* can mean any of a number of optical microscopy techniques involving polarized light. Simple techniques include illumination of the sample with polarized light. Directly transmitted light can, optionally, be blocked with a polarizer orientated at 90 degrees to the illumination. More complex microscopy techniques which take advantage of polarized light include differential interference contrast microscopy and interference reflection microscopy. Scientists will often use a device called a polarizing plate to convert natural light into polarized light. These illumination techniques are most commonly used on birefringent samples where the polarized light interacts strongly with the sample and so generating contrast with the background. Polarized light microscopy is used extensively in optical mineralogy. In pathology, Schaumann bodies are birefringent calcium and protein inclusions inside of Langhans giant cells as part of a granuloma, typically seen in sarcoidosis and less commonly in tuberculosis.

*Fluorescence microscopy*. When certain compounds are illuminated with high energy light, they emit light of a lower frequency. This effect is known as fluorescence. Often specimens show their characteristic autofluorescence image, based on their chemical makeup. This method is of critical importance in the modern life sciences, as it can be extremely sensitive, allowing the detection of single molecules. Many fluorescent dyes can be used to stain structures or chemical compounds. One powerful method is the combination of antibodies coupled to a fluorophore as in immunostaining. Examples of commonly used fluorophores are fluorescein or rhodamine. The antibodies can be tailor-made for a chemical compound.

*Calcofluor White* (CFW) has become a valuable and routine reagent in the clinical mycology laboratory. It binds to β-1–3 and 1–4 polysaccharides, such as cellulose and chitin present in fungal cell walls, and fluoresced when exposed to long-wave UV light.

Until the invention of sub-diffraction microscopy, the wavelength of the light limited the resolution of traditional microscopy to around 0.2 μm. In order to gain higher resolution, the use of an electron beam with a far smaller wavelength is used in electron microscopes.

*Transmission electron microscopy* (TEM) is quite similar to the compound light microscope, by sending an electron beam through a very thin slice of the specimen. The resolution limit in 2005 was around 0.05 [dubious-discuss] nanometer and has not increased appreciably since that time.

*Scanning electron microscopy* (SEM) visualizes details on the surfaces of specimens and gives a very nice 3D view. It gives results much like those of the stereo light microscope. The best resolution for SEM in 2011 was 0.4 nm.

## 11.5 Trichogram

Many factors can lead to a pathologically increased hair loss, including febrile infections. Whatever the cause, the follicle tends to behave in a similar way.

*Telogen effluvium* results from late onset increased shedding of hairs from the telogen phase of the hair cycle and represents by far the commonest cause of hair loss. An increase in the percentage of follicles in telogen >20% leads to increased shedding of hairs in telogen. This can either be due to synchronization phenomena of hair cycling, with shedding of hairs in the hundreds in telogen effluvium or due to a decrease of anagen phase duration in androgenetic alopecia with its sex-typical patterns of alopecia, variable shedding of hair, and increasing diversity of hair shaft diameters.

*Dystrophic anagen effluvium* is an early-onset hair loss that results from the shedding of large numbers of hairs from the anagen phase of growth. It is a major characteristic of anagen that the epithelial hair follicle compartment undergoes proliferation, with the hair matrix keratinocytes showing the highest proliferative activity in building up the hair shaft. The common pathogenesis which unites the different etiologies of dystrophic anagen effluvium is a direct insult to the rapidly dividing bulb matrix cells.

Postfebrile effluvium has traditionally been categorized as telogen effluvium, yet it may present with different pathomechanisms and clinical patterns. Evidence exists that the hair follicle may respond to infection with both shedding patterns, telogen effluvium, or dystrophic anagen effluvium, depending on the type and intensity of the insult.

The trichogram or hair pluck test is a semi-invasive technique for hair analysis on the basis of the hair growth cycle. It involves the forceful plucking of 50–100 hairs with a forceps from specific sites of the scalp and microscopic examination of the hair roots (Fig. 11.2a–o). A major objective of trichogram measurements is to evaluate and count the status of individual hair roots (Fig. 11.3a–e) and to establish the ratio of anagen to telogen roots. Original studies on the dynamics of the follicular cycle have largely depended on the microscopic evaluation of plucked hairs with quantitative measuring of the number of individual hair roots. Subsequently, the trichogram technique was developed and standardized to serve as a diagnostic tool for evaluation of hair loss in daily clinical practice. For this purpose it is simple to perform, repeatable, and reasonably reliable under standardized conditions. The trichogram technique provides reliable results under the condition that hair samples are obtained under a standardized procedure.

Since in 95% of cases hair loss is due to a disorder of hair cycling, trichogram measurements serve as a standard method for quantifying the hair in its different growth cycle phases as it relates to the pathologic dynamics underlying the loss of hair. The percentage of hair roots in anagen, catagen, or telogen reflects either synchronization phenomena of the hair cycle or alterations in the duration of the respective growth cycle phases, while the presence of dystrophic hair roots signalizes a massive damage to anagen hair follicles.

To date, no standardization defines the best way to fix the hair shafts for reading under the microscope. A review of 76 articles indexed in PubMed with the

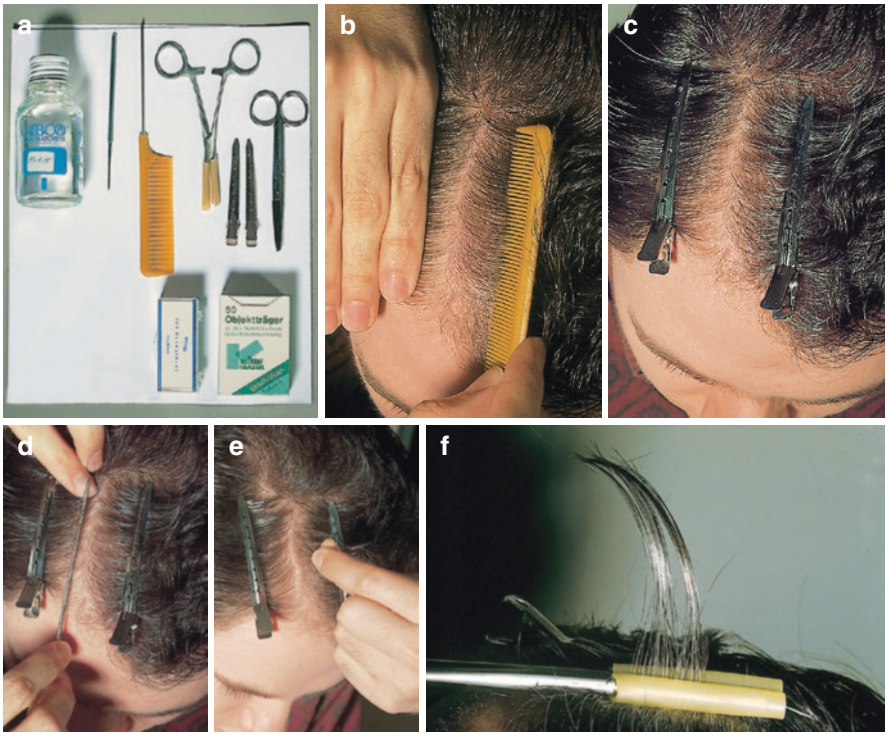


**Fig. 11.2** (**a**–**o**) Trichogram technique. (**a**) The materials necessary for performing a trichogram include a tail comb, hair clips, artery forceps covered with rubber tube, a pair of scissors, microslides, 76 × 26 mm, cover glasses, 50 × 24 mm, Eukitt, xylol, a dissecting needle, and a binocular microscope with variable objectives (2.5 and 4.0. Usually, epilations are carried out from two specified sites at the same time: in diffuse effluvium or androgenetic alopecia frontal (2 cm behind the forehead and 2 cm lateral) and occipital (2 cm lateral from the occipital protuberance) and in circumscribed alopecias one sample is taken from the border zone and the control from the normal appearing contralateral region. (**b**–**e**) Within the chosen area for epilation, the hair is parted and fixed with clips. (**f**, **g**) Along the parting line, a bundle of approximately 50 to 100 hairs is lifted parallel along the course of the hair and grasped close to the scalp with the forceps whose jaws are covered with the rubber tubes. (**h**–**j**) The forceps jaws are pressed together to the maximum and the tuft of hair is then epilated. A sharp quick pull and exact plucking in the direction of the emergence angle of the hairs form the scalp are important to obtain a reliable hair root pattern. Slow or hesitant traction or the wrong pulling direction may induce distortions or alterations of the plucked hairs complicating interpretation. (**k**–**n**) The procedure is repeated at the second site. (**o**) Embedding of epilated hairs occurs immediately to prevent dehydration of the hair roots. A few drops of Eukitt (after condensation, dilute with xylol) are given on two marked microslides. The tuft of hairs is taken with thumb and pointing finger; the roots are dipped in the embedding material (Eukitt), cut off 2 cm above the roots, and arranged in a fast manner with the dissecting needle in a parallel position before being covered. The evaluation can be done when the embedding material no longer runs, usually after 10 min. Correctly embedded hair roots are suitable for unlimited storage

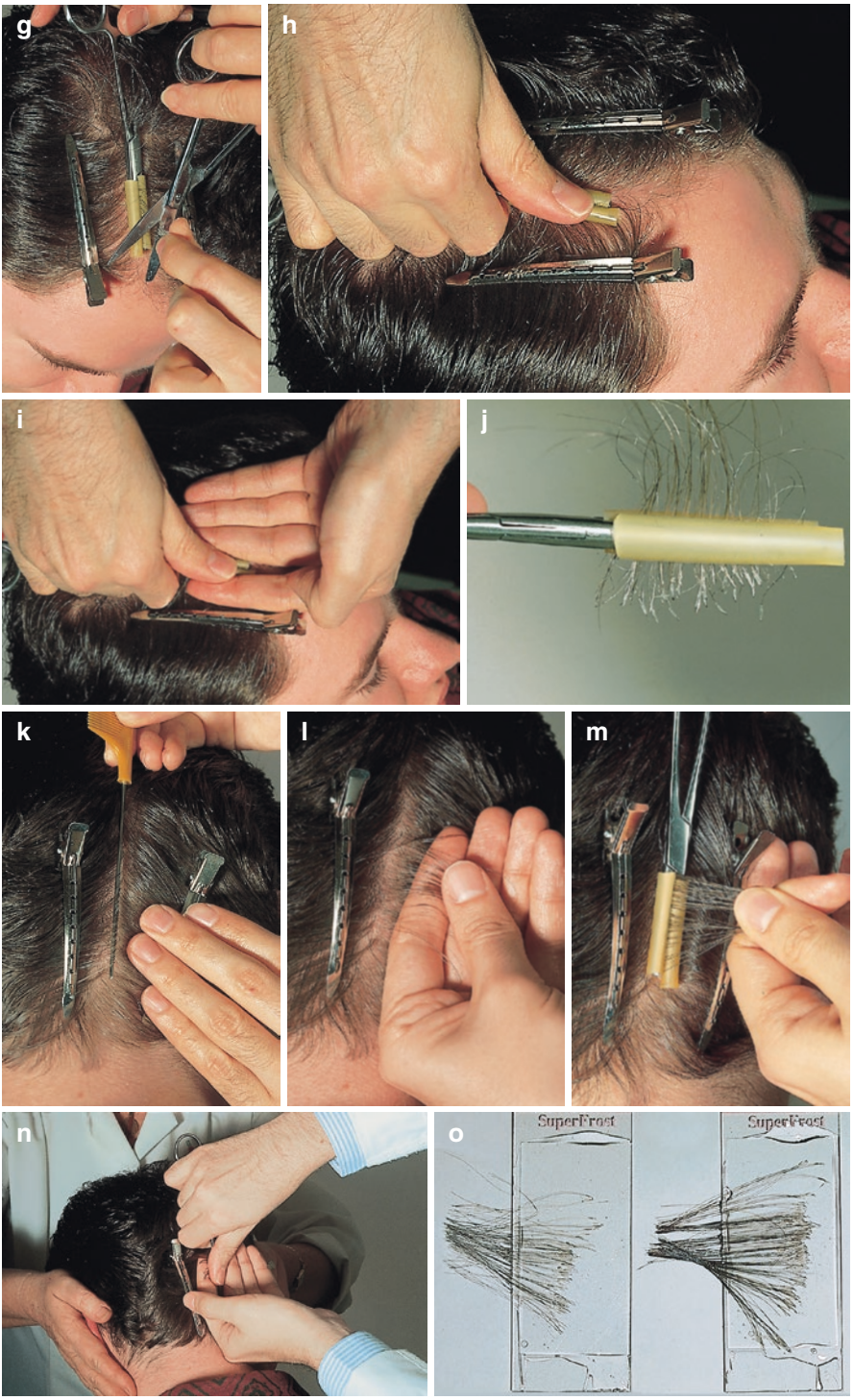


**Fig. 11.2** (continued)

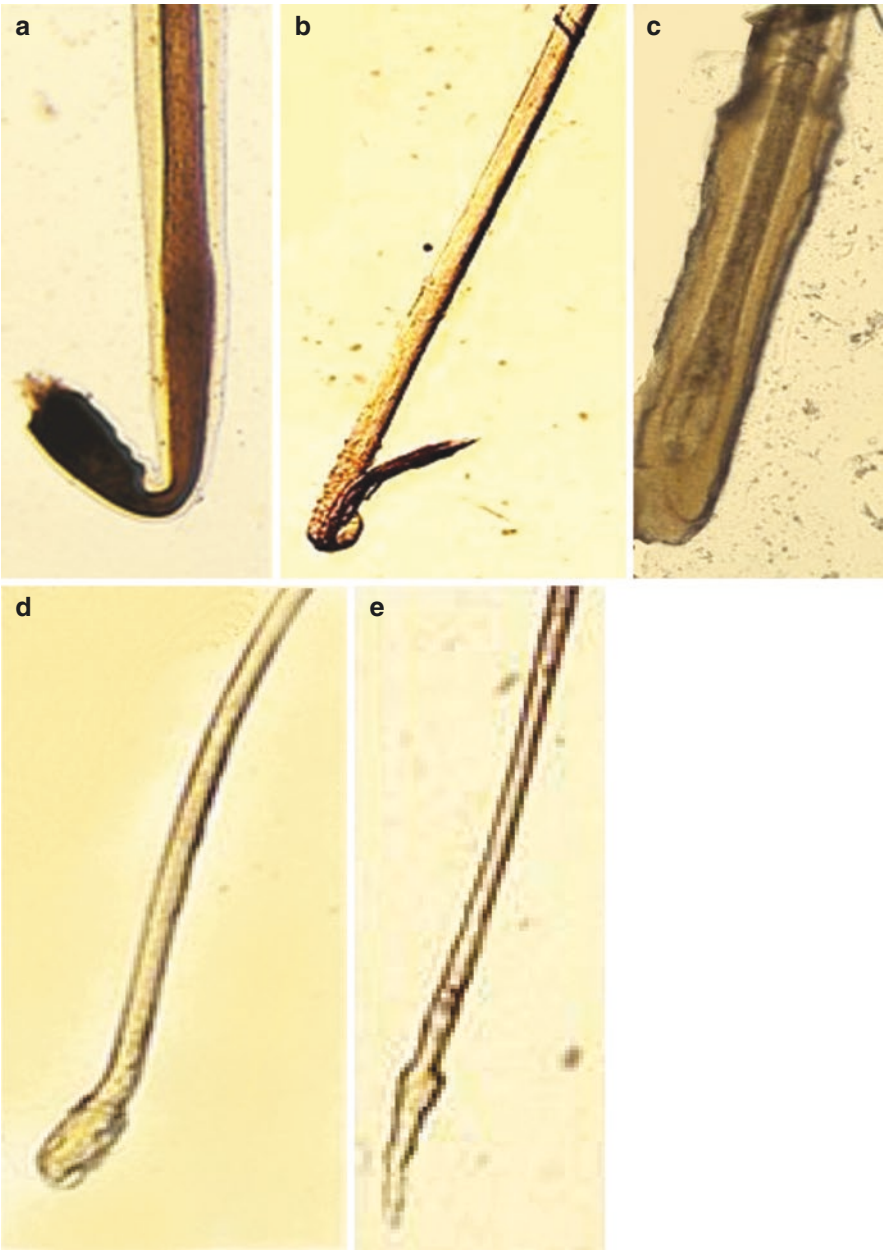


**Fig. 11.3** (**a**–**e**) Hair root forms: (**a**) anagen with hair root sheaths, (**b**) anagen without hair root sheaths, (**c**) catagen, (**d**) telogen, and (**e**) dystrophic anagen

keywords "trichogram" and "technique" published from 1970 to 2021 showed that only 14 studies (18.4%) mentioned some liquid or other fixation media when conducting the technique. Of these, one used formaldehyde (7.15%), two used a drop of Canadian balsam (14.28%), three used only a thin glass slide cover (21.42%), two used double-sided tape (14.28%), five used adhesive tape (37.71%), one used unspecified liquid (7.15%), and 62 (81.57%) did not mention or did not use any form of fixation of the hair strands.

A mixture of 45% acrylic resin and 55% xylenes (Eukitt®) can be used for fixing and reading the trichogram with excellent results. It provides little formation of air bubbles and facilitates exam interpretation, especially for inexperienced examiners. On the other hand, this technique is a more expensive option, and it's more challenging to be found in some parts of Brazil. In turn, the use of liquids that do not promote adherence of the hair strands to the glass slide, such as formaldehyde, 0.9% saline solution, and distilled water, facilitates the movement of hair strands on the slide, making it difficult to visually analyze and count the hairy roots in different optical fields. In the authors' experience, using a transparent enamel base coat (basically, clear nail polish) is a cheap, easy-to-access, and helpful strategy when preparing the hair shafts for the trichogram. When opting for this strategy, the examiner must place the hair strands on a previously prepared slide with a generous amount of enamel base coat and then cover with a coverslip glass slide (Fig. 11.4a–d). Drying is quick, and fixation is adequate, with minimal air bubbles formation (Fig. 11.5a, b). Also, the material can be kept for analysis on subsequent days [11].

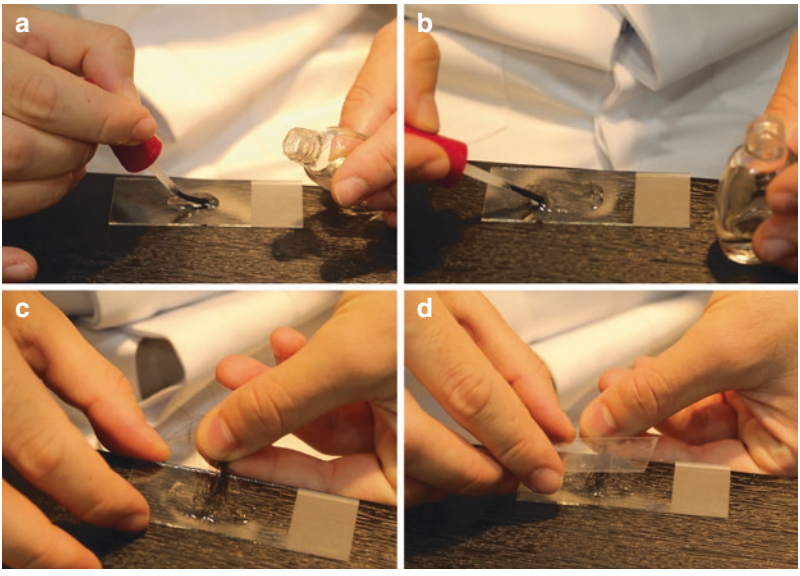


**Fig. 11.4** (**a**–**d**) Preparation of enamel-based slide for trichogram reading: (**a**, **b**) a good amount of base coat must be applied so that all hair shafts are fully soaked in the liquid (**c**, **d**) fixation must be quick, before the base coat dries, and a coverslip helps with further reading

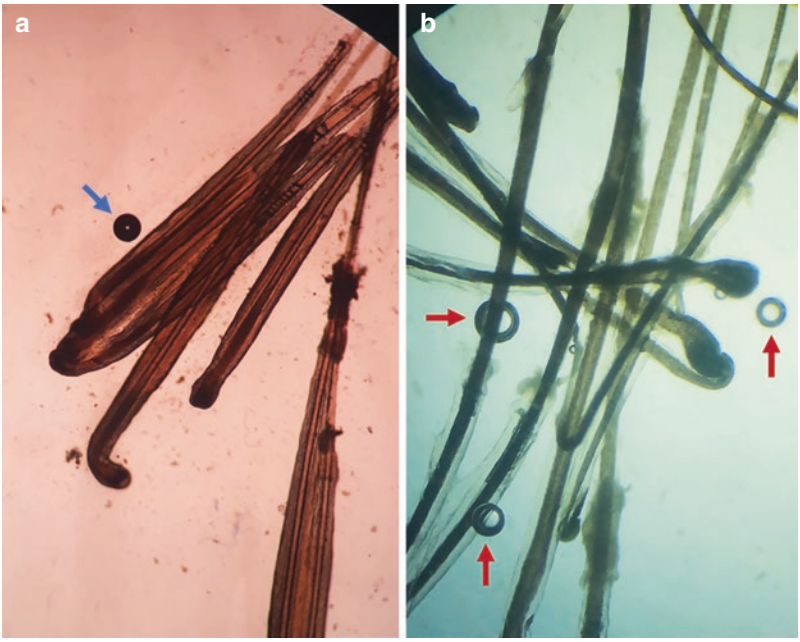


**Fig. 11.5** (**a**, **b**) Trichogram assessment of hair shafts under an optical microscope (4×): (**a**) evaluation with Eukitt®, transparent medium with minimal air bubbles formation (blue arrow); (**b**) evaluation based on enamel, few air bubbles that do not affect the final assessment of the exam

## 11.6 Histopathology

In some cases of alopecia, a diagnosis cannot be made based on results of physical examination, diagnostic hair techniques, and laboratory studies. This is particularly the case in the scarring alopecias. In these cases, a scalp biopsy for histopathological examination may provide the specific diagnosis.

For a biopsy an area of the scalp is chosen where the disease is active, frequently the margin of the involved area shows the pathologic changes best, while areas should be avoided where there are no hair follicles present. After choosing the appropriate site, the hairs are clipped in a 1 $cm^2$ area, leaving a 2 mm stubble (Fig. 11.6a). The area is prepared with 70% alcohol. For adequate anesthesia and hemostasis, 1.5 ml of 1.0% lidocaine with epinephrine is injected raising a large wheal. To obtain an adequate vasoconstrictor effect, it is advisable to wait 20–30 min before proceeding to the biopsy. Also, areas are to be avoided that lie over the temporal or occipital arteries or in which an arterial palpation can be detected. To avoid tying long hairs in the suture material, paper tape is placed over the uncut hairs surrounding the biopsy site. An adequate biopsy specimen can be obtained by using a 6 mm punch instrument that is placed parallel to the emerging angle of the hair stubbles. The punch is turned through the dermis and subcutaneous fat to a level including the hair bulbs. The biopsy specimen can be grasped at the edge with a

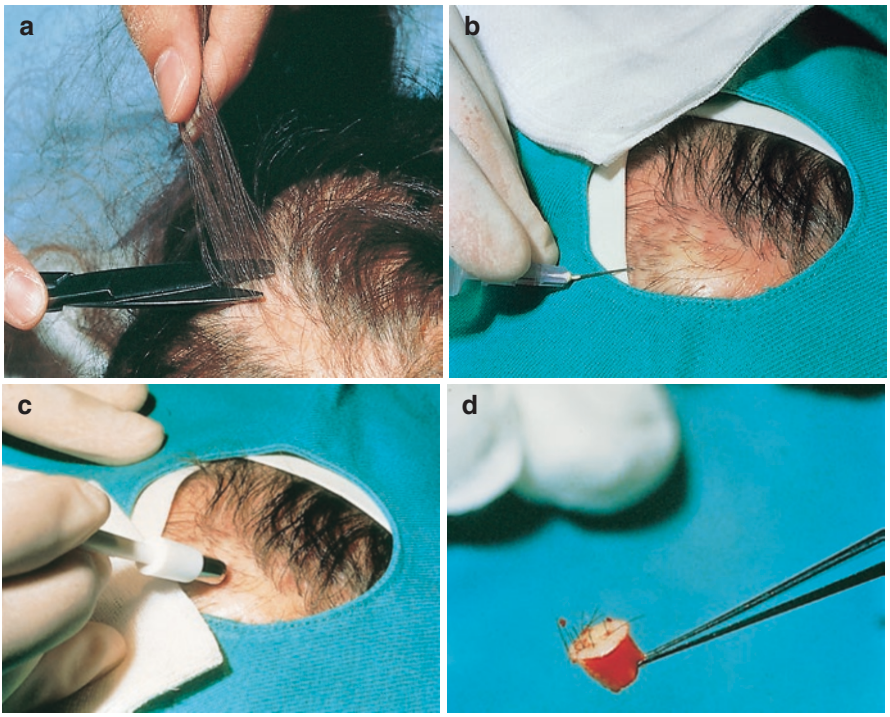


**Fig. 11.6** (**a**–**g**) Scalp biopsy. (**a**) For a biopsy an area of the scalp is chosen where the disease is active, frequently the margin of the involved area shows the pathologic changes best, while areas should be avoided where there are no hair follicles present. After choosing the appropriate site, the hairs are clipped in a 1 $cm^2$ area, leaving a 2 mm stubble. The area is prepared with 70% alcohol. (**b**) For adequate anesthesia and hemostatis, 1.5 ml of 1.0% lidocaine with epinephrine is injected raising a large wheal. To obtain an adequate vasoconstrictor effect, it is advisable to wait 20–30 min before proceeding to the biopsy. Also, areas are to be avoided that lie over the temporal or occipital arteries or in which an arterial palpation can be detected. To avoid tying long hairs in the suture material, paper tape is placed over the uncut hairs surrounding the biopsy site. (**c**) An adequate biopsy specimen can be obtained by using a 6 mm punch instrument that is placed parallel to the emerging angle of the hair stubbles. The punch is turned through the dermis and subcutaneous fat to a level including the hair bulbs. (**d**) The biopsy specimen can be grasped at the edge with a fine-toothed forceps, while it is cut free of attachment deep in the fat with a small, curved scissors. Alternatively, a thin 1 cm ellipse can be made, especially if the scalp is very tight or scarred, and a 6 mm punch site may not be able to be closed with sutures. (**e**) The biopsy site is sutured with blue 4-0 Proline. Three to four stitches are usually adequate for hemostasis. (**f**) The specimen is then cut in half with a #15 blade parallel to the longitudinal axis of the hair shafts. (**g**) One half of the specimen is submitted for the routine hematoxylin and eosin examination, while the other half for immunofluorescence studies as indicated. In some instances, transverse sectioning of a second, entire punch according to the Headington technique may be done for quantitative morphometric analyses of the follicles and hair

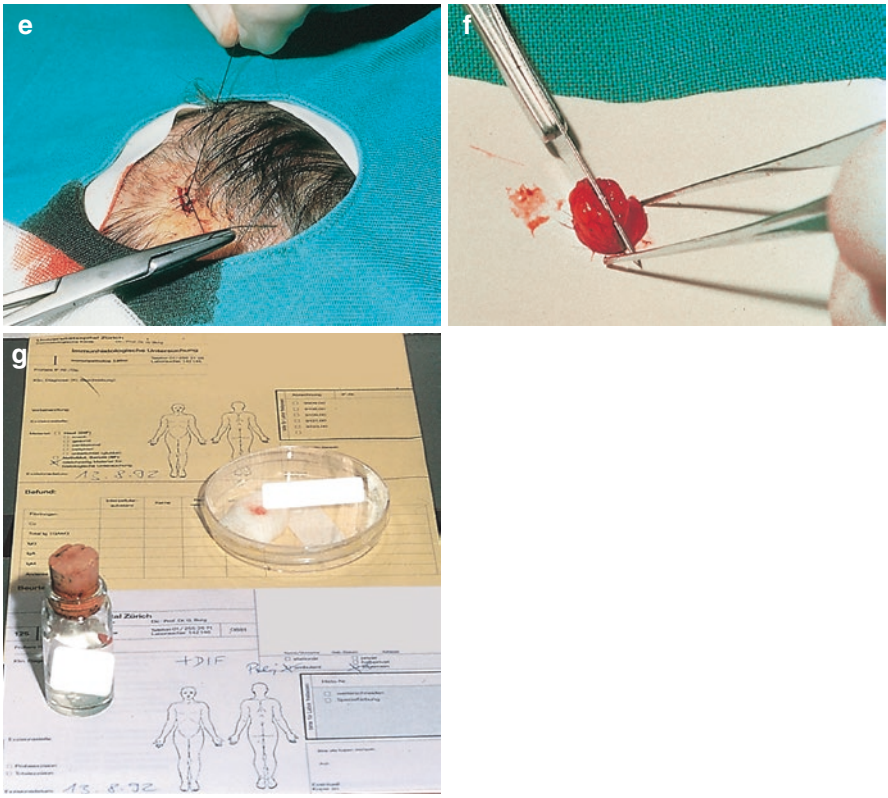


**Fig. 11.6** (continued)

fine-toothed forceps, while it is cut free of attachment deep in the fat with a small, curved scissors. Alternatively, a thin 1 cm ellipse can be made, especially if the scalp is very tight or scarred, and a 6 mm punch site may not be able to be closed with sutures. The biopsy site is sutured with blue 4-0 Proline. Three to four stitches are usually adequate for hemostasis.

Problems related to the scalp biopsy may be the reluctance of dermatologists to perform a scalp biopsy and therefore lack of experience with the proper procedure and the lack of familiarity of some pathologists with scalp histopathology. Nevertheless, if done and examined properly, the scalp biopsy is an easy, relatively painless, and bloodless procedure that represents an invaluable adjunct for confirming or establishing the diagnosis of a specific type of alopecia, whether of infectious or noninfectious origin.

Histopathology refers to the microscopic examination of tissue in order to study the manifestations of disease. Specifically, in clinical medicine, histopathology refers to the examination of a biopsy or surgical specimen by a pathologist, after the specimen has been processed and histological sections have been placed onto glass slides. The tissue is removed from the body and placed after dissection in a fixative.

The most common fixative is 10% neutral buffered formalin (corresponding to 3.7% w/v formaldehyde in neutral buffered water, such as phosphate-buffered saline). Water is removed from the sample in successive stages by the use of increasing concentrations of alcohol. Xylene is used in the last dehydration phase instead of alcohol—this is because the wax used in the next stage is soluble in xylene where it is not in alcohol allowing wax to permeate the specimen. The wax-infiltrated specimen is then transferred to an individual specimen embedding container. Finally, molten wax is introduced around the specimen in the container and cooled to solidification so as to embed it in the wax block. This process is needed to provide a properly oriented sample sturdy enough for obtaining a thin microtome section for the slide. Once the wax-embedded block is finished, sections will be cut from it and usually placed to float on a water bath surface which spreads the section out. A number of slides will usually be prepared from different levels throughout the block. After this the thin section mounted slide is stained, and a protective coverslip is mounted on it. To see the tissue under a microscope, the sections are stained with one or more pigments. The aim of staining is to reveal cellular components; counterstains are used to provide contrast. For common stains, an automatic process is normally used.

The most commonly used stain in histology is a combination of hematoxylin and eosin (H&E). Hematoxylin is used to stain nuclei blue, while eosin stains the cytoplasm and the extracellular connective tissue matrix of most cells pink. There are hundreds of various other techniques which have been used to selectively stain cells. Other compounds used to color tissue sections include gram stain, Brown-Brenn modified gram stain, periodic acid shift (PAS), Giemsa, and silver salts for visualization of pathogens. The histological slides are examined under a microscope by a pathologist, and the medical diagnosis is formulated as a pathology report describing the histological findings and the opinion of the pathologist as it refers to the request of the clinician. For this purpose, effective communication between the clinician and pathologist is important.

## 11.7 Wood Light Examination

Wood light examination is an examination technique used in dermatology by which ultraviolet light is shone at a wavelength of approximately 365 nm onto the skin of the patient, for observation of any subsequent fluorescence. A black light, also called an ultraviolet (UV)-A light, or Wood's lamp is a lamp that emits long-wave ultraviolet light (UV-A) and very little visible light (Fig. 11.7a, b). One type of lamp has a violet filter material, either on the bulb or in a separate glass filter in the lamp housing, which blocks most visible light and allows through UV, so the lamp has a dim violet glow when operating. Ultraviolet radiation is invisible to the human eye, but illuminating certain materials with UV radiation causes the emission of visible light, causing these substances to glow with various colors. This is called fluorescence and has many practical uses. Black lights are essential when UV-A light without visible light is needed, particularly in observing fluorescence.

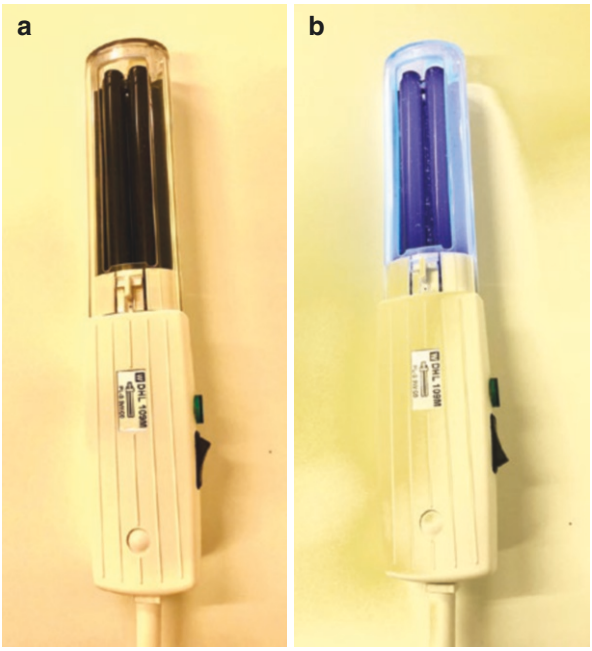


**Fig. 11.7** (**a**, **b**) Wood's lamp

Black lights, for instance, are a common tool for rock-hunting and identification of minerals by their fluorescence (Fig. 11.8: collection of minerals fluorescing under a black light).

In medicine, such a light source is referred to as a Wood's lamp, named after American physicist Robert Williams Wood (1868–1955), who invented the original Wood's glass UV filters. Though the technique for producing a source of ultraviolet light was devised by Robert Williams Wood in 1903, it was only in 1925 that the technique was used introduced into dermatology for the detection of fungal infection of hair. The technique has many uses, both in distinguishing fluorescent conditions and in locating the precise boundaries of the condition. Specifically, it is helpful in diagnosing particular fungal and bacterial infection. The technique is performed in the dark. Normal healthy skin is slightly blue but shows white spots where there is thickened skin, yellow where it is oily, and purple spots where it is dehydrated.

Fluorescence of *Microsporum canis* infections is apple green, *Corynebacterium minutissimum* coral red (Fig. 11.9), *Pseudomonas* yellow-green, and *Cutibacterium acnes* an orange glow.

More recently, band-like green fluorescence of nails and hair on Wood's lamp examination has been observed in the course of the COVID-19 pandemic and been attributed to the use of high-dose favipiravir [12]. The drug's active phosphorylated metabolite was shown in human plasma, and its concentration and fluorescence intensity had shown a linear relationship [13].

**Fig. 11.8** Fluorescence of minerals in black light

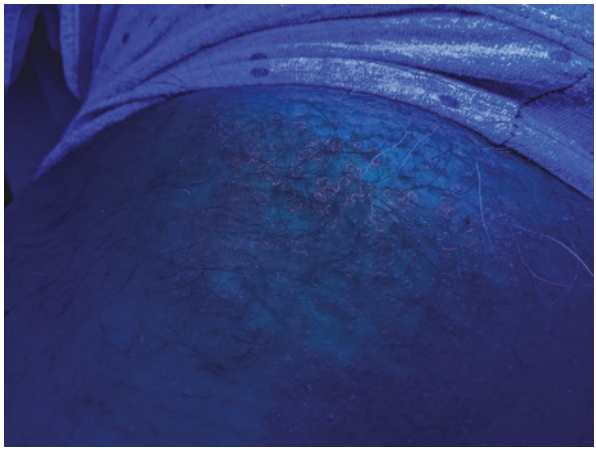

**Fig. 11.9** Coral red fluorescence in *Corynebacterium minutissimum* infection (erythrasma)

Favipiravir is a broad-spectrum antiviral, effective against RNA viruses including influenza and Ebola, and one of the current medications approved for the treatment of COVID-19. The drug selectively inhibits the RNA-dependent RNA polymerase by acting as a guanine analog. It transforms into an active phosphoribosylated form in cells, causing chain termination, slowing viral RNA synthesis and lethal mutagenesis. Favipiravir is effective on COVID-19 only at high doses. Current treatment scheme consists of 1600 mg bid on the first day followed by 600 mg bid po reaching a total dose of 8000 mg [14]. So far, no other cutaneous adverse effect of favipiravir has been reported despite its deposition in the respective tissues [15] and a call for awareness of potential favipiravir-induced phototoxicity [16].

Yellow fluorescence has also been observed in both lunula and nails after oral tetracycline therapy [17], and both phototoxicity [18] and photoonycholysis [19] have been an issue with oral tetracyclines.

UV-A exposure can have negative effects on eyes in both short-term and long-term use, and respective caution is warranted.

## 11.8 Microbiological Studies

Microbiologic studies are mandatory in inflammatory conditions of the scalp with scaling, crusting, and/or pustulation.

While in children fungal infections (tinea capitis) predominate, in the adult, bacterial infection with *S. aureus* is the most prominent. At times, repeated microbiologic studies are recommended, since with prolonged antibiotic treatments, typically in folliculitis decalvans, new and resistant pathogens may emerge, e.g., gram-negative folliculitis.

Diagnosis of fungal and bacterial skin infections requires swabs and test systems for direct visualization of pathogens (KOH preparation, gram stain), cultures and special tests for species identification, and the availability of the appropriate laboratory infrastructure.

The swab is the medical device used for the collection of biological samples from the body and allows for the transport and preservation of the sample. Some of the most common applications of swabs are for the isolation of microorganisms in culture media. A wad of absorbent material usually wound around one end of a small stick and used for removing material from an area. The purpose of microbiological sampling is to allow statements of density, types, and locations of microorganism which reside on the skin. Specimens for culture must be collected properly prior to the initiation particularly of systemic antimicrobial therapy to insure optimal conditions for the recovery of pathogens. The laboratory will identify isolates and perform antibiotic susceptibility testing where appropriate.

For diagnosis of tinea capitis infection and carrier state, different methods for obtaining samples have been reported, including the hairbrush, toothbrush, scalpel blade, gauze, carpet disc, or cotton swab methods. In one study, the hairbrush method was significantly found to be more effective in detecting dermatophyte

fungi than the toothbrush and the cotton swab methods. There was also a statistically significant difference between the use of a single method and the combination of all other three methods [20].

A microbiological culture, or microbial culture, is a method of multiplying microbial organisms by letting them reproduce in predetermined culture medium under controlled laboratory conditions. Microbial cultures are used to determine the type of organism, its abundance in the sample being tested, or both. It is one of the primary diagnostic methods of microbiology and used as a tool to determine the cause of infectious disease.

Developing pure culture techniques is crucial to the observation of the specimen in question. The most common method to isolate individual cells and produce a pure culture is to prepare a streak plate. The streak plate method is a way to physically separate the microbial population and is done by spreading the inoculate back and forth with an inoculating loop over the solid agar plate. Upon incubation, colonies will arise and single cells will have been isolated from the biomass.

A pure or axenic culture is a population of cells or multicellular organisms growing in the absence of other species. For the purpose of gelling the microbial culture, the medium of agarose gel (agar) is used. Agar is a gelatinous substance derived from seaweed. Microbiological cultures can be grown in petri dishes of differing sizes that have a thin layer of agar-based growth medium. There are a variety of additives that can be added to agar before it is poured into a plate and allowed to solidify. Some types of bacteria can only grow in the presence of certain additives. Once a microorganism has been isolated in pure culture, it is necessary to preserve it in a viable state for further study and use.

Once the growth medium in the petri dish is inoculated with the desired bacteria, the plates are incubated at the optimal temperature for the growing of the selected bacteria, usually at 37 degrees Celsius for cultures from humans or animals, or lower for environmental cultures. After the desired level of growth is achieved, agar plates can be stored upside down in a refrigerator for an extended period of time to keep bacteria for future experimentations.

For single-celled eukaryotes, such as yeast, the isolation of pure cultures uses the same techniques as for bacterial cultures. Pure cultures of multicellular organisms are often more easily isolated by simply picking out a single individual to initiate a culture. This is a useful technique for pure culture of fungi.

Characteristics of culture rate of growth; colony morphology, including color of surface and reverse (underside); and microscopic morphologies of organisms allow for identification of specific fungal pathogens.

*Microsporum canis* is the most frequent reported zoophilic agent worldwide, while *Trichophyton violaceum* and *Trichophyton tonsurans* are the predominant anthropophilic agents. Over time, the frequency of these latter fungal infections has increased globally, and these fungi have become the major species globally. Anthropophilic transmission could be explained by the socioeconomic status of affected countries and population groups with associated risk factors and movement of populations importing new causes of infection to areas where they had not been encountered previously [21].

*Microsporum canis* is still the most common reported causative agent of tinea capitis in Europe. The countries reporting the highest incidence of *M. canis* infections are mainly in the Mediterranean but also bordering countries like Austria, Hungary, Germany, and Poland. Besides the increase in *Microsporum*-induced tinea capitis, there is a shift towards anthrophilic tinea capitis mainly in urban areas in Europe. The largest overall increase with anthropophilic dermatophytes has been noted with *Trichophyton tonsurans* mainly in the United Kingdom and with *Trichophyton soudanense* and *Microsporum audouinii* in France. The occurrence of anthropophilic infections seems to be geographically restricted and is possibly linked to the immigration from African countries. Children aged 3–7 years with no predilection of gender remain the most commonly affected, but recently an increase of tinea capitis has been observed in adults and in the elderly [22].

While *Trichophyton rubrum* has led to unprecedented worldwide suppression of other dermatophytes which had been predominant earlier as a causative agent of superficial dermatomycoses, in tinea capitis on the other hand, several other species of *Trichophyton* or *Microsporum* are dominant depending on the region or continent, and tinea capitis caused by *T. rubrum* is a rare event worldwide. The relative frequency of this causative agent in tinea capitis in children is under 1%. In adults, however, where tinea capitis occurs very infrequently indeed, the incidence of *T. rubrum* appears to exceed 10% [23].

On wet preparations of specimens on smeared and dried material, the fluorescent Calcofluor White stain, with or without potassium hydroxide (KOH), is far superior to the traditional KOH alone. It is particularly useful in detecting sparse mounts of fungi and exceptional for exhibiting certain morphologic structures of fungi that have been isolated on culture.

In culture, *Microsporum canis* is characterized by a moderate rate of growth, with maturity within 6–10 days, a whitish surface that is coarsely fluffy, hair to silky or fur-like, with yellow pigment at periphery and closely spaced radial grooves. Reverse is deep yellow and turns brownish yellow with age (Fig. 11.10a, b). Microscopic morphology is characterized by septate hyphae with numerous macroconidia, which are long, spindle-shaped, rough, and thick walls and characteristically taper to knob-like ends. Usually more than six compartments are seen in the macroconidia (Fig. 11.10c).

*Microsporum audouinii* exhibits a moderate rate of growth with maturity in 7–10 days. Colony morphology is characterized by a flat downy to silky, surface, with a radiating edge; it is garish or tannish white. Reverse is light salmon with reddish-brown center. Hyphae are septate with terminal chlamydoconidia that are often pointed at the end. Comb-like hyphae are commonly seen. This species is usually almost devoid of conidia but sometimes forms poorly shaped, abortive macroconidia or occasionally microconidia that are identical to those occurring in other species of the genus *Microsporum*.

*Microsporum gallinae* is a rare cause of tinea capitis and is more often seen as a cause of ringworm in chickens or other fowl. The rate of growth is moderate with maturity in 6–10 days. Colony morphology is characterized by slightly fluffy or satiny becoming pinkish with age. Reverse is yellow at first and later has a red

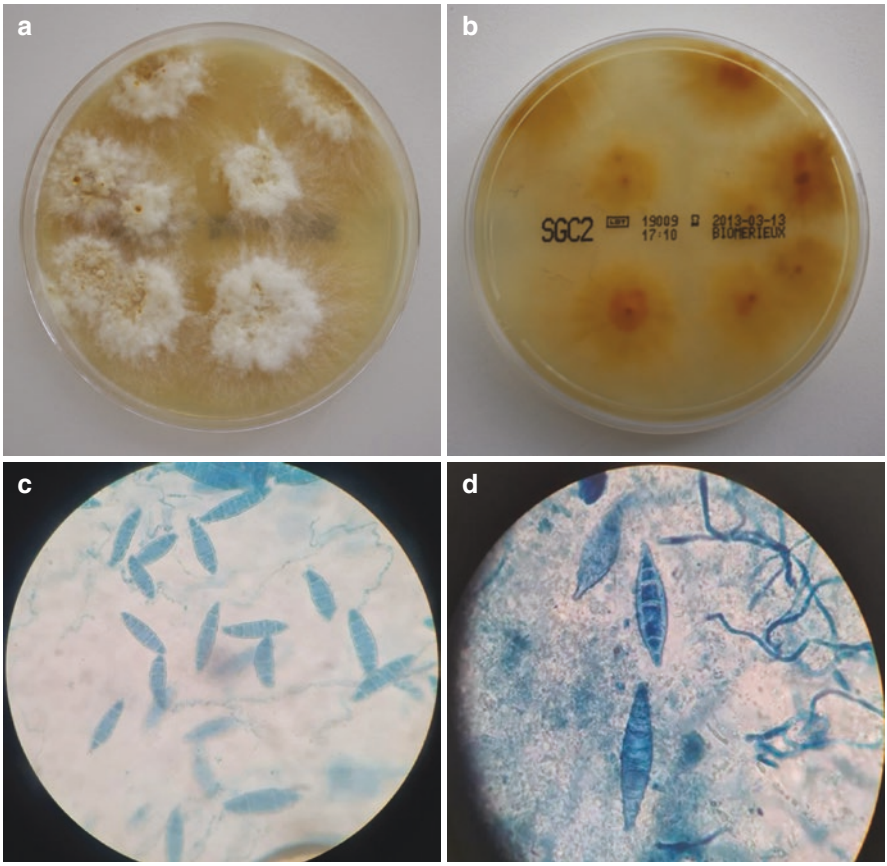


**Fig. 11.10** (**a**–**d**) *Microsporum canis*: (**a**) colony morphology, (**b**) reverse (underside), and (**c**, **d**) microscopic morphology

pigment that diffuses into the medium (Fig. 11.11a, b). Hyphae are septate. Macroconidia have walls that are relatively thin and usually smooth. They contain four to ten cells, are blunt tipped, and are often distinctively curved with a tapering base. Microconidia are usually abundant.

*Trichophyton mentagrophytes* invades all parts of the body surface, including hair and nails, and is a common cause of tinea pedis. The rate of growth is moderate with maturity in 7–10 days. Colony morphology varies greatly. The surface may be buff and powdery or white and downy and may become pinkish or yellowish. The powdery form exhibits concentric radial folds. The colonies rapidly develop a dense fluff. The reverse is usually brownish tan but may be colorless, yellow, or red (Fig. 11.12a, b). The microscopic morphology is characterized by septate hyphae. Microconidia in powdery cultures are very round and clustered on branched conidiophores, in fluffy strains smaller, fewer in number, tear-shaped. Macroconidia are sometimes present, cigar-shaped, and thin-walled and have narrow attachments to hyphae and contain 1–6 cells. Coiled spiral hyphae are often seen.

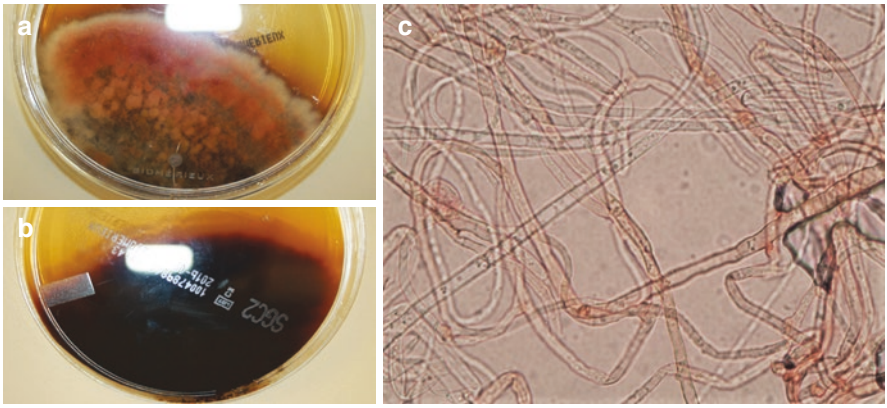


**Fig. 11.11** (**a**–**c**) *Microsporum gallinae*: (**a**) colony morphology, (**b**) reverse (underside), and (**c**) microscopic morphology

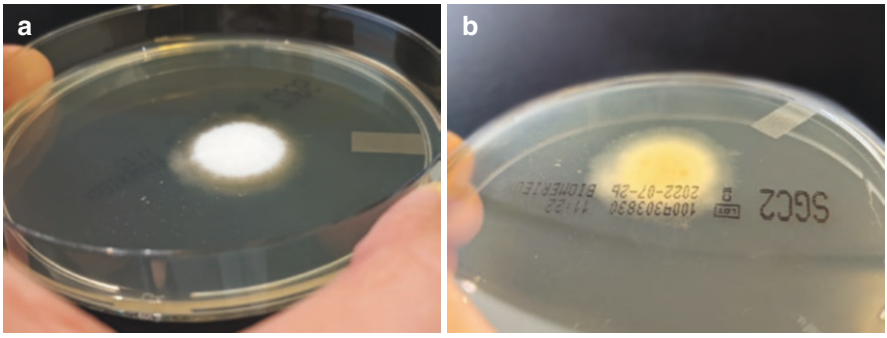


**Fig. 11.12** (**a**, **b**) *Trichophyton mentagrophytes*: (**a**) colony morphology and (**b**) reverse (underside)

*Trichophyton rubrum* is presently the most common dermatophyte infecting humans, primarily the skin and nails, and less frequently the beard or scalp. The rate of growth is moderately slow, with maturity within 14 days. Colony morphology is characterized by a granular or fluffy surface, white to buff. Reverse is deep red; occasionally it is brown, yellow-orange, or even colorless (Fig. 11.13a, b). Microscopic morphology is characterized by septate hyphae, tear-shaped microconidia that usually form singly all along the sides of the hyphae. Macroconidia may be abundant, rare, or absent; they are long, narrow, and thin-walled, with parallel sides (pencil-like), and have four to ten cells. They characteristically form directly on ends of thick hyphae. Microconidia characteristically form directly on macroconidia.

*Trichophyton tonsurans* is the principal etiologic pathogen of tinea capitis in the United States. Rate of growth in colony is moderately slow, with maturity in 12 days. Colony morphology is highly variable. Surface may be white greyish, yellow, rose,

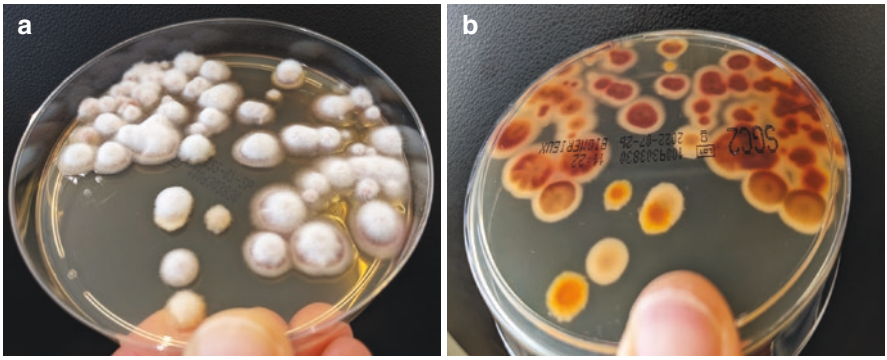


**Fig. 11.13** (**a**, **b**) *Trichophyton rubrum*: (**a**) colony morphology and (**b**) reverse (underside)

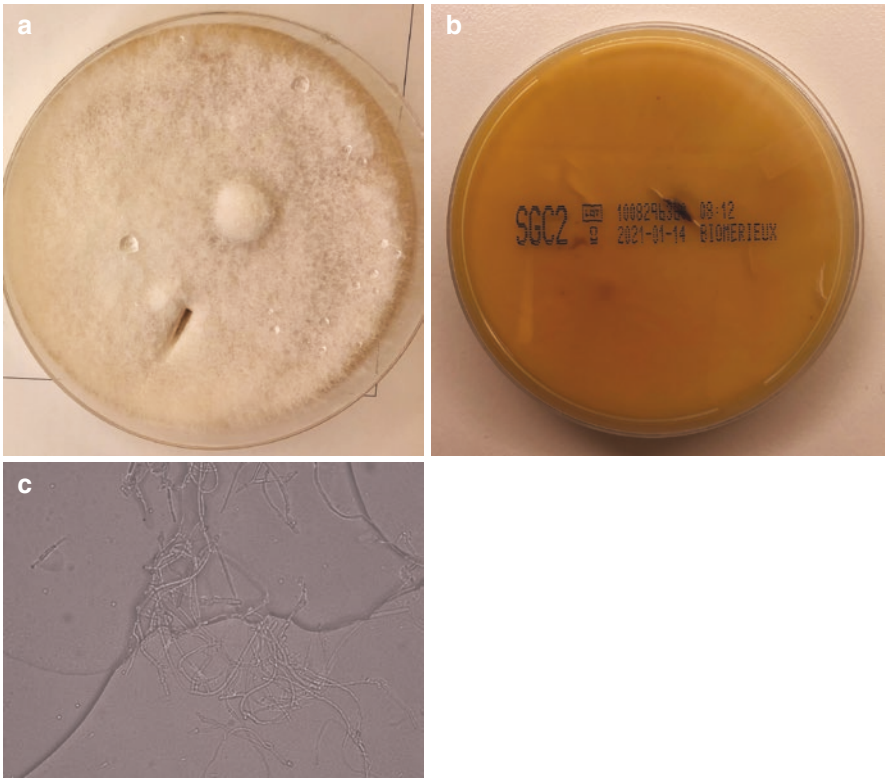


**Fig. 11.14** (**a**–**c**) *Trichophyton tonsurans*: (**a**) colony morphology, (**b**) reverse (underside), and (**c**) and microscopic morphology

or brownish. Surface is usually suede-like, with many radial or concentric folds. Reverse is usually reddish-brown, sometimes yellow, or colorless (Fig. 11.14a, b). Microscopy morphology is characterized by septate hyphae, with many variably

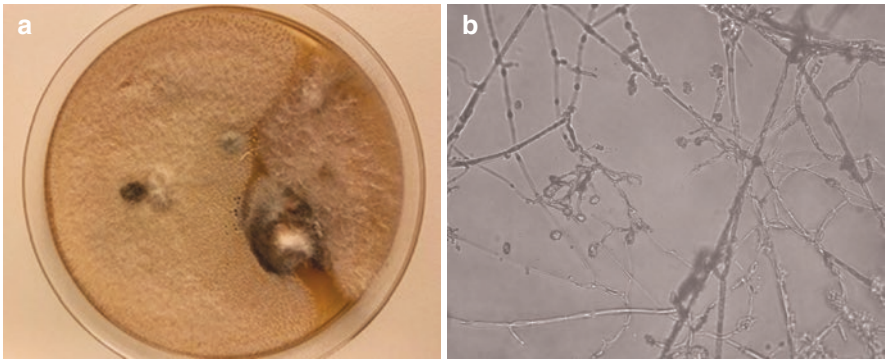


**Fig. 11.15** (**a**, **b**) *Trichophyton schoenleinii*: (**a**) colony morphology and (**b** microscopic morphology

shaped microconidia all along the hyphae or on short conidiophores that are perpendicular to the parent hyphae. Microconidia are usually teardrop- or club-shaped but may be elongate or enlarge to round balloon forms. Macroconidia are rare and irregular in form.

*Trichophyton soudanense* is endemic in Central and West Africa and is increasingly being reported in Europe. Colony growth rate is slow with maturity within 15 days. Colonies show a yellow to orange, suede-like surface that is flat to folded, with a radiating fringe. Reverse is similar in color to the surface. Microscopy features are septate hyphae that often break up to form arthroconidia. Characteristically, branches form at both forward and backward angles to the parent hypha, often giving the appearance of barbed wire. No macroconidia are seen.

*Trichophyton schoenleinii* is the causative agent of favus. This notorious kind of tinea capitis used to be highly frequent globally, mainly in impoverished countries. Currently, it has become a historical form, except in some areas in Asia and Africa. The rate of growth in colony is slow with maturity within 15 days. Colony is whitish, waxy, or slightly downy, heaped, or folded (Fig. 11.15a). Growth is often submerged and splits the agar medium. Reverse is colorless or pale yellowish orange to tan. Microscopic morphology is characterized by septate, highly irregular, and knobby hyphae. The subsurface hyphae usually form characteristic antler-like branching structures with swollen tips resembling nail heads (Fig. 11.15b). Chlamydoconidia are numerous. Microconidia and macroconidia are absent.

*Trichophyton verrucosum* infects the scalp and beard and is usually contracted from cattle. Colony rate of growth is slow, with maturity in 14–21 days. The colonies are usually small, heaped, and button-like but sometimes flat. The texture is skin-like, waxy, or slightly downy, the color usually white, but can be gray or yellow. The reverse varies from nonpigmented to yellow. On Sabouraud dextrose agar at 37 °C forms hyphae with many chlamydoconidia often in chains and some antler-like branches.

*Trichophyton violaceum* is yet another fungal species that has increased in prevalence especially in urban populations of the United Kingdom and Europe with

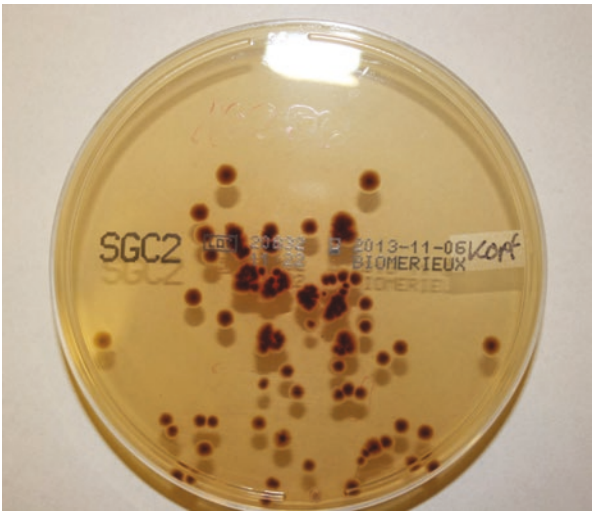


**Fig. 11.16** *Trichophyton violaceum*

changes in immigration patterns and increases in international travel. It most commonly affects the scalp and hair. Colony growth rate is slow, with maturity in 14–21 days. Original cultures are waxy, wrinkled, heaped, and deep purplish red. Reverse is lavender to purple (Fig. 11.16). Microscopic morphology is characterized by tangled, branches, irregular, and granular hyphae, with intercalary chlamydoconidia. Microconidia and macroconidia are not usually seen on Sabouraud dextrose agar.

*Candida albicans* is the most common cause of candidiasis, which is an acute, subacute, or chronic infection involving any part of the body. Rate of growth in colony is rapid, with maturity in 3 days. Colonies are cream-colored, pasty, and smooth (Fig. 11.17). On routine primary media, yeast cells are round to oval.

*Mucor* spp. are known as common contaminants and are occasionally the etiologic agent of zygomycosis. Rate of growth in culture is rapid with maturity with 4 days. Colonies quickly covers agar surface with fluff resembling cotton candy (Fig. 11.18), white, and later turns gray or grayish brown. Reverse is white. Microscopic morphology is characterized by wide hyphae that are practically nonseptate. Sporangiophores are long and often branched and bear terminal round, spore-filled sporangia. The sporangial wall dissolves, scattering the round and slightly oblong spores.

*Aspergillus* spp. are opportunistic invaders, the most common molds to infect various sites in individuals with lowered resistance due to neutropenia and/or treatment with high-dose corticosteroids or cytotoxic drugs. Since the organisms are widespread in the environment, they are commonly found as contaminants in cultures. The rate of growth in culture is usually rapid, with maturity within 3 days. The colony surface is at first white and then any shade of green yellow, orange, brown, or black, depending on the species (Fig. 11.19). Texture is velvety or cottony. Reverse is usually white, goldish, or brown. Microscopic morphology is

**Fig. 11.17** *Candida albicans*

**Fig. 11.18** *Mucor* spp. Most species are unable to infect humans due to their inability to grow in warm environments close to 37 degrees and usually represent a contaminant in culture

characterized by septate hyphae, an unbranched conidiophore arises from a specialized foot cell. The conidiophore is enlarged at the tip, forming a swollen vesicle. Vesicles are completely or partially covered with flask-shaped phialides, which may develop directly on the vesicle and produce chains of mostly round conidia.

*Penicillium* spp. are commonly considered as contaminants but found in a variety of diseases in which their etiologic significance is uncertain. Disseminated disease has been reported in severely immunocompromised patients. Many strains produce toxins. The rate of colony growth is rapid, with maturity within 4 days. The surface of colonies is at first white then becomes powdery and bluish green with a white

**Fig. 11.19** *Aspergillus* spp. The colony surface is at first white and then depending on the species any shade of green yellow (*Aspergillus flavus*), brown (*Aspergillus fumigatus*), or black (*Aspergillus niger*). Bright yellow/orange coloration on AFPA medium indicts aflatoxigenic *Aspergillus* species

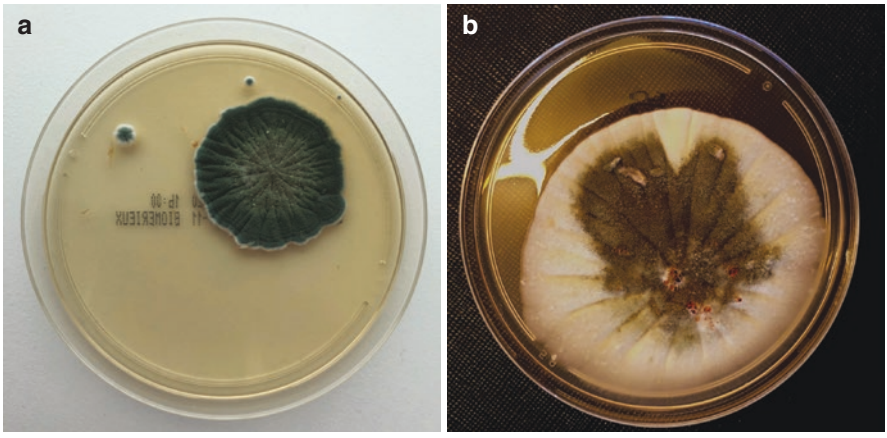


**Fig. 11.20** (**a**, **b**) *Penicillium* spp.: (**a**) the color of the surface is typically a dull dark green, (**b**) *Penicillium chrysogenum* (previously *notatum*). The fungal mycelium is seen, with new growth on the edges. It was the species which led Alexander Fleming (1881–1955) to discover quite by accident that this fungus inhibits the growth of bacteria, which subsequently led to the production of the first antibiotic penicillin

border (Fig. 11.20). Reverse is usually white but may be red or brown. Microscopic morphology is characterized by septate hyphae with branched or unbranched conidiophores that have secondary branches. On those are flask-shaped phialides that bear unbranched chains of smooth or rough, round conidia. The entire structure forms the characteristic "penicillus" or "brush" appearance.

All clinical providers are recommended to ascertain the causative organism in fungal infection, either through fungal culture or newer methods, such as the polymerase chain reaction assay [24]. Those interested in involving in clinical mycology are encouraged to refer to the respective textbooks, such as Davise Honig Larone (author), Thomas J. Walsh (author), Randall T. Hayden (author), and Davise H. Larone (illustrator): *Larone's Medically Important Fungi: A Guide to Identification*. ASM Books, 6th edition, 2018. This is an easy-to-use book that helps laboratory workers identify fungal pathogens under the microscope by their morphology and other readily identifiable features.

*Polymerase chain reaction* (PCR) is a method widely used to rapidly make millions to billions of copies—complete or partial—of a specific DNA sample, allowing investigators to take a very small sample of DNA and amplify it or a part of it to a large enough amount to study in detail. PCR is now a common and often indispensable technique used in medical laboratory research for a broad variety of applications including biomedical research, criminal forensics, and detection of pathogens in nucleic acid tests for the diagnosis of infectious diseases.

Using PCR, copies of very small amounts of DNA sequences are exponentially amplified in a series of cycles of temperature changes. The majority of PCR methods rely on thermal cycling. Thermal cycling exposes reactants to repeated cycles of heating and cooling to permit different temperature-dependent reactions, specifically, DNA melting and enzyme-driven DNA replication. PCR employs two main reagents: primers which are short single-strand DNA fragments known as oligonucleotides that are a complementary sequence to the target DNA region and a DNA polymerase. In the first step of PCR, the two strands of the DNA double helix are physically separated at a high temperature in a process called nucleic acid denaturation. In the second step, the temperature is lowered, and the primers bind to the complementary sequences of DNA. The two DNA strands then become templates for DNA polymerase to enzymatically assemble a new DNA strand from free nucleotides, the building blocks of DNA. As PCR progresses, the DNA generated is itself used as a template for replication, setting in motion a chain reaction in which the original DNA template is exponentially amplified. Almost all PCR applications employ a heat-stable DNA polymerase, such as Taq polymerase, an enzyme originally isolated from the thermophilic bacterium *Thermus aquaticus*. If the polymerase used was heat susceptible, it would denature under the high temperatures of the denaturation step. Before the use of Taq polymerase, DNA polymerase had to be manually added every cycle, which was a tedious and costly process.

## 11.9 Blood Tests

Diagnostic tests are useful when the probability of a disease being present is neither high nor low, since high degree of clinical certainty overrides the uncertainty of the laboratory data. The greater the number of different tests done, the greater the risk of getting false-positive or irrelevant leads. The possibilities for laboratory errors

increase in the automated multiple-screen procedures. Therefore, laboratory testing must be kept sharply focused. Clinical suspicion is the determinant, and knowledge of clinical dermatology is the prerequisite for combining medical sense with economic sense in requesting laboratory tests.

Elevations in the white blood count (WBC) are often associated with infection, though many viral infections are associated with leukopenia. It is important to assess the WBC differential, given that different classes of microbes are associated with various leukocyte types. For example, bacteria are associated with an increase in polymorphonuclear neutrophils, often with elevated levels of earlier developmental forms such as bands; viruses are associated with an increase in lymphocytes, and certain parasites are associated with an increase in eosinophils.

The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level are indirect and direct measures of the acute-phase response, respectively, that can be used to assess a patient's general level of inflammation. Moreover, these markers can be followed serially over time to monitor disease progress/resolution. It is noteworthy that the ESR changes relatively slowly, and its measurement more often than weekly usually is not useful: in contrast, CRP concentrations change rapidly, and daily measurements can be useful in the appropriate context. Although these markers are sensitive indicators of inflammation, neither is very specific. An extremely elevated ESR (>100 mm/h) has a 90% predictive value for a serious underlying disease.

The technology of infectious disease serology assays has been thus evolving ever since the Widal test more than 100 years ago to detect typhoid fever in serum from patients with fever suspected for *Salmonella typhi* infection [25], and it has been advancing rapidly in the last decades. The application of infectious disease serological assays is extremely broad since theoretically it can be developed for every pathogen. Despite the evolving technology in serological assays, serology is seldom used as the sole diagnostic tool. Only for a few bacterial infections, such as syphilis and disseminated manifestations of Lyme disease, are serological assays still used as the primary test for establishing the diagnosis.

In clinical virology, serology is mostly used to determine the stage of infection (acute versus past) by detecting the presence of the IgM antibodies, or by showing significant changes in antibody titers (follow-up serum samples are needed), or by avidity testing (IgG antibody produced early in the infection showing low binding strength between antibodies and virus).

Syphilis may be difficult to diagnose clinically, particularly during early infection. Confirmation is either via direct visual inspection using dark field microscopy or blood tests. Blood tests are more commonly used, as they are easier to perform.

A non-treponemal test is a blood test for diagnosis of infection with syphilis. Non-treponemal tests are an indirect method in that they detect biomarkers that are released during cellular damage that occurs from the syphilis spirochete. Syphilitic infection leads to the production of nonspecific antibodies that react to cardiolipin.

This reaction is the foundation of the non-treponemal assays such as the *VDRL (Venereal Disease Research Laboratory) test* and *rapid plasma reagin (RPR)* test that are flocculation-type tests that use an antigen-antibody interaction. The complexes remain suspended in solution and therefore visible due to the lipid-based antigens. These have replaced the original non-treponemal test, the Wassermann test. The non-treponemal tests measure immunoglobulins G (IgG) and M (IgM) anti-lipid antibodies formed by the host in response both to lipoidal material released from damaged host cells early in infection and to lipid from the cell surfaces of the treponeme itself. These non-treponemal tests are widely used for qualitative syphilis screening, since these tests are relatively simple to perform and interpret and can allow rapid return of results and are very cheap. However, their usefulness is limited by decreased sensitivity in early primary syphilis and during late syphilis. In addition, with non-treponemal tests, false-positive reactions can occur for a large number of reasons, the most common of which is other infections or connective tissue diseases, such as borreliosis and lupus erythematosus, respectively. Moreover, these tests may show false-negative when the patient's antibody titer is very high due to a so-called prozone effect. Because of the issues with false positives, confirmation with a second treponemal test that is specific for *T. pallidum* antibodies is recommended [26].

In contrast, the treponemal tests look for antibodies that are a direct result of the infection thus, anti-treponeme IgG and IgM.

The *fluorescent treponemal antibody absorption (FTA-ABS) test* is a diagnostic test for syphilis. Using antibodies specific for the *Treponema pallidum* species, such tests would be assumed to be more specific than non-treponemal testing such as VDRL but have been shown repeatedly to be sensitive but not specific for the diagnosis of neurosyphilis in CSF. FTA is nearly 100% sensitive in CSF. Negative FTA in CSF and exclude neurosyphilis. In addition, FTA-ABS turns positive earlier and remains positive longer than VDRL. This test is not useful for following therapy, because it does not wane with successful treatment of the disease and will continue to be positive for many years after primary exposure.

The *Treponema pallidum particle agglutination assay (TPPA test)* is an indirect agglutination assay used for detection and titration of antibodies against *Treponema pallidum*. In the test, gelatin particles are sensitized with *T. pallidum* antigen. Patient serum is mixed with the reagent containing the sensitized gelatin particles. The particles aggregate to form clumps when the patient serum is positive for syphilis. In other words, the patient's serum contains antibodies to *T. pallidum*. A negative test shows no clumping of gelatin particles. For primary syphilis, TPPA has a sensitivity of 85–100% and a specificity of 98–100%. In secondary and late-latent syphilis, TPPA has a sensitivity of 98–100%.

A similar specific treponemal test for syphilis is the *Treponema pallidum hemagglutination assay (TPHA)*. TPHA is an indirect hemagglutination assay used for the detection and titration of antibodies against *Treponema pallidum*. In the test, erythrocytes are sensitized with antigens from *T. pallidum*. The cells then aggregate on the surface of a test dish if exposed to the serum of a patient with syphilis.

It is used as a confirmatory test for syphilis infection. A negative test result shows a tight button or spot of red blood cells on the surface of the test dish. Often a plastic test plate containing many small wells is used as the test dish so that many patients may be tested at the same time, but their results can be kept separate from each other.

The traditional testing algorithm for syphilis begins testing with the non-treponemal test. If the non-treponemal test is reactive, a treponemal test is then used to confirm syphilis infection.

The reverse testing algorithm for syphilis begins testing with a treponemal test. If this test is reactive, a non-treponemal test is performed. When the non-treponemal test is nonreactive, a second treponemal test is performed to determine if the first treponemal test was a false positive. The second treponemal test performed must be different than the initial treponemal test. The reverse testing algorithm has been in place since 2009. This algorithm is attractive to laboratories that have a high testing volume because it reduces the amount of manual labor conducted for the non-treponemal tests.

Because the antibodies detected in treponemal tests usually remain detectable for life, even after successful treatment, the non-treponemal titer (RPR or VDRL) must be used to monitor for a reinfection with syphilis. An increase in titer of two dilutions represents reinfection with *Treponema pallidum*.

Two-tiered serological testing is performed for differential diagnosis of *Borrelia* infection (Lyme disease). The first-tier tests detect specific antibodies (IgM and IgG together or separately) and include enzyme-linked immunoassays (EIA) and immunofluorescent assays. Positive results for first-tier tests are confirmed using second-tier testing. The second tier consists of standardized immunoblotting, by using either Western blots or blots striped with diagnostically important purified antigens. Positive results for second-tier tests are confirmatory for the presence of Borrelia infection.

The recommended two-tiered serology for Lyme disease begins with an EIA. If the EIA is positive or equivocal, immunoblotting should be performed. Both a positive or equivocal EIA and a sufficient number of immunoblot bands ($\geq$2 of 3 IgM or $\geq$5 of 10 IgG) are required for a positive test. Clinicians interpreting test results should not focus on individual positive bands as these have no diagnostic value on their own. Patients with Lyme disease symptoms (>30 days) require positive IgG immunoblot results to confirm diagnosis [27].

*QuantiFERON-TB Gold* (QFT) is a simple blood test that aids in the detection of *Mycobacterium tuberculosis*. QFT is an interferon-gamma (IFN-γ) release assay, commonly known as an IGRA, and is a modern alternative to the tuberculin skin test (TST, PPD, or Mantoux). Unlike the TST, QFT is a controlled laboratory test that requires only one patient visit and is unaffected by previous Bacille Calmette-Guerin (BCG) vaccination. QFT is highly specific and sensitive: a positive result is strongly predictive of true infection with *M. tuberculosis*. However, like the TST and other IGRAs, QFT cannot distinguish between active tuberculosis disease and latent tuberculosis infection and is intended for use with risk assessment, radiography, and other medical and

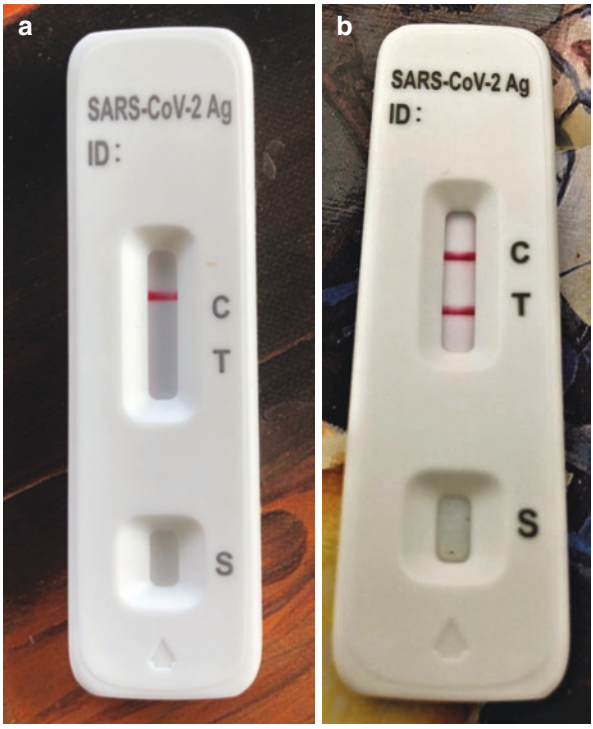


**Fig. 11.21** (**a**, **b**) COVID-19 rapid test: (**a**) negative test result and (**b**) positive test result

diagnostic evaluations. Like any diagnostic aid, QFT cannot replace clinical judgment.

Considering the emerging infectious diseases, Fischer et al. reviewed the use of serological tests to diagnose such as Zika, Dengue fever, and Chikungunya [28].

COVID-19 testing involves analyzing samples to assess the current or past presence of SARS-CoV-2. The two main types of tests detect either the presence of the virus or antibodies produced in response to infection.

Molecular tests for viral presence through its molecular components are used to diagnose individual cases and to allow public health authorities to trace and contain outbreaks. There are multiple types of tests that look for the virus by detecting the presence of the virus's RNA. As of 2021, the most common form of molecular test is the reverse transcription polymerase chain reaction (RT-PCR) test [29]. Antigen tests look for antigen proteins from the viral surface. In the case of a coronavirus, these are usually proteins from the surface spikes. SARS-CoV-2 antigens can be detected before onset of COVID-19 symptoms (as soon as SARS-CoV-2 virus particles) with more rapid test results (Fig. 11.21a, b) but with less sensitivity than PCR tests for the virus [30].

Antibody tests (serology immunoassays) instead show whether someone once had the disease [31]. They are less useful for diagnosing current infections because antibodies may not develop for weeks after infection. It is used to assess disease prevalence, which aids the estimation of the infection fatality rate [32].

Test analysis is often performed in automated, high-throughput, medical laboratories. Rapid self-tests and point-of-care testing are also available and can offer a faster and less expensive method to test for the virus although with a lower accuracy.

## 11.10 Imaging

Imaging provides an important adjunct to the physical examination, allowing evaluation for lymphadenopathy in regions that are not externally accessible, such as the mediastinum, or intra-abdominal sites, and assessment of internal organs for evidence of infection, particularly the lungs, the liver, the kidneys, and the brain.

Ultimately, the dermatologist participates with the other medical disciplines in the diagnosis and treatment of infections as they may relate to systemic disease. Specifically, infection multidisciplinary team meetings allow for detailed and combined review of the history, examination, and imaging findings of a patient, which leads to improved use of radiological investigations and patient management [33]. Particularly in the wake of the COVID-19 pandemic, the importance of interdisciplinary communication has become evident both in research and infectious disease management.

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# Concluding Remarks

The hair in infectious disease exemplarily demonstrates that the professional care for the hair and scalp in health and disease represents a medical discipline as any other.

Originally taken care of by trichologists, whom in most jurisdictions are considered a paramedical discipline, trichologists themselves are not normally medically qualified, although members of the medical profession can undertake courses and/or careers within trichology. Trichologists are taught the practice of care and treatment of the human hair and scalp in health and disease within their restricted but specialized role [1]. However, the limited success rate of trichological management of hair and scalp problems points to a more important complexity of the respective disorders.

In fact, as with any medical problem, the patient complaining of a hair or scalp problem requires a comprehensive medical and drug history, physical examination, and appropriate laboratory evaluation to identify the cause. Prerequisite for delivering appropriate patient care is an understanding of the anatomy of the scalp and hair, of the dynamics underlying hair growth and shedding, and of the various causes of hair and scalp pathology, including the infectious diseases.

It was against this backdrop that in 2018 we and others proposed the term trichiatrist for board-certified dermatologists dealing with the medical care of the hair and scalp in health and disease to distinguish them from the trichologists [2].

The history of medical reasoning has been one of an evolution from magical medicine, through speculative medicine based on speculative philosophical systems rather than the empirical and experimental approach, over pragmatic medicine dealing with things in a way that is based on practical rather than theoretical considerations, to today's evidence-based medicine and precision medicine.

Evidence-based medicine seeks to assess the strength of the evidence of risks and benefits of diagnostic tests and treatments, using techniques from science, engineering, and statistics, such as the systematic review of medical literature, meta-analysis, risk-benefit analysis, and randomized controlled trials [3]. Evidence-based medicine aims for the ideal that healthcare professionals should make conscientious, explicit, and judicious use of the best available evidence gained from the scientific method for clinical decision-making.



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Precision medicine refers to the customization of medical care to the individual characteristics of the patient. It does not literally mean the creation of treatments that are unique to a particular patient but rather the ability to classify patients at hand into subpopulations that differ in their susceptibility to a particular medical condition, in the biology or prognosis of those medical conditions they may develop, or in their response to a specific treatment [4].

The quality and stringency of the trichiatrist's graduate medical training is identical to that of fellow physicians of any other discipline, allowing the trichiatrist to be comprehensive in counselling patients, prescribing medication, conducting physical examinations, ordering laboratory tests, and participating with the other medical disciplines in the diagnosis and treatment of hair problems as they may relate to systemic disease, in this context, specifically the infectious diseases. Prerequisite to successful management of any medical condition is adhering to the principles of evidence-based medicine and precision medicine.

In many instances, a specific diagnosis may be made in a fraction of a second if it is a simple matter of recognition. The informed look is the one most practiced by dermatologists. It comes from knowledge, experience, and visual memory. Where the diagnosis does not come from a glance, the diagnostic tests come in.

Among these, dermoscopy of the hair and scalp has gained popularity in daily clinic practice as an effective tool in the differential diagnosis of hair and scalp disorders and for this purpose has been named trichoscopy [5]. Originally performed by the trichologists before its introduction into dermatology [6], though without the clinicopathologic understanding of dermatologists through their academic learning, the method involves viewing of the hair and scalp at high magnifications using a simple handheld dermatoscope. Nevertheless, as a diagnostic procedure, dermoscopy of the scalp is to be understood as representing an integral part of a more comprehensive dermatological examination and as an integral part of surface or epiluminescence microscopy of the skin. As such, the distinct term trichoscopy suggests too much self-reliance. Moreover, the term is etymologically amiss, since it refers to the hair (Greek τρίχα), while an important part of the dermoscopic signature patterns relates to the condition of the scalp skin. Why refer to dermoscopy of the hair and scalp differently than to that of the skin, while by analogy no distinction is made between stethoscopy of the heart and of the lung? [7].

Ultimately, the golden standard for diagnosis of hair shaft disorders, such as among the infectious diseases and infestations, of trichobacteriosis palmellina, piedra, and pediculosis capitis, remains the light microscopic examination. In case of scalp pathologies with evidence of inflammation and scarring, microbiological studies and performance of a scalp biopsy remain indicated, irrespective of performance of dermoscopy. In fact, dermoscopy has been proposed for guidance to an optimal site for biopsy [8]. It would be imprudent to replace well-tried dermatologic examination procedures and rely on dermoscopy alone, such as the hair pluck in postinfectious effluvium, the light microscopic hair shaft analysis in the infectious disorders of the hair shaft and infestations, the microbiological studies in tinea capitis and the pyodermas, and the scalp biopsy for histopathological examination with the respective stains in the infectious granulomatous diseases. Besides, the

respective microbiologic studies are important for epidemiological reasons, such as a comprehension of the routes of infection and eradication of a soil, animal, or human source of infection. Besides, so far only in the diagnosis of early female androgenetic alopecia has dermoscopy proven to be superior to the respective standard diagnostic procedure [9].

Consequently, we have intentionally omitted the usage of the term trichoscopy in favor of scalp dermoscopy throughout the textbook, exactly as we discourage the further use of the term trichologist for physicians dealing with the diseases of the hair and scalp in favor of trichiatrist.

An understanding of the hair and scalp in relation to the infectious diseases goes well beyond hair loss and trichology. Recently, the novel viral pandemic coronavirus disease 2019 (COVID-19) has sparked uncertainties and controversies as to its origin, epidemiology, and natural course. In this situation, the medical disciplines have strived to contribute to a better understanding of the disease. The study of the cutaneous manifestations of COVID-19, including the hair [10], has evolved with the hope that they may be useful as markers for disease, for prognostication, and for further insights into the pathogenesis of the disease manifestations.

An understanding of the infectious diseases underlying hair loss and scalp disease requires a more comprehensive understanding of the environmental and customary factors, of the individual preconditions, and of the peculiarities of the specific pathogens in their relationship to the varied clinical presentations.

Indeed, "the characteristic microbe of a disease might be a symptom instead of a cause," as George Bernard Shaw (1856–1950) put it forth in his problem play "The Doctor's Dilemma" (first staged in 1906 at the Royal Court Theatre) relating to the moral dilemmas created by the conflicts between the demands of medical practice as a business or a vocation.

Finally, politics has so far focused its attention on the macroscale of climate change, while infamously neglecting the organic microscale in the planetary oikos, the Earth's household. The age of Anthropocene has reshaped the Earth's surface with a force previously thought to be due solely to geological forces. Ultimately, the way we affect the microbiome affects us.

In Greek mythology, Gaia is the personification of the Earth and one of the Greek primordial deities. Gaia is the ancestral mother, sometimes parthenogenic, of all life. The mythological name was revived in 1979 by British scientist James Lovelock, who proposes in the Gaia hypothesis that living organisms interact with their inorganic surroundings on Earth to form a synergistic and self-regulating, complex system that helps to maintain and perpetuate the conditions for life on the planet.

Precedents of the theory have been the German explorer Alexander von Humboldt (1769–1859) who recognized the coevolution of living organisms, climate, and Earth's crust and at the turn to the twentieth century American naturalist Aldo Leopold (1887–1948), pioneer in the development of modern environmental ethics and in the movement for wilderness conservation, who suggested a living Earth in his biocentric or holistic ethics regarding land.

Lovelock started defining the idea of a self-regulating Earth controlled by the community of living organisms in September 1965 and formulated the Gaia Hypothesis in journal articles in 1972 [11, 12], followed by a popularizing 1979 book *Gaia: A New Look at Life on Earth* and a popular book length version of the hypothesis, published in 1979 as *The Quest for Gaia*. In 1971 American biologist Lynn Margulis (1938–2011) joined Lovelock in the effort of fleshing out the initial hypothesis into scientifically proven concepts, contributing her knowledge about how microbes affect the atmosphere and the different layers in the surface of the planet. However, she objected to the widespread personification of Gaia and stressed that Gaia is "not an organism" but "an emergent property of interaction among organisms." She defined Gaia as "the series of interacting ecosystems that compose a single huge ecosystem at the Earth's surface" (Fig. A.1).

In popular culture, "Gaia" is a 2021 South African ecological horror thriller film. Placed in the Tsitsikamma forest in South Africa, a fungus of monumental proportions proliferates at night, gathering strength, threatening to take over the Earth. The opening scene is straight out of Joseph Conrad's (1857–1924) *Heart of Darkness*: two people paddle down a river in a canoe. The river is crowded in on all sides by thick jungly green. It's a lonely sight, often presented from a God's eye view, appropriate since these two people are operating a drone, buzzing above and around them.

**Fig. A.1** Painting by Juan E. Jörgensen. (Courtesy of Beceren Art and Antiques, Zurich)

When night falls, the forest transforms into a sentient being, crawling with mysteries, mushrooms curling upward, with long twirling fronds taking on a life of their own. Directed and produced by Jaco Bouwer, from a screenplay by South African writer Tertius Kapp, "Gaia" has a lot to say about humanity's destruction of the environment, about the tipping point we have collectively reached in Anthropocene, but the film says it with creativity, mad flights of imagination, and even humor. "Gaia" does not feel like homework. It's a thought-provoking and disturbing experience rather than a lecture. "Gaia" is a trip, where literally, magic mushrooms are involved.

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