Epidemiology of nail infection due to keratinophilic fungi

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Summary

The epidemiology of fungal infections of the nails, or onychomycosis, is only partially known since it is a combination of different factors which include, among others, the etiological agent, the clinical form of the infection, the patient's background, other parameters related to the physiology and ecology of the causative fungi, and even the habits of the population.

This chapter is a review of the data available on the most frequent etiological agents as well as several occasional ones, and includes the methods used for a more accurate diagnosis. Although there is no doubting the importance of dermatophyte fungi, especially *Trichophyton rubrum*, as the causative agents of *tinea unguium,* the etiological role of some keratinophilic yeasts and moulds is more controversial as they are so-called opportunistic agents of onychomycosis. To a large extent the clinical forms of onychomycosis refer to a particular fungus or group of fungi, some of which, like *Scytalidium/Hendersonula* for example, are only found in certain regions with a warm climate.

Although there is the belief that onychomycosis has increased its presence, especially in developed countries, the data available on its prevalence is limited and varies considerably according to the origin of the publication and the study method.

Consideration is given to the factors favouring infection, the low incidence of this mycosis among the younger age group, and the social and economic impact of onychomycosis in developed countries.

Key words

Onychomycosis, Nail infection, *Tinea unguium*, Keratinophilic fungi, Epidemiology

In superficial fungal infections the pathogenic invading fungus is confined to the horny stratum of the skin and there is no, or at least minimal, tissue reaction [1]. This differentiates them from skin mycosis where all the keratinised tissues: skin, hair, fur, feathers and nails can be affected. In the latter case, however, the fungi are usually confined to the horny layers of the skin and its surrounding tissues, this causes destruction of these structures and may bring about an immunological host reaction. The main types of mycosis and their etiological agents are shown in Table 1**.** This definition disregards fungal infections of the skin and mucous membranes that could occur in the course of a systemic mycosis where there is a haematogenic dissemination with skin locations, as well as fungal infections that affect the skin as well as subcutaneous tissue or other deeper structures.

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Mycosis of the skin, also called dermatomycosis, affects a large part of the world's population and they had a considerable influence on health in Europe until the middle of the 20th century. Many of these infections occur as hyperendemic diseases capable of producing epidemic outbreaks in susceptible populations, especially in children and teenagers [2]. These infections now mainly affect less-developed countries, and the lower social classes of industrial cities, where there are conditions of poor hygiene and a lack of health care; in this rather large proportion of the world's population, for example, there is still a hyperendemia of *tinea capitis* in prepubertal children.

Infections of the nails are also included in this group of skin mycosis, in spite of the fact that they are usually considered superficial infections; the fungal invasion does in fact frequently cause a hyperkeratosis reaction and a greater or lesser degree of destruction to the external layers or other structures.

Infections of the nails caused by fungi have not been extensively studied. This is partly because traditionally they have been considered more a cosmetic problem than a health problem [3], and therefore of only minor importance.

As dermatomycosis are not diseases requiring declaration, just like other types of mycosis, little is known of their incidence and prevalence in the world's population. As will be seen here, most of the available data proceeds from partial clinical or mycological studies carried out in very specific areas. Sometimes even in an extremely limited population. If the frequency and distribution of dermatomycosis in the general population is

Table 1. Superficial and skin mycosis, etiological agents.

Types of mycosis	Etiology
Superficial	
Black piedra	*Piedraia hortai*
White piedra	*Trichosporon asteroides* *Trichosporon ovoides* *Trichosporon cutaneum* *Trichosporon inkin* *Trichosporon mucoides* [60].
Tinea nigra palmaris	*Exophiala werneckii* (sin.*Cladosporium weneckii)* *Stenella araguata*
Pityriasis versicolor	*Malassezia furfur*
Cutaneous	
Dermatophytosis or *tinea*	Species of dermatophytes beloging to genera: *Microsporum* *Trichophyton* *Epidermophyton*
Cutaneous-mucous Candidosis	*Candida albicans* *Candida* sp.
Mycosis "*tinea*- like"	*Scytalidium dimidiatum* *Hendersonula toruloidea* *(sin: Nattrassia mangiferae)* *Scytalidium hyalinum*
Onychomycosis	Species of dermatophytes Species of yeasts Opportunistic moulds

unknown, the same is also true for onychomycosis, in spite of the fact that some studies have been published over the last few years in an attempt to approach this subject. This article reviews the current concept of infections of the nails produced by different fungi, mainly concentrating on the factors that influence their cause and distribution.

Characteristics of the nail

In order to better understand the mechanism of any infection of the nail it is first necessary to review its anatomical and functional characteristics: the ungual plate or nail is the end product of a continued process of growth and maturity that occurs in a specific and very active base area that is called the matrix: this is the area where the ungual plate is developed, differentiated and where keratinization takes place. The plate is the visible structure, it is rectangular or quadrilateral in shape, hard but flexible, with a convex external surface, shiny and transparent and encases the dorsal face of the last phalanx of the digits of the hands and feet. Its proximal part is yellow or white in colour and the lunule or visible part of the ungual matrix may often be seen in the centre. The proximal and lateral folds of the skin surrounding the nail form the cuticle, that mainly protects the matrix. The internal face of the plate is seated on the ungual bed, a flat epithelium layer which the nail slides over as it grows. The more distal end of the nail is the hyponychium and this is made up of the subungual space and the epithelium that forms the nail bed. The integrity of this structure is essential in preventing any fungal invasion (Figure 1).

The ungual plate grows very slowly, in normal people the rate is 2-3 mm a month for the hands and 1 mm per month for the feet. It is estimated that about six months are required to replace a fingernail and more than 18 months to completely replace the toenail. The growth of the nails is much slower in the elderly and as the result of various diseases.

The function of the nail is to protect the fingers and increase the sensitivity of their tips. They also have an important influence on precise movements of the fingers,

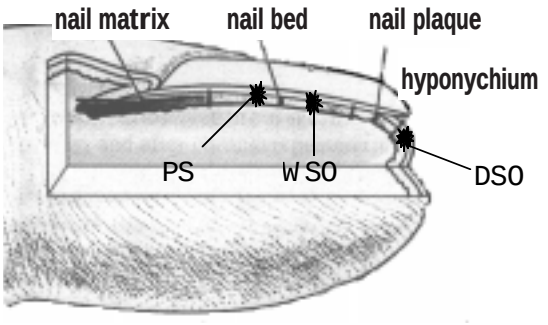

Figure 1. Figure of a human nail. Schematic types of onychomycosis.

especially for grasping, and form part of our defence mechanism. In society they have also assumed an important role in our conception of beauty and cosmetics (Table 2).

The normal structure of the nail alters with age producing changes in the colour, thickness, flexibility and shape. Increased fragility and loss of the surface sheen are the main consequences of ageing; in some cases there are marked dystrophic disturbances, mainly on the toenails. These alterations of the nail mean that it loses most of its function and is more exposed to aggression, including infection by various species of fungi (Figure 1).

Table 2. Functions of the nails.

Protection of the terminal phalanx
Support for fine mobility of the fingers
Base to improve the grasp
Increased distal sensitivity of the fingers
Defence structure
Beauty or cosmetic element

Fungal infections of the nails: onychomycosis

Infections of the nail caused by fungi or ungual mycoses are generically called *onychomycosis*, a term derived from the Greek "*Onychos*" which means nail, and *Mycosis* an infection by fungi. This term is basically for clinical application since as soon as mycological or histopathological studies confirm that the nail is invaded by fungi, and the culture allows the causative species to be identified, this term should be replaced by one that is more descriptive and specific: *tinea unguium* when the agent is a dermatophyte; onyxis if the infection is by yeast-like fungi, or ungual candidiasis if the fungi responsible for the complaint are yeasts of the *Candida* genus and ungual mycosis by species *xxx* in the case of the causative agent being an opportunistic filamentous fungus. According to the recommendations for identification of fungal infections proposed by the International Society for Human and Animal Mycology [4] in this case the name would have to be for example: 'Ungual infections by *Fusarium solani*, or *Fusarium solani* caused ungual mycosis', applicable to each species recognised as a causative agent, after having complied with the requirements that confirm that this particular saprobic fungus is in reality the one responsible for the infection of the nail (see diagnostic chart).

Pathogenesis

Numerous fungi that are parasites of man and other mammals can only develop on keratinised tissues. This means that they are unable to develop in the presence of serum factors and in many cases do not tolerate the body temperature of 37°C. The keratin acts as a barrier, protecting the fungi from the serum [5] and these micro-organisms that grow on the horny layer are not involved in the inflammatory response that mainly affects the dermis. The nail is even more isolated from neighbouring dermal structures.

The dermatophytes are a group of fungi that are highly specialised in invading the keratin of the nails of living beings, many other micro-organisms usually use the keratin of dead animals or hair, feathers, and skin that have been shed and therefore are not subject to any metabolic change. They are all known as keratinophilic fungi, because of their craving for keratin which they use as a substrate to obtain the nutrients necessary for their development.

Dermatophytes is the best studied group of keratinophiles. In some species of *Trichophyton* it has been demonstrated that arthroconidia, very resistant to adverse environmental factors and able to survive for long periods, constitute the main infectious elements [6]. In the case of *T. mentagrophytes* it has been shown that the arthroconidia attach to human corneocytes after just a few hours of contact and this is considered a first step towards development of infection. Arthroconidia comprise a fibrillar material that attaches to the external membrane of the corneocyte. Within just a few hours they undergo a thickening and produce a germinative tube as the first phase of development of the mycelial structure that can penetrate between the keratinised cells or even inside them [7]. Their capacity to metabolise keratin is due to the production of extracellular soluble factors with enzymatic properties capable of digesting keratin. These enzymes include hydrolytic types: endopeptidases, lipases, glucosidases and nucleases, whereas among the proteolytic enzymes there are the keratinases, colagenases and elastases. The serine endopeptidases that are involved in the catabolism of extracellular proteins are secreted by some dermatophytes and could play an important role in the invasion of the skin and the appendages.

The keratinolysis produced by the dermatophytes may be increased by a process of sulfitolysis, denaturalising the keratin. Keratinases have been detected in skin samples of *tinea pedis* produced by *T. rubrum* and also in biopsies of the skin of guinea pigs experimentally infected with *T. mentagrophytes* [8,9].

Recently, these enzymes have been shown to have a certain specificity, thus *T. simii* is capable of producing extracellular keratinases *in vitro* that can degrade the keratin present in buffalo skin but they have much less effect on chicken feathers [10].

These enzymes not only encourage penetration and development of the mycelium but furthermore lead to inflammatory and immune responses that constitute a factor of pathogenicity of the first order. Their specific role in the invasion and destruction of the ungual keratin, however, has been little studied.

Clinical presentation

Several clinical forms of ungual infection have been determined, some of them are produced by certain etiological groups; these clinical forms and their main etiological agents are shown in table 3 and figure 1.

Table 3. Clinical forms of onychomycosis, associated factors and the main etiological agents.

Clinical form	Etiology	Associated factors
Distal Subungual Onychomycosis (DSO)	*Trichophyton rubrum* *Trichophyton mentagrophytes* *Candida albicans* *Aspergillus*	Traumatisms
White Superficial Onychomycosis (WSO)	*Trichophyton rubrum* *Trichophyton mentagrophytes* *Acremonium* *Aspergillus* *Fusarium* *Scopulariopsis*	
Proximal Subungual Onychomycosis (PSO)	*Trichophyton rubrum* *Scytalidium* *Fusarium*	HIV, Paronychia
Total Distrophy Onychomycosis (ODT)	*Candida albicans* *Hendersonula toruloidea*	Immunodeficiencies, Endocrinopathies, neoplasias

Distal Subungual Onychomycosis (DSO) is the most common clinical form and its causative agents are mainly dermatophytes, although it may also be caused by yeasts and some moulds. The infection is initiated by the free edge of the nail propagating itself along the internal face of the plate and invading the hyponychium. The hyphae migrate in a proximal direction and cause focal parakeratosis and subungual hyperkeratosis leading to detachment of the plate from its bed. Changes in the colouring of the nail are usual, with yellow and brown being predominant. The toenails are frequently affected. The fingernails may not present hyperkeratosis but there is always considerable onycholysis, and in this case it is frequent that the agent is *Candida albicans* or another species of this same genus.

Synonym: Lateral Distal Onychopathy.

White Superficial Onychomycosis (WSO) is the next most common after DSO. It begins on the external face of the ungual plate in the form of whitish stains on the surface that become confluent but which may also take on a yellowish or brownish colouration. The structure of the nail is usually preserved so it is considered a totally superficial infection. This mycosis mostly affects the toenails and is caused by dermatophyte fungi and some filamentous opportunist agents such as *Fusarium*, *Acremonium* and *Aspergillus*.

Other synonyms are: Mycotic Leukonychia, Trichophytic Leukonychia and Superficial White Onychopathy.

Proximal Subungual Onychomycosis (PSO). This tends to occur as a proximal paronychia of the cuticle area from where it invades the recently formed ungual plate and migrates distally causing changes in the coloration and destruction of the plate. It is not uncommon to lose the nail. It is produced by dermatophyte fungi, mainly *T. rubrum* but also by *Scytalidium*, in addition to opportunistic moulds such as *Fusarium* (Figure 2). It seems to be more frequent in patients with immunodeficiencies and so has been described as a clinical form common to AIDS patients and has even been considered as a marker of HIV infection [11].

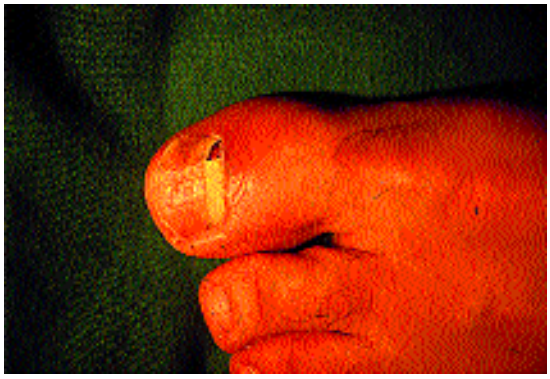

Figure 2. Nail infected by *Fusarium solani.* Proximal Superficial Onychomycosis (PSO).

Total Dystrophic Onychomycosis (TDO). This is the most destructive clinical form and is the end result of the evolution of any of the other three clinical forms (Figure 3). It has also been related with *C. albicans* in the course of chronic mucocutaneous candidiasis where there is a condition of cell immunodeficiency associated with considerable inflammation that affects the tip of the finger. *Candida* granuloma is rather uncommon but extremely aggressive. TDO is also observed in patients with other immunodeficiencies and in neoplastic patients. On rare occasions *Hendersonula toruloidea* has been described as the causative agent.

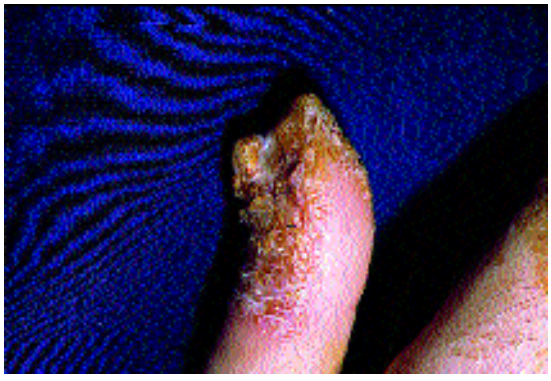

Figure 3. Total Dystrophic Onychomycosis (TDO).

Paronychia. In addition to the affectation of the nail itself, infections produced by yeasts of the *Candida* genus also tend to include an infection of the lateral and proximal periungual folds in the form of a chronic inflammation called Paronychia or Chronic Mycotic Perionyxis. From the initial focus of the cutaneous infection area, it may spread to invade the nail. The hands are more commonly affected and the nails become convex, with transverse grooves (Beau's lines), rough, without sheen, yellowish, with the possibility of evolving into TDO. The factors favouring infection are maceration of the skin of the hands, traumatisms and chemical abrasions. The skin appears oedematous and with erythema, sometimes painful and festering. The usual etiology is *C. albicans* and paronychia tends to lead to the onset of PSO; it is occasionally associated with a bacterial infection by *Pseudomonas aeruginosa* or *Staphylococcus aureus*.

Fungal infection may occur on nails previously altered by congenital processes, psoriasis, rheumatoid arthritis, chronic alcoholism, traumatic injuries or infections by virus or bacteria; in this case the diagnosis of ungual mycosis is much more difficult except when the isolated fungus is a dermatophyte that is always considered a pathogen; if the culture results in other species, it may simply be a contamination without any further transcendence.

In addition to local disturbances that favour fungal infection there are also general factors and diseases that can lead to mycosis. These factors may modify its course and change the clinical presentation, accelerating its progression, hindering diagnosis and making treatment much more difficult.

As can be seen, disease of the nail can exclusively affect the plate, the folds and periungual tissues, or both structures at the same time. The alterations that occur are not specific and may be confused with other pathologies (Table 4) Numerous local or general affections, whether genetic or acquired, can cause alterations that lead to incorrect diagnoses and inadequate treatment. For this reason a mycological study of the ungual material is indispensable to establish the correct diagnosis for fungal infection.

Table 4. Diseases of the nails that can be clinically confused with onychomycosis.

Psoriasis
Lichen planus
Contact dermatitis of the hyponychium
Traumatic onychodystrophies
Vascular onychodystrophies
Yellow-nail syndrome
Chemical onycholysis
Congenital abnormalities
Nail bed tumors

The etiological diagnosis of onychomycosis

It is not possible to make a definite diagnosis of fungal infection of the nail based only on their clinical characteristics, nevertheless the appearance allows an approximation to be made of the causative agent. If the onychomycosis is associated with other injuries to the skin of the feet (athlete's foot, interdigital intertrigo), it is logical to suspect a dermatophyte or *Scytalidium* or *Hendersonula* in zones where they are endemic.

Yeast-like fungi produce perionyxis and paronychia with focal or general lesions of the fingernails (Figure 4). The destructive injuries of TDO are associated with the typical granulomas of chronic mucocutaneous candidiasis.

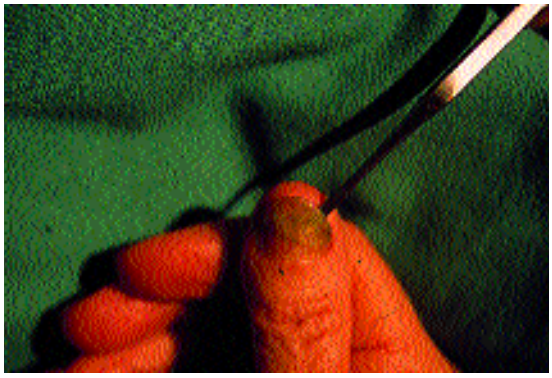

Figure 4. Ungual lesion with perionyxis produced by a yeast (*Candida tropicalis*).

Opportunistic moulds normally exclusively infect the nail, mainly of the feet and initially cause yellowish or brownish lesions that may be local but more often encompass the whole nail, especially if it has suffered previously. The approximate clinical diagnosis always requires confirmation by the laboratory. This is indispensable for making and accurate diagnosis and determining the responsible fungal species. Furthermore, isolation by culture allows a study to be made of the *in vitro* sensitivity to the antifungal agents that may be required to treat some isolated candidiasis that could be resistant to azoles. Mycological analysis is essential for controlling the antifungal treatment [12].

The mycological diagnosis is carried out in two ways: direct microscopic examination and cultures. The first consists of microscopic observation of the ungual material. The second is to sow the material on to an adequate solid culture medium and incubate it for a certain period of time under conditions that favour the growth of the causative fungus and inhibit the numerous contaminants present in the sample.

The procedure for taking the sample is very important to the mycological diagnosis. The first point to be discussed is the patient's background. The patient must not be under any type of treatment at the time that the sample is taken as this could modify the different results (slower or unusual fungal growth). This means that the patient must suspend all treatment for at least one week before being able to provide a good sample; if the antifungal treatment with is triazoles or terbinafine a wait of 3-4 or more weeks would be preferable.

Suitable disinfection of the affected zone is important in preventing contamination and the growth of yeasts belonging to the normal flora of the skin. The samples should be taken from the edges of the lesion, and from below the ungual plate where the fungus is more active.

The equipment required includes scissors, spatulas, curettes and scalpels, the latter should have a slight edge to be able scrape the lesion without causing bleeding. The use of sterile swabs with physiological saline solution is useful for collecting samples in the case of perionyxis.

Assessment by direct examination. The microscopic recognition of fungal elements in the nail is a technique that requires considerable experience and practice and this means it is necessary to rely on the expert staff of the mycology laboratory.

Direct examination is carried out in potassium hydroxide at 30-40% (KOH), to which glycerine has been added to clarify the image and avoid dissecation. The potassium digests the keratin, improving visualisation of the etiological agent. It is also possible to use calcofluor under a fluorescent light microscope.

Sometimes mycelium, short hypha fragments or conidia are observed in the sample but the culture is negative; this is because this fungus is not viable. On other occasions the situation is the reverse and although the direct examination is negative, the culture reveals a dermatophyte or other fungus. This may occur when there is a low fungal load or it is located in only some parts of the sample. The large epithelial cells of the nails, their hardness and high degree of keratinization can all hinder microscopic observation.

Lin *et al*. [13] report 28% of negative cultures from positive microscopic examinations. A distinction should be made here between two situations: when the hyphae are real but unviable to grow in the culture medium or the existence of false positive results, because the hyphae can be confused with the contours of keratinised epithelial cells or with crystals, fibres or lipid deposits.

Direct examination is not a final diagnostic method, but it can be indicative of the etiology of the infection based on the morphology of the hyphae. If they are broad, regular and with arthroconidia laid out more or less in chains, this indicates a dermatophyte. Irregular or distorted hyphae indicate a possible opportunistic mould. Pear-shaped conidia with a truncated base indicate *Scopulariopsis* sp. (Figure 5). Rounded conidia with a

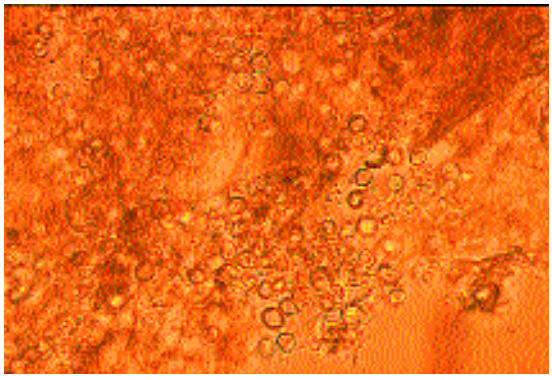

Figure 5. Microscopic direct examination where it is possible to distinguish the typical conidia of *Scopulariopsis* (400x).

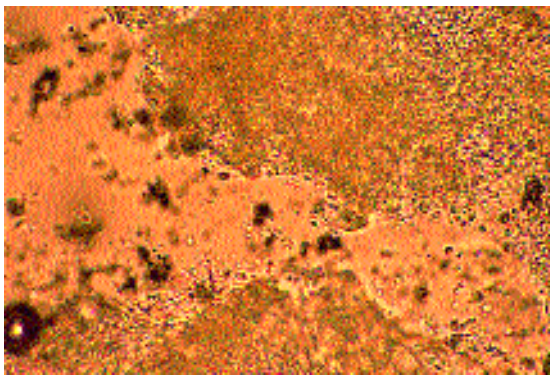

Figure 6. Examination of fresh scrapings of nails showing a large number of yeasts (400x).

very small diameter lead us to consider *Aspergillus*. Occasionally it is possible to observe the typical macroconidium of the *Fusarium* genus [14]. Budding yeasts are always indicative of a probable candidiasis (Figure 6).

In the case of perionyxis (where the expectation is to find yeasts) the sample may be stained to enhance the microscopic observation, the most often used staining agents are Gram's stain, which makes it possible to observe the presence of bacteria and to discriminate against other possible etiologies and methylene blue which makes it easier to visualise yeasts.

Cultures. A culture is indispensable for the etiological diagnosis of this pathology, the standard medium used in the mycology laboratory is Chloramphenicol Sabouraud agar to which gentamicin (50 mg/ml) is usually added to inhibit bacterial growth. Other more specific media have also been proposed for dermatophytes. One example is DTM (dermatophyte test medium) which contains a colour indicator than veers within few days if there is growth of colonies of these fungi [15].

The moulds and commensal yeasts of skin, nails and hair tend to have a more rapid growth rate than some dermatophytes and their development in the culture dish prevents the growth of the pathogen fungus [16]. This is avoided by using media supplemented with cycloheximide (100 µg/ml) but cycloheximide also inhibits the growth of some opportunistic moulds such as *Aspergillus*, *Fusarium* and *Acremonium* as well as the majority of yeasts of the *Candida* genus, except *C. albicans* which grows well in actidione.

The pathogenic role of non-dermatophyte moulds in samples of unhealthy nail is well recognised, although their isolation is frequently regarded as contamination. The interpretation is not always clear, so various proposals have been made to define the situation: there are authors that consider infection when the direct microscopy is positive [17] other authors only consider this fungus as causing the pathology after cultivating a series of several samples where this filamentous fungi is found.

Another of the difficulties involved in assessing a nail culture is the isolation of yeasts: their presence does not imply infection since some of them form part of the normal flora, for example it has been demonstrated that *C. parapsilosis* or *C. guilliermondii* form part of the microbiota, while *C. albicans* is usually found as causative of a pathology because it is not usually present in the normal skin flora.

Grigoriu [18] and English [19] have proposed objective criteria to adequately interpret the isolation of the non- dermatophyte fungi. These criteria are as follows:

1. Even though other species are isolated, whenever a dermatophyte appears in the culture it is considered as responsible pathogen.
2. The yeasts in the culture can not be evaluated unless their implication is demonstrated in a direct or histopathological examination.
3. A mycelial fungus will be considered as causative of onychomycosis if the same mycelial fungus appears in the cultures of a series of several samples and if no dermatophytes are isolated in medium containing cycloheximide.

According to André and Achen the presence of the fungus has to be confirmed by both direct and histological examination [20].

Although some authors have suggested performing biopsies of the nails as a diagnostic method, it is considered that even though the fungi can be better visualised after staining and can also be cultivated, it is not a practical method of diagnosis, since it requires the administration of local anaesthesia and previous experience in the technique, and even then, it is still considered an aggresive method where any affectation of the ungual matrix could cause permanent abnormal growth of the nail [12].

The histological analysis of samples of the ungual keratin collected by bloodless methods (scraped) imbedded in paraffin, and cut with a microtome in slices of 15-20 mm and then stained using the Maac Manus method is the system recommended by Achten and Wanet [21]. However, this method is not that normally used in mycology laboratories. Nevertheless, on certain occasions a biopsy is still required to be absolutely certain of the etiological role of uncommon species (Figure 7).

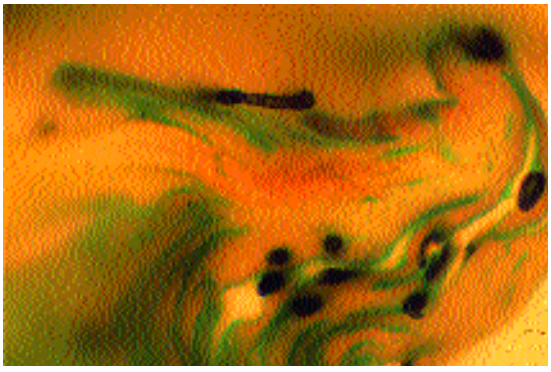

Figure 7. Biopsy of nail showing the hyphae of *Fusarium solani.*

The etiological agents of onychomycosis

The fungi causing infections of the nails come under three different groups: dermatophytes, yeasts, and moulds. The latter are called opportunistic because they do not usually cause a pathology in normal people, but can affect those that present local or general disturbances.

Of these dermatophytes, the *Trichophyton* genus is the one that most frequently invades the nails, especially *Trichophyton rubrum* (Figure 8) followed by *T. mentagrophytes* var. *interdigitale.* Both these species form part of the so-called *anthropophilic dermatophytes*, since they are adapted to development on human keratin and so are transmitted from person to person. Other species mentioned are *T. tonsurans, T. violaceum, T. megnini, T. schoenleinii,* exceptionally *T. concentricum and T. soudanenese*

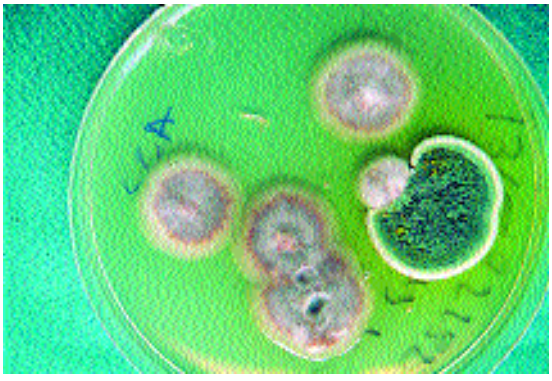

Figure 8. Culture of *Trichophyton rubrum* on a Petri dish of Sabouraud Chloramphenicol.

in endemic areas. The zoophilic variety of *T. mentagrophytes (var. granulare or mentagrophytes*) has been isolated in nails and associated with infections of the skin or scalp, but their presence is very uncommon.

The *Microsporum* genus is isolated with much less frequency including such species as the geophilic *M. gypseum*, zoophilic *M. canis* and anthropophilic *M. audoinii*. *Epidermophyton floccosum* has occasionally been described as an agent causing *tinea unguium*, generally in association with skin infections.

The species isolated in Paris between 1956 and 1980 are shown in table 5. These dates are taken from the statistics published by Badillet [22].

Table 5. Species of dermatophytes isolated in Paris in a large survey between 1956 and 1980 as etiological agents of *tinea unguium* [22].

Species	Fingernails	%	Toenails	%
Trichophyton rubrum	312	93	3326	77.7
Trichophyton interdigitale	4	1.19	932	21.8
Trichophyton violaceum	4	1.19		
Trichophyton megninini	6	1.79		
Trichophyton schoënleinii	2	0.59		
Trichophyton soudanense	3	0.89		
Epidermophyton floccosum	1	0.29	24	0.5
Microsporum canis	3	0.89		

The fact that yeasts of the *Candida* genus produce paronychia has been known since 1904 and experimentally confirmed by inoculation of healthy volunteers in 1925 [23]. The etiological role of *Candida* in producing onyxis primary or secondary to paronychia was determined at a later date. In many cases both affections are of occupational origin.

C. albicans has the greatest pathogenic capacity and has been described as the prevailing species in various series. *C. parapsilosis and C. guilliermondii* are frequently found on the skin as contaminating yeasts but their etiological role has also been demonstrated in onyxis and perionyxis as have *C. famata, C. tropicalis and C. sake*. Other yeasts isolated correspond to the *Trichosporon* genus.

The last group of fungi causing ungual infections are opportunistic moulds. This is the most heterogeneous and debated group [24] since the majority of the species tend to be found as contaminants of the environment or the skin. The most frequent is *Scopulariopsis brevicaulis*, a species that has been demonstrated to have an affinity for keratin. Other species of hyaline moulds are *Scytalidium hyalinum*, species of *Aspergillus (A. fumigatus, A. versicolor, A. terreus, A. flavus, A. candidus)* (Figure 9), together with *Acremonium* and *Fusarium*. The dematiaceae moulds also include *Hendersonula toruloidea, Cladosporium, Alternaria* and *Chaetomium globosum.*

Special mention should also be made of the species *Scytalidium hyalinum, Scytalidium dimidiatum* and their teleomorph *Hendersonula toruloidea (Nattrassia mangiferae).* These geophilic species are very frequently found in tropical areas of the Caribbean and Sub-Saharan Africa and cause lesions that are very similar to *tinea* (*tinea*-like) mainly on the hands and feet and including locations on the nails. Some authors consider that these species are dermatophytes because of their pathogenic ability [25].

Onychocola canadensis [26] is a slow growing mould described in such temperate climates as France, Canada and New Zealand. A recent review of 23 cases showed that ten of them came from Canada [27]. This review revealed that this species is not always pathogenic but when it is it mainly causes white superficial onychomycosis (WSO) or distal subungual onychomycosis (DSO).

Considerable emphasis has been given to the uneven geographical distribution of the etiological agents causing onychomycosis which is conditioned by the climate, habits and customs of the in habitants, among other causes. This is the underlying reason for the interest in performing etiological studies in different countries all over the world [28].

Figure 9. Cultures of *Aspergillus versicolor* on Petri dishes of Sabouraud Chloramphenicol together with colonies of contaminant fungi.

Predisposing elements

There are numerous conditions that are favourable to acquiring mycosis of the nails. In some cases they are only presumptions or based on indirect relations, in others they are considered situations where the influence on onychomycosis was demonstrated clinically or experimentally.

Local factors

The integrity of the corneal layer of the skin and the nails is fundamental to preventing any fungal invasion. Any process that breakdown this barrier will facilitate penetration by different fungi, including species that are considered less pathogenic. These factors include physical and chemical aggressions. In many cases exposure is conditioned by the occupation, habits and customs of the individual. Agricultural workers, construction or iron and steel workers, as well as bar and restaurant staff are constantly exposed to microtraumas. Cleaning employees that do not use adequate gloves tend to have their hands wet for long periods of time and this causes a maceration of

the skin and nails. In addition, this condition may be further prejudiced by the use of detergents and caustic substances that act chemically to potentiate the physical effect. In the feet the maceration is produced under different circumstances such as sports that can damage the nails (football), and constitutional hyperhidrosis due to the use of closed footwear with rubber soles or socks made of synthetic fibres that do not allow transpiration. Some professions such as fishermen, rice growers, and miners often tend to have wet feet or use rubber boots that hinder the elimination of sweat and moisture.

The physical factors include improper footwear, mainly women's shoes with sharply pointed toes, excessively closed, or with heels that displace the body weight toward the toes. Extreme "care of the nails" through manicure can be extremely prejudicial since the elimination of the cuticle, the layer of skin that protects the matrix, in addition to the more or less severe microtraumas caused by the instruments used, all expose the proximal area of the nail to fungal infection.

Finally there is the traumatic effect of nail-biting or finger sucking, quite common among some children, but not all that infrequent in adults as well.

Contact with solvents and caustic chemical products is common among workers in the chemical industry, farmers, painters, barbers, etc that under ideal conditions use protective gloves, but in many under- developed countries they are simply not available to the potential user. Gloves made of plastic or especially latex hinder good aeration of the hands and this can be an eventual cause of contact dermatitis.

General factors

Mention has been made of the possibility that there are hereditary factors [29] based on the appearance of onychomycosis in siblings, but there is no evidence in this sense. Zaias *et al.* [30] consider that there are genetic factors that make certain persons more prone to contracting onychomycosis. A greater prevalence of *tinea unguium* has been shown to occur in the Down syndrome, constituting a higher risk group among children.

Ageing has been shown to be an important factor favouring the appearance of onychomycosis, the prevalence increases with age [31] a cause that is related to the greater possibility of receiving traumatisms and other aggressions, greater exposure to possible pathogenic fungi, the difficulty in maintaining hygiene and care of the feet, deterioration of the structure of the nail itself because of peripheral circulatory insufficiency, decrease in the functionality of the immune system and the greater frequency of susceptible diseases.

Some investigators [32] suggest that estrogens exercise a protective role against onychomycosis since they are more frequent among post menopausal woman. In this same sense, it has also been suggested that the increase in dermatophytosis among the women after menopause could be due to the lack of progesterone since this inhibits the development of dermatophytes *in vitro* [33].

Some endocrinopathies are associated with a greater frequency of fungal infections of the nails, especially the TDO present in chronic mucocutaneous candidiasis, these include thyroid and parathyroid insufficiency, diabetes, states that produce ferropenia, and some primary and acquired immunodeficiencies.

Diabetes mellitus is considered one of the most important factors influencing the development of onychomycosis, especially those produced by *Candida* sp. The skin of patients with inadequately controlled diabetes is much less elastic and more fragile, susceptibility to infection is greater when associated with a neuropathy where there is a loss of sensitivity to touch in the feet, angiopathy and conditions of immunodeficiency [34] particularly in diabetics of a more advanced age [35]. In spite of this situation, according to Rich [36] *tinea unguium* is no more common in diabetics than among the general population [37].

On the other hand, infections of the periungual tissue by *Candida* sp. seem to be more prevalent among diabetics [38]. The importance of ungual disease diabetics is based on the possibility that it produces or worsens the diabetic foot. The loss of sensitivity in the feet because of a neuropathy can mean that the pressure exerted on the ungual bed by a swollen and distorted nail could cause ulceration, bacterial infection by *Pseudomonas* and *Staphylococcus*, followed by inflammation and necrosis. The same thing occurs with a paronychia by *Candida* sp. This population group are recommended to take special care of the feet, particularly the nails and to make an adequate diagnosis of onychomycosis, making sure not to use trauma causing instruments and manoeuvres for obtaining samples. Once the diagnosis is established topical or oral treatment with antifungal agents should be initiated as soon as possible, without overlooking any mechanical measures to eliminate excess keratin and to correct any possibly prejudicial deformities of the nails. Precaution should be exercised if triazolic antifungal agents are administered as they interact with oral hypoglycaemic agents. Any association with itraconazole or fluconazole can bring about an increase of the levels of the hypoglycaemic agent and a reduction of the glycemia [39].

Over the last two decades the great expansion of infection by the human immunodeficiency virus, especially in developed countries, has been associated with mycotic complications at both a cutaneous- mucous as well as a systemic level. It has been pointed out that *tinea unguium* is more frequent in this risk group and is related to the number of the CD4, especially with values below 100 cell/mm^3.

The clinical presentation does not seem to differ from that observed in immunocompetent subjects, but greater prevalence of WSO by *T. rubrum* has been described in association with periungual affectation by this same fungus, and with a tendency to infect all the fingernails. *Candida albicans* is also isolated with greater frequency and on occasions acquires a greater aggressiveness leading to TDO. One study by Torssander *et al.* [40] of homosexual men demonstrated a greater number of dermatophyte infections among a greater number of couples over a 12 month period, and 16 of 46 HIV positive patients presented *tinea unguium*, but this did not manifest itself in any different way than when it appeared in HIV negative patients.

In HIV positive children *Candida* sp. is the species more frequently isolated from the nails and it is not uncommon [41] to find two or more etiological agents associated with chronic paronychia of the same nail, with affectation of other areas of the skin and mucous membranes. In a controlled prospective study carried out in France, Cribier *et al.* [42] demonstrated that onychomycosis is much more frequent in HIV positive patients than in the controls with 48% of the infections being due to *T. rubrum*. This greater prevalence has been related to advanced states of the infection with HIV and a reduction in the number of CD4+ cells. Although the mycological diagnosis is not difficult, there are sometimes problems with the treatment that tends to be less effective than in HIV negative subjects.

In other states of immunosuppression such as the case of patients submitted to organ or bone marrow transplants, the possibility that an ungual focus could develop into a serious systemic infection has led Denning *et al.* [43] and other authors to suggest that the nails of high risk patients be checked. They recommend extirpation of any nails that present infections by opportunistic pathogens such as *Fusarium* that can be very aggressive and furthermore do not respond to the majority of antifungal agents.

Frequency of onychomycosis

The real prevalence of fungal infections of the nails is unknown, although it is considered to be probably the most frequent alteration of the nails as it is in excess of 50% of the ungual complaints in any dermatologist's consultancy [44].

In 1985 Zaias [45] estimated that in the United States of America onychomycosis affected from 15 to 20% of people between 40 and 60 years of age and more than 90% of all elderly people. In Europe there are several publications that refer to the prevalence among the general population in various places such as Finland, the United Kingdom and Spain. These studies proposed a prevalence of 8.4%, 3% and 1.7%, respectively.

It is evident that this prevalence varies greatly when consideration is given to different age groups, the sex of the patient, inclusion in a higher risk group (sportsmen, miners, agricultural workers, etc), social conditions, the possibilities of mycological diagnosis and the existence of favouring associated diseases, among others. There are also variations if only the toenails or fingernails are affected, or both, and above all depending on which etiological agent of the three basic groups is the cause of the mycosis: *tinea unguium*, ungual candidiasis and opportunistic infections by moulds (Table 6).

moulds in 4.3%. In 22% the cultures were negative but the results of direct examination positive. These authors put forward an estimate that the prevalence of onychomycosis in Canada is 6.83%, adjusted for age and sex, and taking the census of the population into account. They also found that this type of infection increased in frequency with age ($P<0.0001$), being very uncommon in the under 40 age group. Men presented a greater number of infections (84%) than women. The investigators found that in most cases of onychomycosis of the fingernails, the toenails were also affected in the UK [47].

In the United Kingdom a study on the prevalence of onychomycosis was carried out using a questionnaire, after determining that the application and interpretation of the explanatory figures were satisfactory through examination by a pilot group of onychomycosis patients. This survey found a prevalence of fungal infection of the nails in between 2 and 3% of the test population. This meant that about 1,5 million people were affected.

Sais *et al.* [48] consider that onychomycosis by dermatophytes or *tinea unguium* has a prevalence in Spain of 2.6% with a point prevalence of 1.7%, this means that more than 800,000 inhabitants of that country would be affected by this mycosis. These conclusions are based on a telephone survey performed between 1992 and 1993 on a total of 10,007 inhabitants of the Iberian Peninsula, Balearic and Canary Islands aged over 15 years. Just as in the study by Roberts *et al.* [47] the authors performed a quality control by means of six interviews with dermatologists, pharmacists and podiatrists and the surveys were supported by photographs that showed lesions that were onychomycosis and others that were not. In no case was there any personal interview with the person presumably infected, nor was there a mycological study.

The data based on this type of survey-studies have a very limited value because the data is very subjective

Table 6. Variation of the percentage isolation of dermatophytes, yeasts and mycelial fungi, in diseased nails in European publications.

	Patients	Dermatophytes	Yeasts	Moulds	Mixed or other infections
Meinhof	1844	44.3	29.2	15.5	11
Fragner	680	65.6	18.8	6.3	9.3
Walshe y English	373	56	33	11	
Blaschke y Helmessen	641	60.3	27.4	4	8.3
Achtten y Wanet-Rouad	1098	32	66	2	
Haneke y Lacour	142	42.2	38.8	17.6	1.4
Madrenys *et al.*.	638	31	61.4	7.6	
Rubio Calvo *et al.*	1628	14.67	74.45	6.4	4.4
Kiraz M *et al.* [61]	759	46.9	50.9	2.1	5.7

Modified from Del Palacio Herranz A, García-Bravo M. Onicomicosis. In: Torres-Rodríguez JM *et al.* Micología Médica. Barcelona, Masson. 1993:65-73.

In a multi-centre prospective study carried out in Ontario (Canada), Gupta *et al.* [46] proceeded to examine the toe and fingernails of new patients that attended the dermatology consultancy, whatever the reason for the visit. Whenever they found disturbances which led them to consider the possibility of an clinical infection of the nails they took samples for mycological examination. A total of 2001 patients were examined of which 23% presented abnormal toenails and onychomycosis of the foot was confirmed in 9,1%. Only five patients presented fungal infections of the fingernails, two produced by *T. rubrum*, two by *C. albicans* and one with only a positive microscopic examination. On the other hand, in the feet the most common agents were dermatophytes (93%) with a prevalence of *T. rubrum* (50% of all the agents), followed by *T. mentagrophytes*, *Candida* sp. (2.8%) and

and only based on the criteria of the patient. They should always be considered approximations, since it is very risky to draw conclusions as many diseases of the nails: psoriasis, lichen planus, traumatisms, etc. are clinically indistinguishable from an onychomycosis. In this study Sais *et al.* [48] rashly defines the dermatophyte etiology or otherwise of the ungual affectation, accepting that it was actually a fungal infection as the same type of injury could be produced by different fungal species. In any case, these studies reflect the high prevalence of the alterations of the nails among the general population of these countries.

The counterpoint to these studies of the general population, are other studies performed in a highly defined and very restricted geographical area. These are based precisely on the analysis of mycological nail lesions that

have been previously verified by dermatologists and in view of the high suspicion that they are mycotic have been sent to a laboratory for confirmation of the presumptive diagnosis. Madrenys *et al.* [49] used a standardised protocol to mycologically process 638 nail samples taken from patients with highly suspected of mycosis. The protocol included instructions on how to obtain the sample, its microscopic examination and cultures in several different media. They applied the criteria of English [19] extended to consider that the isolation of any mould was actually significant of infection. This mainly etiological study showed that 55.4% of samples proved positive, with 94% of positive cultures, the remaining 6% were proved positive on direct examination. These authors found large differences in the etiology depending on whether they considered fingernails or toenails (Table 7). They highlighted the high prevalence of yeasts on the fingernails, mainly among female patients. In the feet, dermatophytes - *T. rubrum* in particular - constituted the most frequent agents, moulds being only isolated in this location, never from the fingernails.

Another study with similar characteristics was carried out in a hospital Microbiology Laboratory in Zaragoza by Rubio Calvo *et al.* [50] who analysed 1,628 nails. They found 33.5% positive cultures, of which dermatophytes constituted 14.7%, yeasts 74.4% and moulds 6.2%. Just like in the previous studies, *T. rubrum* was the most frequently isolated dermatophyte (45%) mainly from toenails, *C. albicans* and *C. parapsilosis* constituted 39% and 24% respectively of the total number of yeasts. For the moulds *S. brevicaulis* represented 4.4%, moulds were only cultured from the toenails.

In Italy, Mercantini *et al.* [17] analysed samples of nails from 6,688 people that attended a dermatological consultancy service in the city of Rome between 1985 and 1994. 25% of the nails presented positive cultures, with the fingernails (57.4%) prevailing over toenails. Yeasts constituted 59% of the fungi isolated, mainly from the fingernails (86%). *C. albicans* was the most frequently identified species (70.6%) among the yeast cultures. Dermatophyte fungi, with *T. rubrum* in the first place, were mainly isolated from toenails (48%) and only in 5.6% of fingernails (Table 7). Moulds occupied the third position with 8.2% of the cultures isolated from fingernails and 31% of those from toenails. This study isolated *Aspergillus* spp. as the main etiological agent in both hands and feet whereas *Scopulariopsis brevicaulis* was isolated with much greater frequency from the feet. In this study there were no indications of the criteria used to certify that a mould that is usually a pollutant such as *Aspergillus* niger was considered an onychomycosis agent. This means that the high prevalence of this species, and others such as *Acremonium*, *Alternaria* or *Chrysosporium*, mainly isolated from the fingernails, could be erroneous and correspond to simple contamination of nails suffering from other processes.

In table 4 it is possible to distinguish the regional differences found between the species identified in Barcelona and in Rome.

Tinea unguium versus other onychomycosis

Ellis *et al.* [51] and other authors consider that the main cause of onychomycosis are dermatophyte fungi, with *T. rubrum and T. mentagrophytes* being the main agents and responsible for 90% of the mycosis of toenails and of more than 50% of those found in fingernails, and even up to 90% if paronychia caused by *Candida* are excluded. Among the moulds, the etiological role of *Scytalidium and Scopulariopsis* is accepted as they are attributed with 1.5 to 6% of all nail infections.

In Australia and New Zealand a multi-centre study was made of 8 to 12 samples of toenails obtained from each of 118 patients during a study lasting 48 weeks. All the patients suffered from *tinea unguium* but a non- dermatophyte fungus, yeast or mould was also isolated in 64% of cases at some time during the study. This non-dermatophyte fungus only persisted in other samples from the same subject in a very small number of patients. In view of these results, the investigators considered that the non- dermatophyte fungi isolated from toenails were only secondary contaminants of the *tinea unguium* and that they had no influence on the evolution of the disease, nor the response to treatment. The evidence of this study is based on a population previously selected as a carrier of *tinea unguium* and therefore excluding other fungi that were not isolated at the same time as the dermatophytes or after carrying out the controls.

Even though Elewski [52] considers that the culture of a non- dermatophyte fungus from a sample does not definitely prove that it is the etiological agent, there is irrefutable evidence of the causative role of non- derma-

Table 7. Distribution in percentage of the main etiological agents for onychomycosis in relation to their location on fingernails or toenails in two European cities: Barcelona (N = 338) and Rome (N = 1675).

Etiological agents	Fingernails		Toenails	
	Barcelona	Roma	Barcelona	Roma
Dermatophytes	7.8	5.6	57.6	48
Trichophyton rubrum	3.6	4	38.78	23.4
Trichophyton mentagrophytes	3.6	0.6	18.18	21.0
Others	0.6	1	0.6	3.6
Yeast	92.1	86.2	26	21.1
Candida albicans	34.73	70.06	0.6	15.9
Candida parapsilosis	41.02	2	18.18	2
Candida tropicalis	10	1.1	2.4	0.1
Others	6.35	13.04	4.82	3.1
Moulds	0	8.2	16.0	30.9
Scopulariopsis brevicaulis	0	0.4	10.3	10.5
Aspergillus spp.	0	4.2	5.4	13,2
Acremonium spp.	0	2.0	0.3	3.8
Others	0	1.6		3.4

Table 8. Fungal species described as causes of onychomycosis.

Dermatophyte fungi	Yeast	Nondermatophyte mycelial fungi
Epidermophyton floccosum	*Candida albicans* *	*Acremonium* spp.
Trichophyton concentricum	*Candida famata*	*Alternaria* spp.
Trichophyton mentagrophytes *	*Candida guilliermondii*	*Aspergillus candidus*
Trichophyton megnini	*Candida.parapsilosis* *	*Aspergillus flavus*
Trichophyton rubrum *	*Candida tropicalis*	*Aspergillus fumigatus*
Trichophyton shoënleinii	*Candida sake*	*Aspergillus sydowii*
Trichophyton soudanense		*Aspergillus terreus*
Trichophyton tonsurans		*Aspergillus ustus*
Trichophyton violaceum		*Aspergillus versicolor*
		Arhtroderma tuberculatum
		Botryodiplodia theobromae
		Geotrichum candidum
		Fusarium spp.*
		Onychocola canadensis
		Pyrenochaeta unguis-hominis
		Phyllosticta sydowii
		Scopulariopsis brevicaulis *
		Scytalidium dimidiatum *
		*Scytalidium hyalinum**

* Considered as major causes.

tophyte fungi in onychomycosis. There is no doubt of *C. albicans* as the etiological agent for the TDO that is observed in immunodepressed patients and as the cause of the majority of paronychia and perionyxis that accompany onyxis caused by yeasts and which are clinically expressed as a proximal, lateral or distal onychopathy. As for the role of moulds such as *S. brevicaulis* and *Scytalidium* sp., their capacity for digesting keratin has also been demonstrated *in vitro* and *in vivo*, together with that of other species of the *Aspergillus, Fusarium and Acremonium* genera (Table 8).

Other mycelial fungi have only been isolated on occasions (*Onychocola canadensis, Botryodiplodia theobromae,* etc) and it is difficult to consider them as etiological agents, although in individual studies, in the absence of other etiologies, their causative role has been demonstrated without any room for doubt.

It is necessary to have *in vitro* and *in vivo* experimental models using horny structures from animals or from human beings that would allow us to define the pathogenic role of many of the moulds and yeasts that are described as potential onychomycosis pathogens.

Several decades ago, English[19] proposed a study method and certain clear conditions to be fulfilled before accepting the etiological role of non- dermatophyte fungi in onychomycosis (Refer to diagnostic chart). These conditions have even been modified to adapt them to the new requirements of some authors by adding, for example, a biopsy of the nail and, in spite of these strict requirements, that species other than dermatophytes be accepted as capable of causing infections in nails.

Our experience, in a multi-centre study carried out at the Dermatology Departments of 14 hospitals throughout Spain between 1994 and 1996 [53], included 427 patients with a clinical diagnosis of onychomycosis of the toenails. All the out- patients were selected in accordance with a strict protocol that rejected any subjects with immunodeficiencies, and only accepted those that presented lesions of one or more nails with more than 80% of the surface affected and exclusion of the nail of the fifth digit. The study did not include any patients that had received topical or oral antifungal treatment for 60 days prior to obtaining the sample. The samples were only collected after careful previous disinfection of the nail and all the samples were sent by urgent courier service to our Laboratory that processed them within 72 hours of having been collected. The procedure used was always the same and included direct microscopic examination with KOH 40%, and culture in at least two culture media (Sabouraud agar with chloramphenicol, and the same medium with cycloheximide). Only patients that had two positive results, microscopic examination and culture, were included.

The sown plates were incubated for at least two weeks and observed three times a week by the same people. All the colonies that developed at the seeding sites were tested both macro and microscopically and isolated for identification of what were at all times considered possible pathogens. Determinations were made of mycelial non- dermatophyte fungi if the same fungus was isolated in at least two different samples taken on different days, if the culture was pure, and the same fungus was growing in more than half the seed sites (12 to 20, depending on the volume of the sample).

Under this extremely strict protocol 200 isolations taken from 187 samples were considered valid. In 13 samples there was a simultaneous development of a dermatophyte fungus and a yeast. 75.4% of the cultures were dermatophytes, 81.5% *T. rubrum*, 18% yeasts with a predominance of *C. parapsilosis* (61%), and 11.5% were moulds, of which 10.6% were *S. brevicaulis*. It was noted that yeasts were isolated with greater frequency in some areas of the country (South) than in others.

This data demonstrates that dermatophytes do in fact produce the great majority of fungal infections of the toenails, but they are not the only etiological agents in this process. Non- dermatophyte fungi varied in their presence in relation to the geographical area in which the study takes place. This means that species that are mainly found in tropical countries, *Scytalidium* for example, are not isolated in more temperate countries such as Spain, unless they constitute an imported mycosis. On the other hand, other species of moulds or yeasts seem be more prevalent in non- tropical countries. This is the case of *Aspergillus versicolor*. This species has been described with a relatively greater prevalence in Barcelona and other areas of Spain by Torres-Rodríguez *et al*. [53]. These authors analysed twelve cases of onychomycosis produced by this species and determined its *in vitro* susceptibility to the main antifungal agents. Ungual infections by *A. versicolor* were diagnosed in a similar proportion of men as well as women, the majority over 60 years of age, that all presented chronic lesions of between 1 to 20 years of evolution. Susceptibility factors such as diabetes, circulatory insufficiency, arthritis, or traumatism were only detected in six patients. The injuries, similar in all cases, were exclusi-

vely limited to the toenails and always involved the large toe, bilaterally in three patients. Although all patients had followed one or more treatments with topical antifungal agents there was no cure nor evident improvement. *A. versicolor* proved to be sensitive to terbinafine *in vitro*, followed by itraconazole and ketoconazole, though, on the other hand, considerable resistance was observed to fluconazole as well as to griseofulvin. A knowledge of the in vitro sensitivity to the different oral antifungal available on the market seems to be of interest, especially when faced with such little known fungal species as *A. versicolor*. This could be a first approximation to a more effective therapeutic indication.

Nail infections in children

In paediatrics, mycotic infections of the nails due to dermatophyte fungi are very uncommon, unlike *tinea capitis*, which is relatively common in the under-12 age group. There is very little specific information available on the prevalence of onychomycosis in children, with the exception of data provided by authors from Canada [54] and the United Kingdom [55]. In Canada a multi-centre study examined 2,500 people under 18 years of age searching for lesions of the nails that were compatible with fungal infection. Any possible cases were then subject to sampling for submission to a mycological study. Of all the children examined there was only one confirmed case of infection of fingernails and ten cases of infection of toenails. This was a general prevalence of 0.44% and, based on this result, the authors made an overall estimate of 0.16%. These authors revealed that half the children also presented *tinea pedis* and 65% had family with a history of *tinea*. In almost all cases the etiological agent was *T. rubrum* (Figure 10).

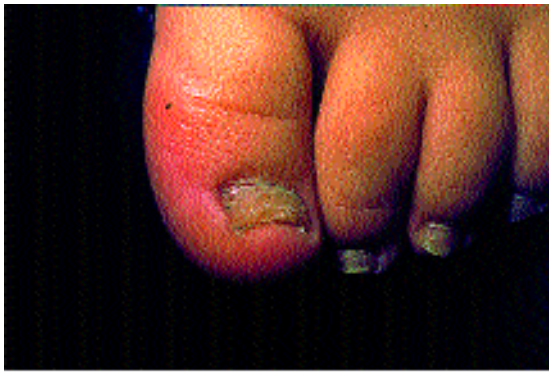

Figure 10. Ungual lesion of a 5 year old child produced by *Trichophyton rubrum.*

In other paediatric studies performed in countries as different as Sudan, India, USA, Mexico, or Guatemala, the prevalence oscillated between 0% in the United States to 1.3% in Mexico [56]. The reason why fungal infections of the nails are so infrequent in children has been attributed to a shorter period of exposure to infectious fungi in environments most favourable to infection (gymnasiums, public showers, pools, etc), the smaller nail surface that can be attacked by the fungi, the greater rate of growth of the nails, the lower possibility of occupational or sporting injuries, and the possible differential structural characteristics of the toenails that reduce the possibility of infection by dermatophytosis. The existence of a source of environmental dermatophyte infection, within the family or on other parts of the patient's own body seems to be of considerable importance. This is probably why infantile *tinea capitis* was a health problem of the first order in European countries in the 19th century. A high proportion of dermatophytosis of the fingernails was also described because it was acquired by scratching the scalp. So it was then, that in 1799 Pinel in his book '*Application of Analysis to Medicine and Skin Diseases*' (Madrid, 1803) made the following considerations '*Should we consider tinea as a purely local and peculiar affection of the scalp? … on occasions warts appear on other parts of the body and deformities of the nails that release viscous fluids when cut'* [2].

The differential diagnosis of onychomycosis in infancy includes numerous congenital alterations that could be due to the effect of teratogenous drugs such as phenytoin, warfarin, alcohol, etc., various ectodermal dysplasias, non-fungal inflammatory processes, and hypertrophies that manifest themselves as part of other general processes.

Chronic mucocutaneous candidiasis affecting the nails, although rare, is more wide-spread in infancy since it is related to primary immunodeficiencies such as Nezelof or DiGeorge syndrome, to deficiencies of myeloperoxidase and other acquired immunosuppressed states as well as different endocrinopathies: diabetes, parathyroid, thyroid and adrenal insufficiency, as well as in states of ferropenia.

Onychomycosis produced by mycelial fungi seem practically non-existent in children, probably because of the lower pathogenic power of these species and the absence of the local favouring factors that are observed in adult and elderly subjects.

Economic impact of onychomycosis

The statistics available on the prevalence of this mycosis are partial and vary considerably from country to country. Scher [3]. calculated that more than 600,000 patients over 65 years of age make more than 1,300,000 visits to the doctor to be diagnosed and treated for onychomycosis, this representing a cost of US$ 43,000,000.

In some occupations the acute and chronic *Candida* infections that occur in the onyxis and paronychia can be extremely painful and cause such discomfort that they prevent work. However, the repercussion in terms of lost man-hours has not been considered nor estimated. Onychomycosis in some types of employment such as health care, bar and restaurant staff, with attention to the public, may require sick leave which, in the event of requiring a clinical and mycological cure, the return to work could take months. This aspect of chronic lesions related to occupational diseases has not been considered to date nor has any estimate been made of the cost.

Onychomycosis have a negative impact on the quality of life of those who suffer from them and so safe effective treatments should be available. The introduction of new oral antifungal agents such as terbinafine, itraconazole and fluconazole, has brought about an advance in the treatment of *tinea unguium* and onyxis - perionyxis by *Candida*. However these substances have become more expensive. In 1988, it was estimated that in the United Kingdom a patient with *tinea unguium* represented a cost of 169 pounds. In 1993 in Canada the cost of a complete treatment ranging between 682 $Can and 1,300 $Can depending on whether terbinafine or itraconazol was used [57,58]. These expenses can certainly be significantly smaller when the therapy is discontinued or intermittent as is routinely applied in the case of itraconazole [56].

No data is available on the economic cost of surgical treatment or for the use of topical antimycotic treatments. Consideration should be given to the fact that on many occasions it is necessary to resort to combined therapies that are more expensive but that without doubt provide better therapeutic results.

Whenever an analysis is made of the economic cost of a treatment it should be compared to the social cost of non- treatment, and considering that there is a consensus on the need to treat any type of onychomycosis, choosing the method, drug and route of administration that best suits the needs of the patient and the possibilities of the medium, it can be concluded that the patient affected by a fungal infection of the nails should be provided with the most effective drug, at a suitable therapeutic dose for the minimum amount of time to ensure sterilisation of the infection. In the case of oral drugs, the possibility of intermittent treatment, apart from simplifying the dose required and reducing the possibility of adverse effects, also means a reduction of the economic cost [59]. In any case, a long and costly treatment should always be subject to mycological controls to ensure that clinical improvement is accompanied by negative culture results to reduce the possibility of relapse.

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