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The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases

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CONTINUING MEDICAL EDUCATION: CUTANEOUS BIOLOGY

REPORTS

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Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002

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Background: Cutaneous fungal infections are common in the United States, and causative organisms include dermatophytes, yeasts, and nondermatophyte molds. These organisms are in constant competition for their particular environmental niche, often resulting in the emergence of one or more predominant pathogens and displacement of other less competitive species. Changes in the incidence of fungal pathogens can be followed from laboratory culture results of infected cutaneous tissues over time. These data can be used to ascertain past and present trends in incidence, predict increases in antifungal resistance and the adequacy of our current pharmacologic repertoire, and provide insight into future developments.

Objective: This study identifies epidemiologic trends and the predominant organisms causing superficial fungal infections in the United States.

Methods: A total of 15,381 specimens were collected from clinically suspected tinea corporis, tinea cruris, tinea capitis, tinea faciei, tinea pedis, tinea manuum, and finger and toe onychomycosis from 1999 through 2002. Specimens were submitted to the Center for Medical Mycology in Cleveland, Ohio, for fungal culture and identification, and the incidence of each species was calculated.

Results: Dermatophytes remain the most commonly isolated fungal organisms except from clinically suspected finger onychomycosis, in which case *Candida* species comprise >70% of isolates. *Trichophyton rubrum* remains the most prevalent fungal pathogen, and increased incidence of this species was observed in finger and toe onychomycosis, tinea corporis and tinea cruris, tinea manuum, and tinea pedis. As the causal agent of tinea capitis, *T tonsurans* continues to increase in incidence, achieving near exclusionary proportions in the United States.

Conclusion: Consideration of the current epidemiologic trends in the incidence of cutaneous fungal pathogens is of key importance to investigational efforts, diagnosis, and treatment. (J Am Acad Dermatol 2004;50:748-52.)

Mycotic infection of the skin can be caused by dermatophytes, yeasts, and nondermatophyte molds, although dermatophytes are the most frequently encountered causative agent. Together, these organisms account for a high number of office visits and treatment-related expenses.[1] Superficial fungal infections comprise a complex host-parasite relationship that is in constant flux. Species compete to exploit an environmental niche within a host population, often resulting in the emergence of one or more predominant pathogens and displacement of organisms with less adaptive qualities.[2,3] Changes in the incidence of a pathogen affect the physician's ability to render a diagnosis and can change the approach to treatment.[4] Multiple factors may affect the incidence of fungal pathogens within a population. These include the geographic area and climate, immunocompetence of the host, the pathogenicity of the infectious agent, and the availability of medical treatment. This study provides insight into recent trends in the incidence of fungal species isolated from skin infections in the United States.

METHODS

A total of 15,381 patient samples including nail clippings, subungual debris, hair, and skin scrapings were collected at the Center for Medical Mycology in

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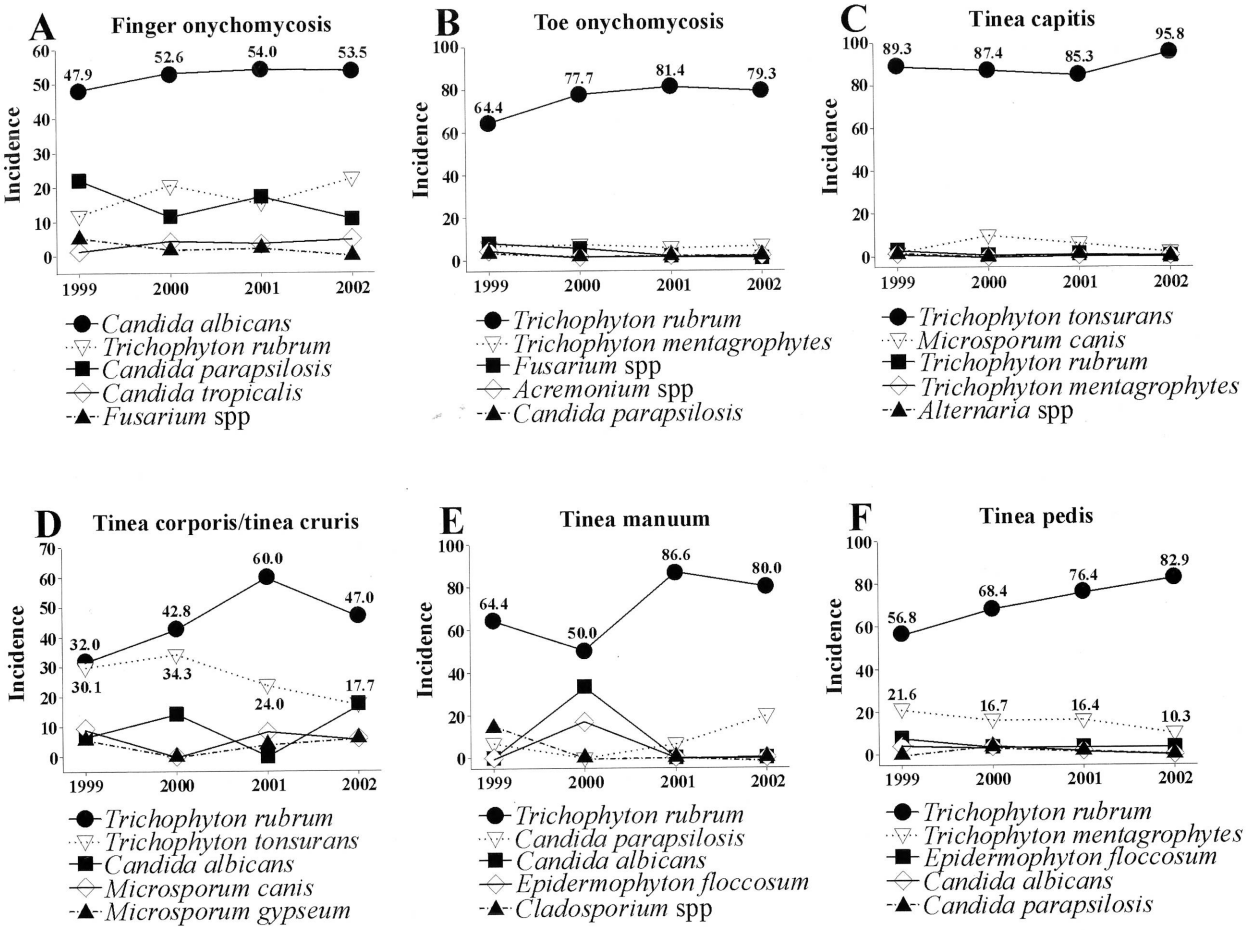

Fig 1. Incidence of cutaneous fungal species from 1999 to 2002. Values represent the incidence of the 5 most common species isolated from finger onychomycosis (**A**), toe onychomycosis (**B**), tinea capitis (**C**), tinea corporis and tinea cruris (**D**), tinea manuum (**E**), and tinea pedis (**F**). Tabular presentation of complete data sets for each body site is available online at www.eblue.org.

Cleveland, Ohio, from January 4, 1999, through September 4, 2002. Specimens were obtained from clinically suspected fungal infections of various body sites including fingernail, toenail, body and groin, head and scalp, face, hand, and foot by US podiatrists, dermatologists, and primary care physicians. In all, 11 states were represented in the study: Alabama, California, Florida, Illinois, Michigan, Missouri, New York, Ohio, Pennsylvania, Tennessee, and Texas. Specimens were submitted in a Derma-Pak (Microbiological Supply Co, Toddington, United Kingdom) on Mycosel agar (BBL, Cockeysville, Md) or on dermatophyte testing agar, as described.[5] Primary isolation medium included Mycosel agar and potato dextrose agar supplemented with chloramphenicol and gentamycin, as described.[6] Cultures were incubated at 30°C for up to 28 days and checked twice weekly for growth. Negative cultures were confirmed after 4 weeks of no growth. Identification of dermatophyte isolates was on the basis of microscopic morphology, urea testing, growth on *Trichophyton* agars, and hair perforation assays. Nondermatophyte molds were identified by microscopic morphology. Recovered yeasts were subjected to the germ tube test,[6] analyzed using an identification system (API 20C, bioMérieux Inc, Durham, NC),[7] and checked for morphology in cornmeal agar (BBL). All specimens were sent as part of routine medical workup and analyses were conducted retrospectively. The incidence of the 5 most common species from each body site is presented graphically (Fig 1). A more detailed analysis is presented in a series of tables that can be accessed online at www.eblue.org.

RESULTS

From fingernail debris, 674 isolates were obtained. The incidence of nondermatophyte molds

decreased 5-fold from 1999 to 2002, yet the incidence of *Candida* species remained relatively constant, ranging from 70.3% to 75.8%. *C albicans* was the predominant isolate, accounting for 47.9% to 54% of positive cultures (Fig 1, *A*). The incidence of dermatophytes increased nearly 2-fold during the study period, fueled by upward trends in the incidence of *T rubrum*. *T rubrum* was also the predominant dermatophyte, accounting for >90% of all fingernail-derived dermatophyte isolates in each of the 4 years analyzed.

From infected toenail debris, 3698 isolates were obtained. The fungal isolates were diverse and included 29 species of nondermatophyte molds, 8 species of *Candida*, and 6 species of dermatophytes. As with finger onychomycosis, the incidence of nondermatophyte molds decreased during the study period, with a pronounced decline in the incidence of *Fusarium* species. In contrast to finger onychomycosis, incidence of *Candida* species was low, ranging from only 3.5% to 6.7%. Incidence of dermatophytes ranged from 72.4% to 88.2% and trended upward during the study period secondary to increases in the incidence of *T rubrum*, the predominant dermatophyte (Fig 1, *B*). Analysis of combined (fingernail- and toenail-derived) data identified *T rubrum* as the predominant causative agent of onychomycosis, with incidence ranging from 55.2% in 1999 and increasing steadily to 72.8% in 2002. Conversely, analysis of combined nail data showed that *Candida* species accounted for a much smaller fraction of onychomycosis, and a steady decline in incidence from 18.9% in 1999 to 11.3% in 2002 was observed.

From hair- and scalp-derived tissues, 775 isolates were obtained. Nondermatophyte molds and *Candida* species were isolated in low abundance from hair and scalp tissues, accounting for <5.4% and <1.6% of isolates, respectively. Dermatophytes comprised the majority of isolates, with incidence ranging from 94.6% to 99.7%. *T tonsurans* remains the most commonly isolated pathogen, with incidence reaching 95.8% in 2002 (Fig 1, *C*). As with tinea capitis, the predominant isolate from face-derived tissues was *T tonsurans*, with incidence ranging from 50% to 100% during the study period.

From body- and groin-derived tissues, 130 fungal isolates were obtained. The incidence of nondermatophytes was low, ranging from 0% to 4%. The incidence of *Candida* species was higher, but with somewhat more erratic fluctuations from year to year, ranging from 0% in 2001 to 23.5% in 2002. Dermatophytes had the highest incidence throughout the study ranging from 76.5% to 96%. Although several species of dermatophytes were isolated, the predominant pathogens were *T rubrum* and *T tonsurans* (Fig 1, *D*). The incidence of *T rubrum* increased during the study period, comprising 32% of isolates in 1999 and increasing to 47% in 2002. Conversely, *T tonsurans* accounted for 30.1% and only 17.7% of isolates in 1999 and 2002, respectively.

A total of 40 isolates were obtained from the hand. An abrupt decrease in the incidence of nondermatophyte molds from 21.4% in 1999 to 0% thereafter was observed. The incidence of *Candida* species was variable, ranging from 6.7% to 33.3% during the study period. Dermatophyte incidence trended upward, from 64.4% in 1999 to 80% in 2002, secondary to increases in the incidence of *T rubrum*, the most common isolate (Fig 1, *E*).

From foot-derived tissues, 189 fungal isolates were obtained. Both nondermatophytes and *Candida* species had relatively low incidence, whereas dermatophytes accounted for 86.2% to 100% of isolates. *T rubrum* was the most common isolate, and the incidence of this species increased steadily during the study period (Fig 1, *F*).

DISCUSSION

Analysis of finger and toe onychomycosis in this study showed an inverse relationship between *T rubrum* and *Candida* species. In finger onychomycosis, *Candida* species have high incidence and *T rubrum* has relatively low incidence. In toe onychomycosis, the opposite is true. The high incidence of *Candida* species in finger onychomycosis has been noted previously, albeit not to the degree present in this study. Work conducted in The Netherlands confirmed analogous roles for *T rubrum* and *Candida* species in onychomycosis, with *C albicans* accounting for 58.5% and 6.4% of finger and toe onychomycosis, respectively.[8] Similarly, in the United Kingdom, *T rubrum* and *Candida* species accounted for 39% and 58% of fingernail- and 80% and 1% of toenail-derived isolates, respectively.[9] In Canada, the organisms causing toe onychomycosis were 90.5% dermatophyte and 1.7% *Candida* species, whereas the corresponding organisms causing finger onychomycosis were 70.8% and 29.2%, respectively.[10] The incidence of *Candida* species in finger onychomycosis in the current study ranged from 70.3% to 75.8%, somewhat higher than that noted by other groups. Although these observations are intriguing, the data are difficult to interpret for a number of reasons, including the lack of clinical correlation and microscopic observation and the possibility that the high incidence of *Candida* observed in this study represents only secondary infection.[11] Furthermore, recent studies have demonstrated that *Candida* species, particularly *C*

parapsilosis and *C albicans*, are capable of hand colonization without causing apparent disease.[12] Further study of this phenomenon is required before definitive conclusions may be drawn.

The incidence of organisms causing tinea capitis varies according to region.[2] Studies conducted in The Netherlands identified multiple causative species including *T rubrum* and *T mentagrophytes*, but *T verrucosum*, *T schonleinii*, *T violaceum*, and *Microsporum canis* were most common, accounting for 25.3%, 24%, 17.3%, and 14.4% of infections, respectively. *T tonsurans* was not isolated in this study.[8] In Germany, the predominant organism causing tinea capitis is *M canis*, accounting for >54% of infections, and the incidence of *T tonsurans* was <4%.[13] In contrast to Western Europe, *T tonsurans* remains the predominant causative agent in North America and currently accounts for >95% of tinea capitis in the United States. The observations reported here are in general agreement with previous studies conducted in the United States and Canada, showing that *T tonsurans* accounts for 88.1% and 76% of tinea capitis, respectively.[3,5] In addition to the recent increases in the incidence of *T tonsurans* in tinea capitis in this country, studies in Canada report a more rapidly increasing incidence initially observed at only 9% in 1985 but climbing to 76% in 1996.[3] The nearly exclusive role of *T tonsurans* in tinea capitis and its increasing incidence in tinea faciei in this study highlight the success of this organism as a pathogen.

Of isolates obtained from the groin and body, *T rubrum*, *T tonsurans*, and *Candida* species accounted for 32% to 60%, 17.7% to 34.3%, and <24% of isolates, respectively. Although these results are in general agreement with previous Canadian and US studies,[3,5] the incidence gap between *T rubrum* and *T tonsurans* has widened in the United States since 1999. Compared with previous studies conducted in the United States where *T rubrum* and *C albicans* accounted for 20.3% and 47.9% of isolates, respectively,[5] we observed a decrease in the incidence of *C albicans* and an increase in the incidence of *T rubrum*, reaching 47% in 2002. These observations taken together indicate an increasingly important role for *T rubrum* in tinea corporis and tinea cruris.

T rubrum, continues to play a significant role in tinea manuum and tinea pedis as well, accounting for 80% and 82.9% of isolates, respectively, in 2002. The incidence of *T rubrum* in tinea manuum and tinea pedis continues to rise in the United States but is still noticeably less than that observed in Canada, where it has achieved near exclusionary proportions.[3]

This work identifies both annual changes and even broader trends in the incidence of cutaneous fungal pathogens that span or even extend beyond the length of this study. Monitoring the incidence of these species enables the detection of emerging organisms and allows for assessment of the adequacy of current pharmacologic regimens. Emerging species with increased resistance to mainstay antifungal agents must prompt testing of novel therapeutic drugs or drug combinations. Two types of resistance are currently recognized. The first of these, termed "clinical resistance," denotes a lack of clinical response to an antifungal agent, likely secondary to low circulating levels of drug, noncompliance with therapeutic regimens, or immunosuppression. The other type of antifungal resistance, in vitro resistance, is manifest in organisms with increased minimum inhibitory concentration values and is classified as either primary, denoting an innate resistance to the pharmacologic agent, or secondary, indicating an acquired resistance to a drug.[14] Acquired resistance is becoming more common in individuals who are immunosuppressed, lack the ability to effectively clear infections, and in whom the selective pressures of multiple antifungal agents are at work.[14] Dermatophyte resistance to antifungal agents has been previously demonstrated. Specifically, griseofulvin-resistant *T rubrum* has been obtained from clinical sources and induced in the laboratory setting after mutagenesis.[15,16] Moreover, increased minimum inhibitory concentration values for griseofulvin, ketoconazole, and itraconazole have been observed in subsets of *T rubrum* and *T interdigitale*.[17] As with dermatophytes, triazole-resistant *Candida* species, including *C glabrata*, *C albicans*, and *C krusei*,[14,18] and nondermatophyte molds exhibiting single- or multi-drug resistance are becoming increasingly prevalent.[19,20] These observations taken together emphasize the growing problem of antifungal resistance, predict future increases in severity, and underscore the importance of continued epidemiologic surveillance.

In conclusion, these data reiterate the continued predominance of dermatophytes as the principal pathogens in cutaneous fungal infections. *T rubrum* remains the most prevalent pathogen, and increased incidence of this organism was observed in finger and toe onychomycosis, tinea corporis and tinea cruris, tinea manuum, and tinea pedis. High incidence of *Candida* species was documented in finger onychomycosis, but necessitates clinical correlation and further study. As the causal agent of tinea capitis, *T tonsurans* continues its expansion to near exclusionary proportions in the United States and exhibits parallel increases in incidence in tinea fa-

ciei. Diagnosis, treatment, and investigational efforts should include consideration of these recent data.

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