Although *Candida albicans* remains the most common opportunistic yeast pathogen in patients with AIDS and other immunocompromised persons, species less susceptible to fluconazole are becoming more common (1). Recently, a newly described species, *Candida dubliniensis*, was isolated from oropharyngeal lesions in patients with AIDS living in Dublin, Ireland (2). *C. dubliniensis*, phenotypically very similar to *C. albicans* in producing both germ tubes and chlamydospores, has since been recovered from the oral washings of approximately 25% of 94 HIV-positive Irish patients with or without AIDS and 3% of 150 HIV-negative Irish persons (3,4), which suggests that this species belongs to the indigenous microflora of the oral cavity, albeit in a minority of healthy persons. Subsequent reports indicate that the species has a worldwide distribution (4).

The role of *C. dubliniensis* as a pathogen has been limited to oral candidiasis. We now report three cases of candidemia due to this newly emerging *Candida* species in HIV-negative patients with chemotherapy-induced immunosuppression and bone marrow transplantation.

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The role of *C. dubliniensis* as a pathogen has been limited to oral candidiasis. We now report three cases of candidemia due to *C. dubliniensis* in patients not infected with HIV. The yeasts were initially identified as *C. albicans* because each produced germ tubes and chlamydospores; this identification became suspect when equivocal carbohydrate assimilation patterns were obtained.

**Case 1**

Graft-versus-host disease of the skin, liver, and digestive tract developed in a 39-year-old woman with chronic myelogenous leukemia after an allogeneic hematopoietic stem cell transplant in September 1995, during which she was treated with cyclosporine and high-dose prednisolone. Germ tube–producing *Candida* spp., later identified as *C. dubliniensis*, were isolated from stool samples obtained for routine testing. The white-cell count was 2.7 x 10^9/L (72% granulocytes); 4 days later fever and ascites developed, and *C. dubliniensis* was cultured from three separate blood cultures (two sets obtained by venipuncture and one by the central venous line) taken on the same day (MIC fluconazole, 0.25 µg/ml). Ascitic fluid obtained by a sterile puncture also grew *C. dubliniensis*. Ascites was probably related to hypoalbuminemia. An echogram showed no radiologic evidence of liver candidiasis, although alkaline phosphatase was elevated (222 U/L; normal < 120 U/L). Treatment was started intravenously with fluconazole, 800 mg/day; 3 days later, *C. dubliniensis* were still recovered in one of five blood cultures taken over 2 days, but from then on, blood
cultures were yeast-negative. Because the patient was in stable condition, the central line was not removed. Cytomegalovirus (CMV) disease also developed, which could explain the elevated alkaline phosphatase, with severe thrombopenia (<20 x 10⁹/L). The patient was given ganciclovir and hyperimmune gammaglobulin (Cytotect); Staphylococcus epidermidis bacteremia also developed, and the patient died 3 weeks after the onset of candidemia, with severe graft-versus-host disease stage IV, complicated by candidemia and CMV disease. Permission for autopsy was not granted.

Case 2
In July 1995, a 5-year-old boy was treated with cytotoxic chemotherapy for relapsed nasopharyngeal rhabdomyosarcoma. Two episodes of bacteremia caused by Streptococcus mitis and S. epidermidis followed, and the boy was treated with ceftazidime and later ciprofloxacin (combined with vancomycin) for 3 weeks. Cultures of stools and oral specimens yielded germ tube–producing Candida spp. later identified as C. dubliniensis. Four days before the onset of candidemia the patient became febrile; Staphylococcus aureus and C. dubliniensis were cultured from sputum. At this time, the child was not aplastic (leukocyte count 2 x 10⁹/L). Flucloxacillin and ceftazidime were started. When fungal blood cultures were taken, the patient was very ill, had profuse diarrhea and high fever, and was leukopenic with a total leukocyte count of 0.3 x 10⁹/L (granulocytes <0.1 x 10⁹/L; thrombocytes 12 x 10⁹/L); 1 day later, three blood cultures, taken over 24 hours through a central line, yielded C. dubliniensis (MIC fluconazole, 0.5 µg/ml). Treatment with 12 mg/kg fluconazole was started immediately. C. dubliniensis were still being recovered from two blood cultures 2 days after treatment began, but after that, cultures remained sterile, and the patient gradually improved. The central line was removed 20 days after the last positive blood culture but was not submitted for culture. The patient was treated with fluconazole for 1 month (3 weeks intravenously, and 1 week orally) and was discharged 2 months after the onset of candidemia. Yeasts were not recovered from cultures (oral washes and stools). At this time the patient had already been treated for 72 hours with imipenem and vancomycin. Because of persistent fever unresponsive to broad-spectrum antibacterial agents, intravenous amphotericin B (30 mg) was empirically added. Once the results of the positive blood cultures became known, 5-flucytosine (100 mg/kg) was added to the regimen. After initiation of amphotericin B, later blood cultures remained negative for yeasts. The Hickman catheter was removed 14 days later when the patient had recovered from neutropenia. Catheter tip cultures remained negative. However, low grade fever persisted. Nonetheless, because the patient’s condition was stable, treatment was changed to oral fluconazole (50 mg t.i.d.) for another 2 weeks and the patient was discharged. The cause of persistent fever was not identified, but approximately 6 months later, the patient recovered.

Microbiologic Results
All yeast isolates were initially identified by germ tube and chlamydospore formation as C. albicans, but carbohydrate assimilation patterns by commercial test kits (Auxacolor,
C. krusei, and RP02 were clearly different from
Furthermore, banding patterns obtained with
intensity, ranging from 0.65 kb to 2.4 kb.
yielded approximately 15 bands of various
C. dubliniensis
with primer RP02 (5’-GCGATCCCCA-3’). Each
chain reaction patterns for
istic arbitrary primer phosphatase-polymerase
Ca3 fingerprinting probe (5) and gave character-
hybridized poorly with the yeasts isolated from our patients’ specimens
C. albicans, the yeasts isolated from our patients’ specimens
C. albicans—specific Ca3 fingerprinting probe (5) and gave character-
C. dubliniensis
with primer RP02 (5’-GCGATCCCCA-3’). Each
C. dubliniensis
C. albicans,
C. albicans,
The Netherlands)
C. dubliniensis
with primer RP02 (5’-GCGATCCCCA-3’). Each
C. dubliniensis
C. albicans,
C. dubliniensis
C. albicans, the two major bands were never
observed. Instead, each C. albicans isolate
yielded approximately 15 bands of various
intensity, ranging from 0.65 kb to 2.4 kb.
Furthermore, banding patterns obtained with
RP02 were clearly different from C. glabrata, C. krusei, C. tropicalis, and C. parapsilosis. In vitro susceptibility testing for fluconazole
(powder provided by Pfizer BV, Capelle a/d IJssel, The Netherlands) was performed by the
broth microdilution method with RPMI-1640
with L-glutamine, buffered with MOPS incu-
bated at 35°C, and read after 48 hours according
to NCCLS M-27A (7). C. parapsilosis ATCC
22019 and C. krusei ATCC 6258 were included as
quality control strains. The isolates from
patients 1 and 2 were deposited as CBS 8500
and CBS 8501 at the yeast division, Centraalbureau voor Schimmelcultures (CBS), Delft, The Netherlands.

C. dubliniensis
was first described 3 years
ago (2) and is genetically and phylogenetically
distinct from C. albicans (8). Hitherto, its
pathogenic role has been mainly restricted to
opharyngitis infections in HIV-infected per-
sons and AIDS patients (3,5). In a recent study of
C. dubliniensis, one isolate recovered from a
blood culture and one from postmortem lung
tissue was examined (6); however, no clinical
data were described to allow determination of
the pathogenic role. The cases we have described
show that C. dubliniensis can cause candidemia
in immunocompromised patients. However,
these may not be the first cases of invasive
disease due to this yeast. Identification and
differentiation from other germ tube–producing
yeasts on the basis of phenotypic characteristics
has been problematic (8); therefore, the
incidence and prevalence of this organism and its
role in invasive disease have been difficult to
determine. For instance, a strain of C. stellatoidea
originally isolated in 1957 from the sputum of a
patient with bronchopneumonia and deposited in
the British Culture Collection of Pathogenic
Fungi has been shown to be C. dubliniensis (2,3),
and an isolate of C. albicans (from sputum of a
Dutch patient) deposited in the culture collection
of CBS in 1952 has been shown to be
C. dubliniensis (Meis, unpub. obs.). In both
cases, it has not been established whether the
C. dubliniensis isolates were responsible for
invasive infections.

Fluconazole appears to be less active against
C. dubliniensis than against C. albicans (4) since
C. dubliniensis is usually associated with
recurrent episodes of candidiasis and protracted
exposure to azole antifungal drugs in patients
with AIDS. Fluconazole showed excellent in
vitro activity against each of the C. dubliniensis
isolated from the blood cultures of our patients;
each patient responded well clinically. Never-
thless, it is too early to estimate the true
susceptibility of this species to fluconazole. This
requires the correct identification of the species,
which now seems necessary, given its ability to
cause invasive disease in patients treated for
malignant diseases.

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