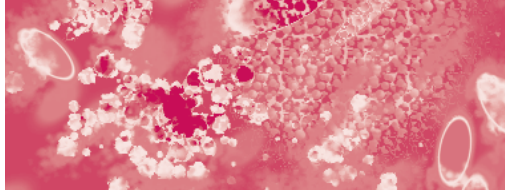

Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients

Philippe Eggimann, Jorge Garbino, and Didier Pittet

A substantial proportion of patients become colonised with *Candida* spp during hospital stay, but only few subsequently develop severe infection. Clinical signs of severe infection manifest early but lack specificity until late in the course of the disease, thus representing a particular challenge for diagnosis. Mostly nosocomial, invasive candidiasis occurs in only 1–8% of patients admitted to hospitals, but in around 10% of patients housed in intensive care units where it can represent up to 15% of all nosocomial infections. We review the epidemiology of invasive candidiasis in non-immunocompromised, critically ill patients with special emphasis on disease trends over time, pathophysiology, diagnostic approach, risk factors, and impact. Recent epidemiological data suggesting that the emergence of non-albicans candida strains with reduced susceptibility to azoles, previously linked to the use of new antifungals for empiric and prophylactic therapy in immunocompromised patients, may not have occurred in the critically ill. Management of invasive candidiasis in these patients will be addressed in the December issue of *The Lancet Infectious Diseases*.

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Candida is ubiquitous and more than 200 species have been described.[1,2] Some species are part of our microbiological flora and only 10% are known to be responsible for infections in people.[3] Common manifestations of superficial candidiasis such as thrush, chronic atrophic stomatitis, chronic mucocutaneous candidiasis, and vulvovaginitis are quite specific, usually self-limited in non-immunocompromised hosts, and easy to treat with basic hygiene measures and local treatment.[4] However, candida may also be responsible for life-threatening infections, associated with an overall prognosis comparable with that of septic shock with multiple organ failure.[5–8]

Candidiasis is most frequent in immunocompromised hosts.[3,9] However, data over the past two decades clearly indicate that invasive candidiasis in critically ill, non-immunocompromised patients—the main focus of our review—is of increasing importance and has different characteristics.[10–13]

This work reviews the epidemiology of severe *Candida* spp infections among critically ill patients with special emphasis on microbiology and resistance to antifungals, the clinical spectrum, pathophysiology, and impact of the disease. A second review (to be published in the next issue of the journal) will address management of the disease.

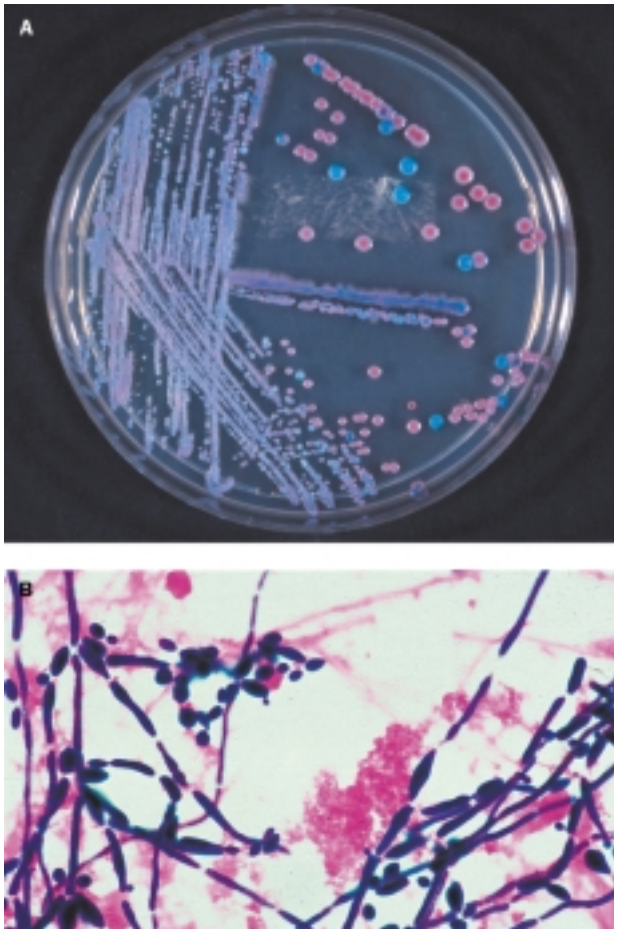

Figure 1. Macroscopic (A) and microscopic (B) features of Candida *spp. (A) Colonies of* C albicans *(blue) and* C glabrata *(red) grown on Chromagar candida plates. (B) Yeast (2–4 µm) and septate hyphae (15–30 µm) of* C albicans*, Gram stain 1000x. Images courtesy of P Rohner and K Bouchuiguir-Wafa, Laboratory of Clinical Microbiology, University of Geneva Hospitals.*

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Table 1. Summarised susceptibilities of *Candida* spp to various antifungals

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Ravuconazole	Caspofungin	Flucytosine	Liposomal amphotericin B
C albicans	S	S	S	S	S	S	S	S
C tropicalis	S	S	S	S	S	S	S	S
C parapsilosis	S	S	S	S	S	S	S	S
C glabrata	S-DD to R	S-DD to R	S	S	S	S	S	S to I
C krusei	R	S-DD to R	S	S	S	S	I to R	S to I
C lusitaniae	S	S	S	S	S to R	S	S	S to R

Adapted from references 19–24. S=susceptible. S-DD=susceptible-dose dependent. I=intermediate. R=resistant

Microbiology

Candida is a normal inhabitant of the human microbiological flora of skin, gastrointestinal, and genitourinary tracts, and may also be seen in the respiratory tract.[14,15] It is also recovered from the environment, particularly on surfaces.[16] *Candida albicans* is the most abundant and significant species in human beings.

Microbiological characteristics

Macroscopically, colonies of *Candida* spp are cream-coloured to yellowish. Depending on the species, their texture may be pasty, smooth, glistening or dry, wrinkled, and dull. Microscopic features show important species-related variations. All species produce blastoconidia, which may be round or elongated. Most produce pseudohyphae that are long, branched, or curved. In addition, true hyphae and chlamydospores are produced by some candida strains (figure 1). Although members of the same genus, the various species present a degree of unique behaviour with respect to their colony texture, microscopic morphology on cornmeal Tween 80 agar at 25°C (Dalmau method), and fermentation or assimilation profiles in biochemical tests that help to differentiate candida from other yeasts.[17] Commercial kits are available for rapid identification.[18]

Mechanisms of resistance

The susceptibility of *Candida* spp to antifungal agents is not uniform (table 1).[19–24] Several resistance mechanisms have been seen in *Candida* spp and have been extensively reviewed in this journal.[25] In brief, resistance often arises from different synergistic combinations of a limited number of molecular mechanisms. These include: changes in the cell wall or plasma membrane leading to an impaired uptake of antifungals; efflux pumps that take antifungals outside the cell; overexpression of the antifungal targets; mutations of the antifungal target that decrease its binding ability; activation of alternate pathways that increase the metabolism of the antifungal; sequestration of the antifungal in organelle-like vacuoles; or chromosomal changes to increase the number of copies of the required gene.[26,27]

Structural changes in the sterol content of the cell wall are associated with the ability of some candida strains to resist polyenes.[28] The lack of ergosterol, replaced by more saturated forms, results in a reduced binding of liposomal amphotericin B and nystatin to *Candida lusitaniae* and *Trichosporon beigelii*, but those strains remain, however, sensitive to azoles.[20] *Candida krusei* is intrinsically resistant to some triazoles.[29] *Candida glabrata* can be resistant to usual doses of triazoles, but sensitive to higher doses.[29–31]

In the largest surveys done in the 1990s, the proportion of *C albicans* resistant to triazoles was extremely low, ranging from 0–0·5%; almost all cases were reported in previously exposed, immunocompromised patients.[32,33]

Standards for susceptibility testing

Until recently, susceptibility testing was rarely done and had not been standardised.[29,34] The US National Committee for Clinical Laboratory Standards (NCCLS) established a subcommittee to coordinate the standardisation of broth-

Table 2. Dose-dependent susceptibility of *Candida* spp to various antifungals

	Minimum inhibitory concentration (μg/mL)		
	S	S-DD or I	R
Fluconazole	≤8	16–32	>32
Itraconazole	≤0·125	0·25–0·5	>0·5
Voriconazole	≤1	Not defined	..
Posaconazole	≤1	Not defined	..
Ravuconazole	≤1	Not defined	..
Caspofungin	≤1	Not defined	..
Flucytosine	≤4	8–16	>16
Liposomal amphotericin B	≤1		

Adapted from references 20,21,23,37,40. S=susceptible. S-DD=susceptible-dose dependent. I=intermediate. R=resistant

Table 3. Candida infections in human beings: spectrum of diseases

Haematogenous infections	Non-haematogenous infections
Candidaemia	***Superficial infections***
Endophthalmitis	Cutaneous candidiasis
Vascular-access-related infection	Oropharyngeal candidiasis
Septic thrombophlebitis	Vaginitis
Infectious endocarditis	
Arthritis	***Deep-seated infections***
Osteomyelitis	Oesophageal candidiasis
Spondylodiscitis	Cystitis
Meningitis	Peritonitis
Pyelonephritis	Tracheitis/bronchitis
Pulmonary candidiasis	
Hepatosplenic candidiasis	

based macrodilution and microdilution methods for the determination of *Candida* spp susceptibility towards antifungals.[35] The complexity and slowness of this methodology explain why many laboratories prefer to use commercial tests despite poor reproducibility.[36–39]

Based on the relation between the minimum inhibitory concentration (MIC) of the bloodstream isolates and the clinical responses seen in the treatment of a series of candidaemia, Rex et al introduced the concept of an interpretative breakpoint for antifungal susceptibility that was seen in clinical practice as dose-dependent susceptibility (table 2).[20,21,23,37,40] However, susceptibility testing with a reference method cannot be routine in many institutions. Knowledge of the local epidemiology may allow restriction of susceptibility testing to particular conditions. Treatment should be guided by in-vitro testing in clinical failures despite adequate surgical treatment, in cases of candidaemia due to non-albicans *Candida* spp with potential dose-dependent susceptibility, or in the case of prior antifungal prophylaxis. In all cases, agreement between the clinician, microbiologist, and infectious disease specialist remains essential.[21,41–45]

Epidemiology

Clinical spectrum and definitions

The spectrum of diseases related to *Candida* spp is wide (table 3). Some entities are difficult to characterise, and there is no consensus on definitions in published work.[2,43] For immunocompromised patients such a consensus was reached by investigators from the Invasive Fungal Infections Cooperative Group (IFICG) of the European Organisation for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) of the US National Institute of Allergy and Infectious Diseases (NIAID).[46]

Although there is no strict definition for critically ill, non-immunocompromised patients, it may be considered that invasive candidiasis describes two close but distinct entities: candidaemia and systemic or disseminated candidiasis. The first refers to the isolation of *Candida* spp from the blood. If the patient presents temporally related signs of infection, candidaemia is considered to be proven. Candidemia without clinical signs in a neutropenic patient, in the presence of graft-versus-host disease, or in a patient receiving steroids is considered probable. Disseminated candidiasis refers to conditions where candida invasion is shown from culture or histology results at non-adjacent, normally sterile sites. Such findings confirm haematogenous dissemination, and accordingly, these infections are considered to be proven. These definitions are used in large prospective multicentre trials. However, the definitions are restrictive and should not be used to guide clinical practice that usually does not restrict antifungals to these situations only.[46] Moreover, they have not been validated for non-immunocompromised patients. The term invasive candidiasis is sometimes used instead of haematogenous candidiasis and may refer to the fact that the development of the infection follows host colonisation.[21,42,44]

Although *C albicans* is responsible for most infections in human beings, specific clinical features have been described in association with non-albicans *Candida* spp (table 4).

Table 4. Candida infections in human beings: species-related clinical features

Species	Common clinical features
C albicans	Mucocutaneous infections: oropharyngeal, oesophagitis, vaginitis
	Deep-seated infections: pyelonephritis, peritonitis
	Haematogenous infections: candidaemia, meningitis, hepatosplenic
C parapsilosis	Candidaemia, deep infections associated with implanted devices, infections related to contaminated solutions
	Responsible for most candidaemia among neonates
C tropicalis	Candidaemia and systemic candidiasis in immunosuppressed patients
	Candidaemia may be associated with severe myalgia and myositis
C glabrata	Systemic candidiasis, candidaemia, urinary tract infections
C krusei	Candidaemia, endophthalmitis, diarrhoea in newborns
	Rare clinical features
C ciferrii	Onychomycosis
C dubliniensis	Oropharyngeal infections in HIV-positive patients
C guilliermondii	Systemic candidiasis, endocarditis in intravenous drug addicts
C haemulonii	Candidaemia, cutaneous infections
C kefyr	Systemic candidiasis
C lipolytica	Intravenous catheter-associated candidaemia
C lusitaniae	Candidaemia and disseminated infections
	May develop resistance to liposomal amphotericin B
C norvegensis	Infections in renal transplant recipients
C pulcherrima	Invasive infections in immunocompromised patients
C rugosa	Intravenous catheter-associated candidaemia
	Frequently seen in burn patients
	May be poorly responsive to liposomal amphotericin B
C viswanathii	Meningitis
C zeylanoides	Candidaemia, arthritis

Incidence and time trends

Invasive candidiasis accounted for 17% of hospital-acquired infections reported during the European Study on the Prevalence of Nosocomial Infections in Critically Ill patients (EPIC), which included 10 038 patients from 1417 intensive care units (ICUs) in 17 countries in 1992.[47,48]

Candidemia represents 10–20% of all candidiasis and is considered as the tip of the iceberg of *Candida* spp infections.[3,49,50] Data from 790 ICUs from nearly 300 institutions reporting to the US National Nosocomial Infection Surveillance (NNIS) system between 1990 and 1999 showed that *Candida* spp were responsible for 5–10% of all bloodstream infections.[3,51–53] They represented the fourth leading organism, preceded by coagulase-negative staphylococci, *Staphylococcus aureus*, and enterococci.[54,55] Candidemia rates vary according to the characteristics of the population considered and the type of institution. Rates calculated as incidence-densities (ie, per 10 000 patient-days) better express the risk associated with case-mix and allow for some comparisons (table 5). As shown, the incidence of candidaemia is higher in the overall hospital

Table 5. Incidence of candidaemia in different patient populations

Author	Year of publication	Period of observation	Type of population, country	Rate/1000 admissions*	Rate/10 000 patient-days
General population					
Diekema et al[22]	2002	1998–2001	General population, Iowa, USA	0·006	··
Kao et al[56]	1999	1992–1993	General population, California, USA	0·008	··
			General population >65 years, California, USA	0·026	··
			General population cancer patients, California, USA	0·070	··
			General population HIV-infected, California, USA	0·071	··
			General population neonates, California, USA	0·075	··
Hospital (overall)					
Richet et al[57]	1998	1995	General hospitals, France	0·17	0·17
Slavin et al[58]	2002	1995–1998	Referral hospitals, Australia	0·10–0·27	··
Sandven et al[59]	1998	1991–1996	All hospitals, Norway	0·17	0·26
			University hospitals, Norway	··	0·36
			Country hospitals, Norway	··	0·19
Doczi et al[60]	2002	1996–2000	University hospital, Hungary	0·2–0·4	··
Marchetti et al[61]	2003	1991–2000	University and university-affiliated hospitals, Switzerland	0·27	0·50
Banerjee et al[62]	1991	1989	Non-teaching hospitals, USA	0·28	··
Rennert et al[63]	2000	1994	Internal medicine, Israel	0·36	··
Banerjee et al[62]	1991	1989	Small teaching hospitals (<500), USA	0·37	··
Tortorano et al[64]	2002	1997–1999	General hospitals, Lombardy, Italy	0·38	0·44
Richet et al[57]	1998	1995	University hospitals, France	0·38	0·52
Bregenzer et al[65]	1996	1987–1992	University hospital, Switzerland	0·12–0·67	··
Luzzati et al[66]	2000	1997	University hospitals, Italy	··	1·2
Macphail et al[67]	2002	1992–1996	University hospitals, Canada	0·45	··
Rennert et al[63]	2000	1994	General surgery, Israel	0·47	··
Jarvis et al[3]	1995	1990	180 hospitals reporting to NNIS, USA	0·50	··
Banerjee et al[62]	1991	1989	Large teaching hospitals (>500), USA	0·61	··
Voss et al[68]	1996	1995	University hospitals, Holland	··	0·71
Garbino et al[69]	2000	1990–1999	University hospital, Switzerland	0·62	0·27
Viudes et al[70]	2002	1995–1997	University hospital, Spain	0·76	··
Alonso-Valle et al[71]	2003	1995–1999	University hospital. Spain	0·81	··
Wey et al[5]	1988	1977–1985	University hospital, USA	0·85	··
Pittet et al[72]	1995	1983–1992	University hospitals, USA	0·96	1·12
Fraser et al[6]	1992	1988–1989	Referral hospital, USA	3·3	··
Hung et al[73]	1996	1994–1995	University hospital, Taiwan	3·7	··
Cancer centre					
Richet et al[57]	1998	1995	Cancer centres, France	0·71	0·16
Abi-Said et al[11]	1997	1988–1992	Cancer centre, USA	6·0†	··
Girmenia et al[10]	1998	1986–1997	Cancer centre, Italy	15·5	··
Hung et al[73]	1996	1994–1995	University hospital, Taiwan	24·0	··
Intensive care units					
Hung et al[73]	1996	1994–1995	Medical ICU, Taiwan	63·4	··
Rangel-Frausto et al[32]	1999	1993–1995	Surgical ICUs, USA	9·8	9·9
Blumberg et al[74]	2001	1993–1995	Surgical ICUs, US	9·81	9·8
Hung et al[73]	1996	1994–1995	Surgical ICU, Taiwan	94·0	··
Hung et al[73]	1996	1994–1995	Burn ICU, Taiwan	27·0	··
Garbino et al[69]	2002	1990–1999	Mixed ICUs, Switzerland	1·12	2·8
Blot et al[75]	2002	1992–2000	Mixed ICUs, Belgium	2·5	··
Nolla-Salas et al[76]	1997	1991–1992	Mixed ICUs, Spain	2·0	··
Voss et al[77]	1997	1989–1993	Mixed ICUs, Holland	··	5·5
Leleu et al[8]	1999	1998	Mixed ICUs, France	3·1	22·0

(continues on next page)

Table 5. Incidence of candidaemia in different patient populations (continued)

Author	Year of publication	Period of observation	Type of population, country	Rate/1000 admissions*	Rate/10 000 patient-days
Rennert et al[53]	2000	1994	Mixed ICUs, Israel	6·06	..
Macphail et al[67]	2002	1992–1996	Mixed ICUs, Canada	..	12·4
Petri et al[78]	1997	1989–1990	Mixed ICUs, Germany	20·0‡	..
Rangel-Frausto et al[32]	1999	1993–1995	Paediatric ICUs, USA	12·3	6·4
Rennert et al[53]	2000	1994	Neonatology, Israel	8·29	..
Kossoff et al[79]	1999	1990–1995	Neonatology, USA	28·5	..
Hung et al[73]	1996	1994–1995	Neonatology, Taiwan	46·0	..

*classified by ascending order for each category; rates are given per 1000 admissions or per 1000 discharges. †Incidences were 20, 10, and 34 per 1000 admissions for patients with leukaemia, lymphoma, or myeloma and solid tumour, respectively. ‡Per 1000 patients staying more than 10 days in ICU.

than in the general population, but much lower than among cancer and critically ill patients.

Trends over time are also important to consider. Between 1980 and 1990, the incidence of severe fungal infections reported by 115 NNIS hospitals increased from 2·0 to 3·8 episodes per 1000 admissions.[49] In a single referral centre in the USA, candidaemia incidence increased linearly from 0·1 in 1980 to 2·0 episodes per 10 000 patient-days in 1992.[72] Similarly, candidaemia continuously increased in five Dutch hospitals from 0·37 in 1987 to 0·72 episodes per 10 000 patient-days in 1995. Similar trends were reported from other centres, in particular in the USA (table 6).

By contrast with data reported during the 1980s, the rate of candidaemia may have stabilised during the 1990s, at least in some institutions.[7,59,60,66,69,83–85] In a series of 294 consecutive candidaemia patients between 1989 and 2000 at a large referral centre, candidaemia incidence ranged from 0·21–0·56 per 10 000 patient-days with the highest incidence in 1993 and the lowest in 2000.[69]

These findings confirm that severe *Candida* spp infections can no longer be considered as rare infections restricted to neutropenic or immunocompromised patients. All types of patients are now concerned, particularly those with severe underlying disease or critical illnesses that need aggressive diagnostic or treatment procedures.

Table 6. Secular trends of candidaemia, selected series, 1975–2002

Reference	Year of publication	Period of observation	Type of population, country	Rate/10 000 beginning of study period	Rate/10 000 end of study period	Ratio of change (% increase)
5	1988	1983–1985	University hospital, USA	5·1*	10·3*	202
62	1991	1980–1989	Large teaching hospitals, USA	1·6*	6·1*	381
80	1991	1983–1987	Cancer hospital, France	10·0*	32·0*	320
7	1994	1986–1988	University hospital, USA	2·0*	13·0*	650
7	1994	1989–1991	University hospital, USA	13·0*	8·0*	–62
72	1995	1983–1992	University hospitals, USA	0·15†	1·75†	1167
65	1996	1987–1992	University hospital, Switzerland	1·2*	6·7*	558
68	1996	1987–1995	University hospitals, Holland	0·37†	0·72†	195
81	1996	1978–82 to 1983–87	Autopsy series, Germany	220·0*	320·0*	145
81	1996	1983–87 to 1988–92	Autopsy series, Germany	320·0*	510·0*	159
10	1996	1983–86 to 1991–94	Cancer hospital, Italy	34·0*‡	63·0*‡	185
10	1996	1983–86 to 1991–94	Cancer hospital, Italy	7·5*§	74·0*§	987
73	1996	1980–1994	University hospital, Taiwan	0·9*	25·3*	2811
77	1997	1987–1994	Intensive care, Holland	4·7†	7·4†	157
82	1998	1989–1993	Paediatric university hospital, USA	0·12†	0·28†	233
59	1998	1991–1996	All hospitals, Norway	0·29†	0·27†	–9
79	1999	1981–85 to 1987–90	Neonatology, USA	25·0*	46·0*	184
79	1999	1987–90 to 1990–95	Neonatology, USA	46·0*	285·0*	620
66	2000	1992–1997	University hospital, Italy	1·01†	1·14†	113
69	2002	1989–2000	University hospital, Switzerland	0·32†	0·24†	–75
67	2002	1992–2002	University hospitals, Canada	4·5*	7·6*	169
60	2002	1996–2000	University hospital, Hungary	2·0–4·1*	2·0–4·1*	0–205
61	2003	1991–2000	University and referral hospitals	0·37†	0·48†	130

*Per 10 000 patient admissions or discharges. †Per 10 000 patient–days. ‡*C albicans* per 10 000 patient admissions. §*C parapsilosis* per 10 000 patient admissions

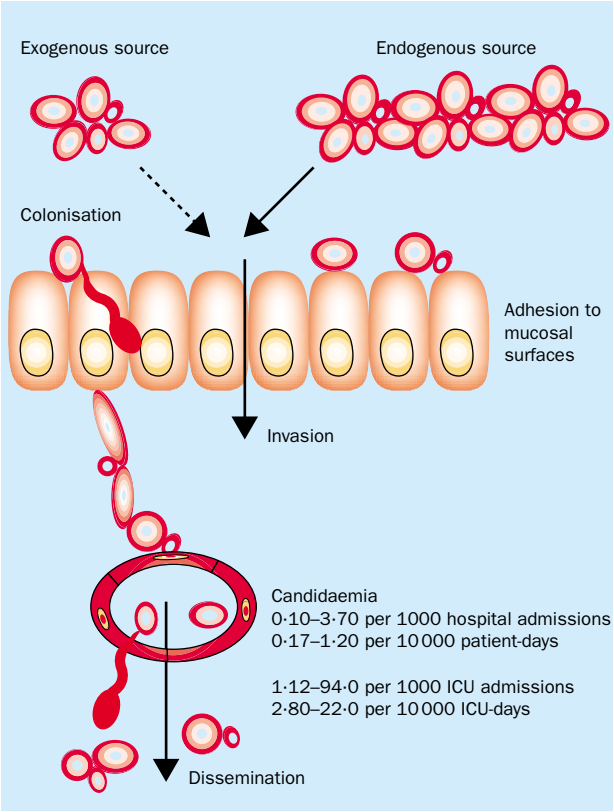

Figure 2. Pathophysiology of invasive candidiasis.

Emergence of non-albicans candida strains

Triazole-based antifungal prophylaxis was generalised in the 1980s for use in chemotherapy-induced neutropenia or for conditioning before bone-marrow transplantation. A meta-analysis of 38 randomised, controlled clinical studies including more than 7000 patients showed that prophylaxis reduces the use of parenteral antifungal therapy (odds ratio [OR] 0·57; 95% CI 0·48–0·68), the rate of superficial (0·29; 0·20–0·43) and invasive fungal infection (0·29; 0·20–0·55), as well as fungal-infection-related mortality (0·58; 0·20–0·93).[86] These effects were more pronounced in patients with malignant diseases and prolonged neutropenia (0·72; 0·55–0·95) and among haematopoietic stem-cell transplantation recipients (0·77; 0·59–0·99). In parallel, a marked increase in the proportion of non-albicans candida bloodstream isolates has been reported in several countries. In particular, it has been higher than 50% in many cancer centres since the late 1980s (table 7).[6,10,11,30,87–91] Thus, prophylaxis has repeatedly been shown to increase the risk of infection due to non-albicans candida strains such as *C krusei*, intrinsically resistant to some triazoles, or *C glabrata* which may be sensitive only to higher doses.[10–13,83,117] A similar event was reported in HIV patients receiving azole prophylaxis to prevent candida oesophagitis.[85,118]

The effect of this epidemiological shift on the management of severe candidiasis has generated considerable debate in specialised published work and, accordingly, guidelines have been revised.[9,21,42] Compared with the benefit of prophylaxis, the effect of this shift seems, however, to be of limited importance. In a review of 491 episodes of candidaemia from the M D Anderson Cancer Center (Houston, TX, USA), Abi-Said et al reported that prophylaxis with fluconazole was highly protective against infections with *Candida tropicalis* (relative risk [RR] 0·08; 95% CI 0·01–0·58) and *C albicans* (0·15; 0·05–0·45). Prophylaxis also promoted infections due to *C glabrata* (5·08; 2·32–11·11) and *C krusei* (27·07; 9·23–79·36).[11] However, it is important to note that in this large series, the reduction of both the incidence and absolute number of cases of candidaemia due *C albicans* and *C tropicalis* was largely superior to the increased incidence of those due to *C krusei* and *C glabrata*. Comparable trends were reported at the Fred Hutchinson Cancer Research Center (Seattle, OR, USA) after the introduction of fluconazole-based prophylaxis.[119] In a series of 355 autopsies of patients who died after bone marrow transplant between 1990 and 1994, the incidence of candidiasis decreased from 27% to 8% in patients without and with prophylaxis, respectively.[119] This decrease was associated with a significant reduction of infections due to *C albicans* in the absence of a significant increase of those related to non-albicans strains. In addition, the proportion of hepatosplenic candidiasis was significantly lower in patients under prophylaxis—ie, 3% (5/168) versus 16% (26/161), respectively.

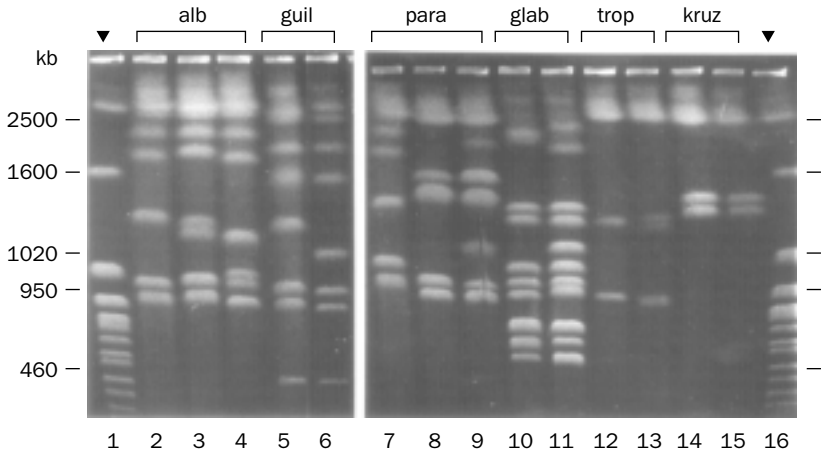

Figure 3. Interspecies and intraspecies delineation of Candida *spp. Electrophoretic karyotypes of various* Candida *spp strains separated by contour-clamped homogeneous electric field (CHEF) gel electrophoresis. There are different migration patterns of three different strains of* C albicans *(lines 2–4), two different strains of* C guillermondii *(lines 5,6), three different strains of* C parapsilosis *(lines 7–9), two different strains of* C glabrata *(lines 10, 11), two different strains of* C tropicalis *(lines 12,13) and* C krusei *(lines 14,15). Interspecies delineation is shown by comparison of two strains of* C krusei*, which show only two bands between 1120 and 1600 kDa, and* C glabrata *with bands below 1500 kDa. Intraspecies delineation is shown by comparison of the migration patterns of the two different strains of* C glabrata *(D Pittet, unpublished data). For further details, see reference 136.*

Table 7. Distribution of *Candida* spp bloodstream isolates among various types of populations

References	Year of publication	Year of observation	Number of studies	Region/ country	Number of strains	*C albicans* (%)	*C tropicalis* (%)	*C parapsilosis* (%)	*C glabrata* (%)	*C krusei* (%)	Other candida
*Immunosuppressed patients, selected series**											
6,10,11,30,87–91	1985–2001	1978–1998	9	USA in 6 of 9	2143	44	18	15	12	5	6
Laboratory–based surveillance programmes†											
32,33,54,92–95	1998–2001	1993–2000	7	USA	4292	54	10	12	18	2	4
33,92,93	1999–2001	1993–1998	3	Canada	340	56	7	20	12	2	3
33,92,93	1999–2001	1993–1998	3	S America	281	43	14	32	4	<1	6
33,94	1999–2001	1993–1998	2	Europe	472	56	7	20	11	1	5
Epidemiological surveillance in single or multiple hospitals, worldwide (1976–2002)‡											
6,7,22,56,67,79, 96–100,101	1992–2002	1976–2001	12	USA in 10 of 12	5235	52	12	14	14	2	6
102–104	1998–2002	1994–1999	3	Brazil	458	34	25	22	4	4	11
57,59,61,63–66, 68–71,75–77,83, 105,107–109	1989–2003	1986–2002	19	Europe	5194	63	5	9	10	2	11
73,84,110	1992–2002	1981–1998	3	Asia	369	34	43	7	6	1	9
58	2002	1995–1998	1	Australia	732	56	4	13	9	5	13
Large therapeutic series (>100 episodes)§											
111–116	1994–2003	1989–2001	6	USA in 4 of 6	1361	54	13	13	13	2	5

*Detailed data are presented in table 7-1 available on the journal's website. †Detailed data are presented in table 7-2 available on the journal's website. ‡Detailed data are presented in table 7-3 available on the journal's website. §Detailed data are presented in table 7-4 available on the journal's website.

During the 1990s, international surveillance programmes were established to provide more general epidemiological information on species distribution among candida bloodstream isolates (table 7).[32,33,54,92–95] Despite important geographic and demographic variations, *C albicans* remained the predominant strain in most countries. Similar trends were reported in series where immunocompromised patients did not represent the majority of cases, and in particular among critically ill patients (table 7)[6,7,22,56–61,63–71,73,75–77,79,83,84,96–101] From these reports, it is also important to consider that the proportion of strains without high potential or intrinsic resistance to triazole compounds represented more than 80% of all *Candida* spp isolated in most ICUs. The proportion of *C albicans* resistant to triazoles remained extremely low in these surveys (<1%) and was almost exclusively reported from patients previously exposed to azoles. These data contrast with trends reported among immunocompromised patients (table 7).[6,10,11,30,87–91]

Data extracted from large therapeutic studies including more than 100 episodes of candidaemia with a proportion of neutropenic and immunocompromised patients ranging from 5–25% showed large variations in the distribution of *Candida* spp (table 7).[111–116] In these series, the proportion of *C albicans* progressively decreased over time, but remained above or close to 50%. Importantly, the proportion of *C krusei* intrinsically resistant to some triazole compounds remained below 3% in most series.

As will be discussed in detail in the section on antifungal prophylaxis in the second part of this review, these data strongly suggest that antifungal prophylaxis in critically ill, non-immunocompromised patients could be considered for selected groups where the incidence of candidiasis is expected to be higher than 10%.[43,120] This approach may help to limit the quantity of antifungals used for prophylaxis and delay the emergence of infections due to non-albicans candida strains seen in immunocompromised patients.

In summary, it is essential to take into account case mix, time trends, centre specificity, and the proportions of immunosuppressed patients to understand the epidemiology of candidaemia, all of which may have a direct impact on management.

Pathophysiology

Candida spp are part of the normal endogenous flora; temporary or permanent carriage in the gastrointestinal tract is documented among 40–50% of human beings. Mucocutaneous surface colonisation is rare under normal conditions.[3] Colonisation is a prerequisite for the development of candidiasis;[78,121–123] it develops secondary to changes in the ecology of the endogenous flora that promote *Candida* spp overgrowth on mucosal and skin surfaces.[124] *Candida* spp can also translocate across the gut barrier, mostly when its integrity is lost.[125–128] Continuous exposure to risk factors is then responsible for further invasion with possible secondary haematogenous dissemination (figure 2).[74,129,130]

Nosocomial exogenous transmission of *Candida* spp has been reported.[131,132] However, carefully designed studies using genotyping of candida strains confirmed that endogenous colonisation is responsible for most severe candidiasis.[123,132–136] Both endogenous and exogenous colonisation can, however, coexist in the clinical setting. Surveillance cultures done over

an 18-month period in 13 ICUs showed that the stools of 312 of 910 adults (34%) and 286 of 957 children (30%) were colonised by *Candida* spp during ICU stay.[132] Over the same period, *Candida* spp grew from the hands of 33% and 29% of the adult and paediatric ICU staff, respectively. Further analysis of the epidemiology, including strain molecular typing, established that cross-transmission may have occurred.[74]

Risk factors

In some patients the portal of entry can be traced to intravascular devices, facilitated by their frequent use, by parenteral nutrition, and the potential for contamination of catheters by *Candida* species. In other patients, underlying disease such as peritonitis or bowel function impairment may be the source of candidaemia. A large number of studies have attempted to assess risk factors for candidaemia, most of them in critically ill non-immunosuppressed patients. Main results are summarised in table 8.[11,73,80,82,99,104,121,129,137–144] Major predisposing factors identified through univariate and multivariate analysis are shown; leading factors are discussed below.

Colonisation

Colonisation by *Candida* spp is the leading risk factor for infection in most series in which it has been explored.[80,90,99,104,121,129,133,137,139,140,145–150] Several elements support candidal colonisation as a prerequisite for subsequent infection. Sequential spread from the abdominal cavity to other body sites before candidaemia occured was shown by Solomkin early in the 1980s.[145,146] Heavy or increasing growth of *Candida* spp in specimens obtained from the peritoneal cavity is predictive of subsequent infections.[148,151,152] High amounts of *Candida* spp in the stool of cancer patients and in low-birthweight neonates are reported to be a significant risk factor for candidaemia.[80,153] Multiple site colonisation is an independent risk factor for invasive infection.[80,129,136–138]

Using intraspecies delineation of *Candida* spp (figure 3),[136] *Candida* spp carriage was proven to be patient-specific and to precede infection in surgical patients.[136] Other authors confirmed this finding in both neutropenic and non-neutropenic patients: *Candida* spp colonisation or superficial infection with a genotypically identical strain usually precedes bloodstream or invasive infections.[99,133,136,154–156]

It is, however, often difficult to distinguish colonisation with *Candida* spp from invasive infection in critically ill patients. Only 5–15% of hospitalised patients are already colonised at entry, but this proportion irremediably increases with time and exposure to risk factors. Accordingly, as many as 50 to 86% of critically ill patients may become colonised with *Candida* spp during prolonged ICU stay.[75,78,99,148,157] However, only 5 to 30% will develop severe candidiasis.[78,141,144,151]

Multiple surveillance cultures are often done, but the clinical significance of positive candida cultures is difficult to assess.[74,75] Some authors have suggested that in cases of clinical suspicion, the colonisation of more than two body sites may be sufficient to predict candidiasis and require the initiation of antifungal therapy.[42,43,145,158] Nevertheless, this strategy has never been tested in a prospective study, and both the sensitivity and the specificity of such findings may be low.[121]

Antibiotics

Prior or concomitant exposure to antibiotics is a major risk factor for candidiasis. In a study from Wey et al,[129] the number of different antibiotics was the most significant factor. Similarly, 94% of candidemic patients in the study by Fraser et al had prior exposure to antibiotics, with 61% having been treated with more than four different agents.[6] Although potentially associated with any agent, selection pressure seems to be more pronounced for cephalosporins and drugs with anti-anaerobic activity.[124,126,153] The broader the antimicrobial spectrum and the duration of exposure, the higher the risk.[121,159]

Neutropenia

Since neutrophils are essential host defence components against most fungi, neutropenia was identified early as one of the major risk factors for invasive candidiasis.[11,80,104,137,140]

Vascular access

Multiple vascular access devices are often needed to manage critically ill patients, and candidaemia has been suspected or proved to be catheter-related in proportions ranging from 35% to 80%.[66] In some studies, parenteral nutrition was associated with a significantly increased risk of candidaemia, in particular in outbreak settings.[11,74,82,91,111,122,129,137,140,160]

Others

Additional risk factors for severe *Candida* spp infection have been identified and include surgical procedures, the presence of renal failure, the use of steroids and H_2 blockers, a high severity of illness score, or longer ICU stay (table 8). Some risk factors did not independently predict candidaemia; others constituted surrogate markers of illness rather than specific risk factors for infection. The higher the number and the longer the exposure to these factors, the higher the risk.[129,160]

Virulence factors

Candida spp have the ability to produce virulence factors that enhance their capacity to colonise mucosal or synthetic surfaces[161] and to invade host tissues by disrupting host cell membranes. Proteinases and species-specific phospolipases account for most secretory proteins acting as virulence factors in host cell and animal models of candidiasis.[162]

The ability of *Candida* spp to switch between different phenotypic forms in response to environmental conditions has been studied. Increased secretion of proteolytic enzymes and hyphae formation have been associated with switching phenomena. *C albicans* isolates from active infection have been reported to show a higher prevalence of phenotypic switching than those associated with commensalism. Moreover, some characteristics of azole resistance may be related to phenotyping switching.[25] Hyphae may penetrate tissues more rapidly than yeast, but both forms can invade tissues.[163,164]

Table 8. Predisposing factors for candidaemia

Reference	Study design	Univariate analysis		Multivariate analysis		Comments
		OR/RR	95% CI	OR	95% CI	
Candida colonisation						
Wey et al[129]	C	10·63	3·33 to 33·97	..	..	From 1 body site other than blood
		4·43	1·44 to 13·65	10·37	2·33 to 46·16	From >1 body sites other than blood
Karabinis et al[137]	C	10·20	NS	12·00	1·00 to 119·00	From >1 body sites other than blood
Verfaillie et al[138]	R	NS	NS	4·64	2·61 to 8·24	From >1 body sites other than blood
Wiley et al[139]	R	NS	NS	..	..	Multiple sites
Richet et al[80]	R	..	..	25·00	1·30 to 129·00	Increase >4 log in stools
Pittet et al[121]	P	..	..	4·01	2·16 to 7·45	Sites other than blood
Bross et al[140]	C	17·90	4·60 to 70·40	27·00	1·70 to 424·00	Candiduria
Saiman et al[99]	P	3·00	1·38 to 6·30	..	..	Rectal swabs
Pelz et al[141]	P	9·82	1·34 to 72·19	10·64	1·43 to 78·74	
Antibiotics						
Weese-Mayer et al[142]	C	..	..	1·74	NS	Prolonged use
Karabinis et al[137]	C	2·20	NS	..	..	Cephalosporins
		3·50	NS	..	..	Vancomycin
		7·90	NS	..	..	Carboxypenicillins
		10·00	NS	..	..	Aminoglycosides
		..	..	2·00	1·00 to 27·00	Any agent in cancer patients
Wey et al[129]	C	12·50	2·95 to 52·91	..	..	3–5 agents
		30·51	5·23 to 178·02	..	..	>5 agents
		5·04	1·24 to 20·55	..	..	Duration 15–21 days
		6·25	1·62 to 24·14	..	..	Duration 22–28 days
		11·17	2·78 to 44·82	1·73	1·23 to 2·43	Duration >28 days
Bross et al[140]	C	15·50	4·20 to 57·3	25·10	2·10 to 318·00	>2 agents
Richet et al[80]	R	NS	2·30 to ∞	275·00	NS	Vancomycin use
		NS	1·10 to ∞	25·00	NS	Imipenem use
Hung et al[73]	P	NS	NS	..	..	Multiple agents
Saiman et al[99]	P	11·81	1·97 to 480·60	..	..	5 days
		9·41	4·00 to 25·63	9·41	1·41 to 11·44	>2 agents
Nucci et al[104]	R	2·93	1·13 to 7·26	2·93	1·13 to 7·61	>2 agents for >14 days
Vascular access						
Wey et al[129]	C	5·66	1·64 to 19·53	..	..	Arterial catheter, >7 days
		5·17	1·01 to 26·64	..	..	Swan-Ganz catheter, 1–7 days
		17·44	1·91 to 158·92	..	..	Swan-Ganz catheter, >7 days
		..	..	7·23	1·14 to 46·06	Hickman catheter
Karabinis et al[137]	C	3·30	NS	..	..	Central venous catheter, 1–14 days
		4·20	NS	NS	1·00 to 39·00	Central venous catheter, >14 days
Bross et al[140]	C	5·50	1·90 to 15·80	..	..	Arterial catheter
		NS	NS	26·40	1·50 to 451·00	Central venous catheter
Abi-Said et al[11]	R	3·89	1·88 to 8·05	3·80	1·80 to 7·98	For *C parapsilosis vs* other strains
MacDonald et al[82]	C	NS	NS	..	..	
Hung et al[73]	P	NS	NS	..	..	Retained catheter
Saiman et al[99]	P	8·62	3·50 to 24·45	3·94	1·48 to 12·34	Central venous catheter
Blumberg et al[74]	P	..	..	5·40	1·20 to 23·60	Catheter and prior surgery
Bladder catheter						
Wey et al[129]	C	6·20	1·65 to 23·30	..	..	>7 days
Bross et al[140]	C	6·50	2·40 to 17·70	13·00	1·30 to 131·40	Any duration

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Table 8. Predisposing factors for candidaemia (continued)

Reference	Study design	Univariate analysis		Multivariate analysis		Comments
		OR/RR	95% CI	OR	95% CI	
Neutropenia						
Karabinis et al[137]	C	9·20	NS	..	..	Cancer patients, 1–7 days
		17·40	NS	45·00	NS	Cancer patients, >7 days
Richet et al[80]	R	NS	NS	NS	NS	Duration of neutropenia
Wiley et al[139]	R	NS	NS	NS	NS	Duration of neutropenia
Verfaillie et al[138]	R	..	..	5·19	2·04 to 13·25	Duration of neutropenia
Abi-Said et al[11]	R	3·69	2·20 to 6·19	3·50	1·98 to 6·18	*C tropicalis vs* other strains
		6·98	2·02 to 24·17	3·70	2·23 to 14·05	*C krusei vs* other strains
Nucci et al[104]	R	5·89	2·46 to 14·11	..	..	<500/μL
Nucci et al[104]	R	9·91	3·58 to 27·56	9·14	3·30 to 25·27	<100/μL
Diarrhoea						
Bross et al[140]	C	3·70	1·30 to 10·20	..	..	
		30·60	3·80 to 243·80	10·20	1·03 to 101·40	Ileus
Parenteral nutrition						
Weese-Mayer et al[142]	C	NS	NS	..	..	Hyperalimentation with lipids
Wey et al[129]	C	2·98	1·38 to 6·40	..	..	1–14 days
Karabinis et al[137]	C	2·90	NS	..	..	
Bross et al[140]	C	8·10	3·10 to 13·10	..	..	
Hung et al[73]	P	NS	NS	..	..	
MacDonald et al[82]	C	NS	NS	NS	NS	Children
Saiman et al[99]	P	..	..	2·93	1·11 to 8·39	Duration >5 days
		..	..	2·91	1·22 to 7·19	Lipid use, >7 days
Pelz et al[141]	P	2·53	1·08 to 5·94	NS		
Anti-H_2						
Bross et al[140]	C	4·60	1·60 to 223·20	..	..	>2 agents
Saiman et al[99]	P	..	..	2·44	1·11 to 5·29	Any agent
Gastrointestinal bleeding						
Bross et al[140]	C	4·10	1·60 to 10·60	..	..	Symptomatic bleeding
Surgery						
Karabinis et al[137]	C	..	..	20·00	NS	In cancer patients
Bross et al[140]	C	..	..	0·10	0·01 to 0·90	Protective, any type of surgery
Petri et al[77]	P	10·00	1·99 to 60·60	..	..	Abdominal drainage
Abi-Said et al[11]	R	2·38	1·45 to 3·92	..	..	*C albicans vs* other strains
Saiman et al[99]	P	2·84	1·31 to 5·95	..	..	Any type of surgery
Blumberg et al[74]	P	..	..	7·30	1·00 to 53·80	Any type of surgery
		..	..	0·20	0·04 to 0·70	Protective, neurosurgery
		..	..	0·30	0·10 to 0·90	Protective, ear, nose, and throat surgery
Slavin et al[58]	R	..	..	2·02	1·23 to 3·13	Any type of surgery
Antifungal prophylaxis						
Abi-Said et al[11]	R	36·70	13·03 to 103·36	27·07	9·23 to 79·36	For *C krusei vs* other strains
		3·91	1·85 to 8·27	5·08	2·32 to 11·11	For *C glabrata vs* other strains
Goodrich et al[143]	R	NS	NS	..	..	Prophylaxis of graft-versus-host disease
Pelz et al[141]	P	2·70	1·23 to 5·88	2·22	1·02 to 4·76	Absence of prophylaxis
Steroids						
Wey et al[129]	C	4·25	1·43 to 12·63	..	..	
Bross et al[140]	C	3·60	1·40 to 9·10	..	..	
Botas et al[144]	C	..	..	7·50	5·00 to 11·00	Preterm neonates
Abi-Said et al[11]	R	2·20	1·37 to 3·55	..	..	For *C tropicalis vs* other strains
		2·63	1·05 to 6·57	..	..	For *C krusei vs* other strains

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Table 8. Predisposing factors for candidaemia (continued)

Reference	Study design	Univariate analysis		Multivariate analysis		Comments
		OR/RR	95% CI	OR	95% CI	
Chemotherapy						
Richet et al[80]	R	0·10	0·30 to 0·90	..	..	After response to chemotherapy
		..	..	2·17	NS	Relapse of leukaemia
Abi-Said et al[11]	R	2·85	1·49 to 5·45	..	..	For *C tropicalis vs* other strains
		8·00	1·06 to 60·34	..	..	For *C krusei vs* other strains
		..	..	0·58	0·35 to 0·96	For *C albicans vs* other strains
Goodrich et al[143]	R	NS	NS	..	..	Conditioning regimen
		NS	NS	..	..	Graft-versus-host disease
Verfaillie et al[138]	R	..	..	3·24	1·02 to 10·34	Total body irradiation
Multiple transfusion						
Wey et al[129]	C	3·60	1·34 to 9·70	..	..	
Renal failure						
Wey et al[129]	C	NS	NS	18·13	1·48 to 221·84	For haemodialysis
Bross et al[140]	C	6·00	2·10 to 17·00	22·10	2·20 to 223·20	
Blumberg et al[74]	P	..	..	3·83	2·10 to 8·30	
Mechanical ventilation						
Weese-Mayer et al[142]	C	NS	NS	..	..	Tracheal intubation
Wey et al[129]	C	4·76	1·19 to 19·03	..	..	Duration, 1–7 days
		3·73	1·19 to 11·68	..	..	Duration, >7 days
Saiman et al[99]	P	..	..	10·71	1·66 to 450·13	Intubation and antibiotics
Length of stay						
Wey et al[129]	C	9·83	2·03 to 47·67	..	..	ICU stay >7 days
Bross et al[140]	C	21·30	1·70 to 274·30	3·70	1·20 to 11·40	Transfer from another hospital
Saiman et al[99]	P	12·69	3·23 to 109·20	..	..	Paediatric ICU stay >7 days
		5·35	2·42 to 13·04	..	..	Paediatric ICU stay >14 days
Severity of disease						
Bross et al[140]	C	15·00	3·20 to 70·10			Prior bacteraemia
Wiley et al[139]	R	NS	NS	..	..	Acute non–lymphocytic leukaemia
Goodrich et al[143]	R	..	..	1·90	NS	Mismatched donor
		..	..	1·80	NS	Acute graft-versus-host disease
Pittet et al[121]	P	..	..	1·03	1·01 to 1·05	Per additional APACHE II point
Abi–Said et al[11]	R	1·02	1·01 to 1·03	1·01	1·001 to 1·02	For *C tropicalis vs* other strains
Saiman et al[99]	P	..	..	3·55	1·61 to 7·73	SNAP >10
Pelz et al[141]	P	3·15	1·01 to 1·03	1·02	1·01 to 1·04	Per additional APACHE III point
Birthweight						
Saiman et al[99]	P	3·82	1·02 to 14·36	..	..	< 801 g
		10·99	3·13 to 39·99	..	..	801–1000
		7·25	9·48 to 81·66	..	..	1001–1500 g
Age						
Verfaillie et al[138]	R	NS	NS	1·60	1·35 to 1·90	>40 years
Goodrich et al[143]	R	NS	NS	1·50	NS	>40 years
Saiman et al[102]	P	–	–	4·00	1·20 to 14·39	<32 weeks

R=retrospective cohort study; P=prospective cohort study; C=matched case-control/historical cohort study; NS=not specified in the original reference; OR=odds ratio; RR=relative risk; 95% CI=95% confidence interval; SNAP=score for neonatal acute physiology.

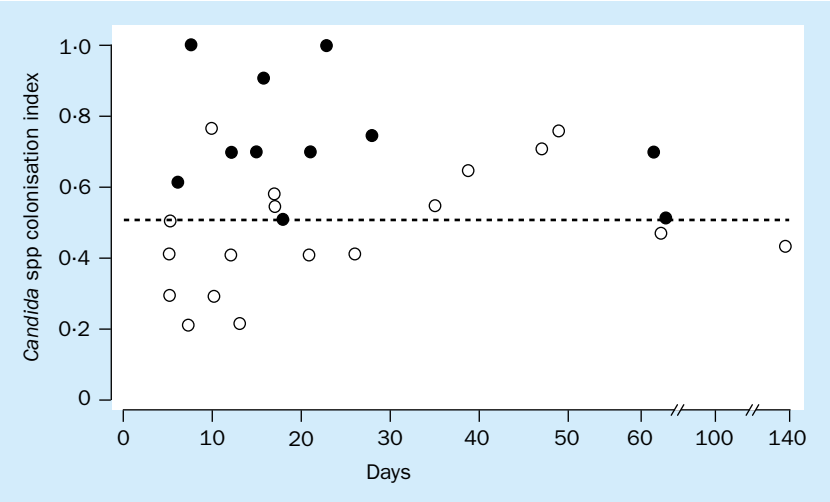

Figure 4. Candida *spp colonisation index. Colonisation index is defined as the ratio of the number of non-blood, distinct body sites colonised by* Candida *spp to the total number of distinct body sites tested. It was recorded for each patient from the first day of colonisation until discharge from the ICU among non-infected patients and until time of severe candidiasis among infected patients. 29 of approximately 650 patients admitted to the surgical ICU were colonised at several distinct body sites. All patients were at high risk for nosocomial infections and carried multiple risk factors for candidiasis, including invasive devices and broad-spectrum antibiotics. Eleven of 29 patients developed severe candida infection (black circles), including candidaemia in eight. 18 patients were heavily colonised but did not develop candidiasis (empty circles). Among potential risk factors for candidiasis, two independently discriminated the colonised from the infected patients: severity of illness and the degree of colonisation (table 8). Reproduced with permission from reference 121.*

Further exploration of some genetically determined aspects of the host response will probably help to define new management strategies in the future but will not be discussed in this review.[165]

Diagnostic tools

The diagnosis of severe candidiasis remains a challenge.[21,41–45] Cultures other than blood or from normally sterile body sites are non-specific and may become positive only late in the course of infection.[121] Despite significant progress over the past decades and preliminary encouraging results, serology testing or molecular methods for the diagnosis of candidiasis are not currently used in clinical practice.[166–168] The capacity to explore gene expression by microarray technology is promising and may also allow to detect early differences associated with *Candida* spp drug-susceptiblity profiles.[169]

The early clinical manifestations, which are basically those of sepsis, are non-specific and no clinical sign or symptom has sufficient specificity to be highlighted with the exception of a positive fundoscopic examination.[6,57,65,76,105] Although quite specific, candida endophthalmitis is, however, infrequent during candidaemia, occurring at an incidence of 3·7–25% in prospective series.[76,111,115,170] In general, the diagnosis of candidiasis is made only late in the course of a torpid infection or is an autopsy finding. A review of 8124 consecutive autopsies, representing 75% of all deaths over a period of 15 years at a single German university hospital, showed that only 22% of the 272 invasive fungal infections were suspected or documented before death.[81] This finding may explain persisting high mortality despite the availability of new antifungal agents,[11] and also illustrates the problematic of disease diagnosis.

Colonisation index

In a prospective cohort study of critically ill surgical patients, we assessed the degree of patient colonisation by using a specific index[121] and a powerful epidemiologic tool (figure 3) to identify the origin of colonisation.[136] The degree of colonisation was established daily as the ratio of the number of distinct body sites colonised with genotypically identical strains of *Candida* spp over the total number of sites tested—ie, the candida colonisation index (figure 4).[121] The average candida colonisation index significantly differed between colonised and infected patients (0·47 *vs* 0·70, respectively, p<0·01); a threshold of 0·5 or more correctly identified the infected patients. All patients who

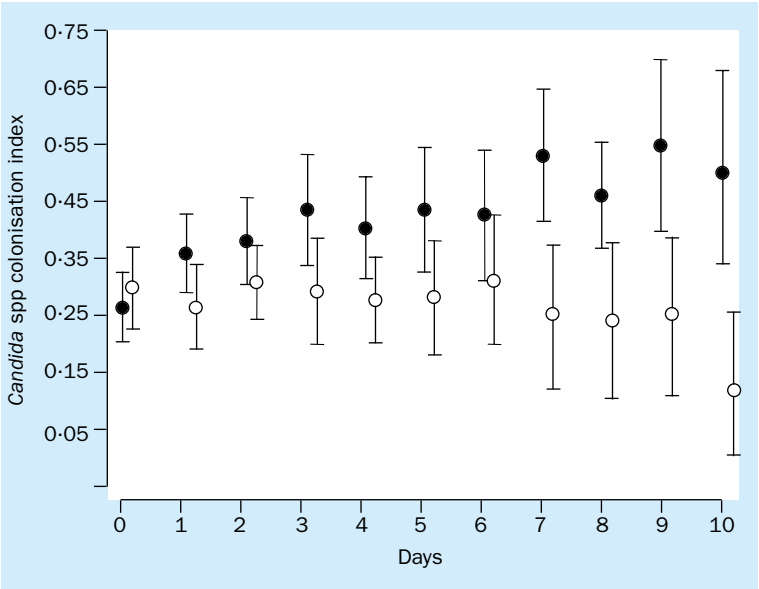

Figure 5. Dynamics of candida colonisation in patients assigned fluconazole (empty circles) prophylaxis or placebo (black circles). Candida *spp colonisation index was measured daily in the fluconazole-treated and placebo-treated patients. Median values and interquantile range are shown. Candida colonisation developed in 53% (29/55) of patients free of colonisation at study entry in the fluconazole group versus 78% (40/51) of patients in the placebo group. Candida infection occurred less frequently in patients in the fluconazole group and 90% of candidaemia developed in patients in the placebo group. It developed only in patients heavily colonised with* Candida *spp. Reproduced with permission from reference 145.*

Table 9. Impact of candidaemia

Reference*	Year of publication	Period of observation	Country	Number of cases	Crude mortality (%)	Attributable mortality (%)
General hospitals						
111	1994	1989–1993	USA	206	36	7
115	2002	1997–2001	17 countries	224	34	6
Cancer centre						
138	1991	1979–1987	USA	76	58	30
Teaching hospitals						
5	1988	1977–1984	USA	95	57	38†
105	1989	1980–1986	Switzerland	52	46	21
173	1991	1983–1986	USA	135	59	45
6	1992	1988–1989	USA	106	57	48
7	1994	1986–1991	USA	106	55	35
97	1995	1988–1992	USA	70	19	19
73	1996	1994–1995	Taiwan	118	59	43
65	1996	1987–1992	Switzerland	41	44	13
114§	1997	1991–1994	Canada	106	30	12
98	1997	1976–1996	Canada	95	52	23
82	1998	1992–1993	USA	24	21	21
70¶	2002	1995–1997	Spain	145	44	30
71	2003	1995–1999	Spain	143	45	29
101	2003	1995–1997	USA	1447	40	10
Neonatology/paediatric ICU						
106	2000	1989–1998	Slovakia	80	34	20
174	2000	1981–1999	USA	96	36	11
99	2000	1993–1995	USA	35	23	18·5
101	2003	1995–1997	USA	144	22	9
Intensive care						
77	1997	1987–1994	Netherlands	40	58	20†
76	1997	1991–1992	Spain	46	56	22
8	2002	1995–1997	France	121	56	31†
75	2002	1992–2000	Belgium	73	48	43†‡

*Only studies for which both crude and attributable mortality were available have been used. †Attributable mortality determined in matched case–control studies or matched historical cohort studies. ‡5 difference (CI –8 to 19). §Crude and attributable mortality were 52 and 33 in adults as compared to 31 and 24 in children, respectively.·Crude and attributable mortality were 80 and 40, 40 and 49, 34 and 44, 25 and 25, 31 and 20 for *C krusei, C glabrata, C albicans, C tropicalis, and C parapsilosis*, respectively. ¶Multicentre prospective randomised trial of fluconazole *vs* amphotericin B for treatment of candidaemia in non-neutropenic patients. All numbers are percentages.

ultimately developed infection reached this threshold value before infection, compared with eight of 18 patients who remained colonised ($p<0·001$). In addition, the threshold value was reached at an average of 6 days before documented candidiasis.

The predictive value of this index has never been tested in a large prospective clinical trial. It was used by Dubau et al in 89 of 669 consecutively admitted patients who stayed for more than 7 days in a surgical ICU, or in whom the protein C level was greater than 100 mg/mL.[171] Of the 35 patients empirically treated with antifungals after the threshold of 0·5 was reached, only one developed candidiasis and the degree of colonisation rapidly decreased in the remaining 34. These preliminary results suggest that this strategy could potentially improve the prognosis of subsets of patients at risk and avoid the unnecessary exposure of a large proportion of critically ill patients to antifungals.

In a survey on candiduria in 15 French ICUs, Chabasse[172] reported a correlation between quantitative urinary cultures above 10^4 CFU/mL and a colonisation index of 0·5 or more. According to these data, the value of a simplified diagnostic strategy based on the periodic quantification of a possible candiduria could be tested prospectively.

We prospectively established the colonisation index of all patients included in a double-blind, placebo-controlled study on antifungal prophylaxis in critically ill patients mechanically ventilated for at least 5 days (figure 5).[145] Colonisation increased over time in the placebo group but decreased in the fluconazole recipients, reaching a statistically significant difference after 7 days.

Impact of candidiasis

Candidaemia is the only severe candidiasis for which the precise impact has been repeatedly established. Globally, the

Table 10. Candidaemia: independent risk factors for mortality*

Risk factor	Study design	OR	95% CI	Comments
Duration of blood culture positivity				
Goodrich et al[143]	R	1·10	NA	For each additional day
Fraser et al[6]	R	3·87	1·21 to 12·37	Sustained candidaemia
Hung et al[73]	P	NA	NA	
Luzzati et al[66]	R	1·08	1·03 to 1·12	For each additional day
Neutropenia†				
Goodrich et al[143]	R	3·60	NA	Acute leukaemia
	R	2·00	NA	Conditioning therapy
Anaissie et al[91]	R	11·00	4·60 to 24·00	
Nucci et al[102]	P	33·10	2·20 to 498·00	
Viudes et al[70]	R	8·00	2·05 to 31·15	
Pappas et al[101]	P	NA	NA	Age <13 years
Steroid therapy				
Nguyen et al[112]	P	NA	NA	
Macphail et al[67]	R	2·40	1·20 to 5·00	
Viudes et al[70]	R	4·22	1·35 to 13·15	
Pappas et al[101]	P	NA	NA	Age ⩾13 years
Lack of antifungal therapy				
Anaissie et al[91]	R	4·76	2·00 to 11·11	
Luzzati et al[66]	R	1·85	1·27 to 2·70	
Macphail et al[67]	R	4·00	1·70 to 9·20	
Viudes et al[70]	R	15·32	3·99 to 58·72	
Hung et al[73]	P	NA	NA	
Blot et al[75]	R	2·10	1·10 to 4·40	During the first 48 h
Pappas et al[101]	P	NA	NA	Other than *C parapsillosis* (age ⩾13 years)
Central venous catheter (CVC) not changed				
Nguyen et al[112]	P	NA	NA	
Hung et al[73]	P	NA	NA	Catheter retained
Nucci et al[177]	P	4·81	2·00 to 11·60	For neutropenic patients
Anaissie et al[91]	R	2·20	1·60 to 3·20	
Viudes et al[70]	R	3·54	1·16 to 10·77	
Luzzati et al[66]	R	1·61	1·01 to 2·63	CVC not removed
Arterial catheter in place				
Pappas et al[101]	P	NA	NA	Age >13 years
Urinary catheter				
Pappas et al[101]	P	NA	NA	Age >13 years
Age				
Nguyen et al[112]	P	NA	NA	>60 years
Petri et al[78]	P	1·36	1·17 to 1·58	
Nucci et al[102]	P	1·06	1·01 to 1·11	For each additional year
Luzzati et al[66]	R	1·44	1·00 to 2·07	>59 years
Garbino et al[69]	R	1·04	1·02 to 1·06	>65 years
Blot et al[75]	C	1·13	1·04 to 1·23	For each 10 additional years
Sex				
Goodrich et al[143]	R	1·80	NA	Female versus male
Pappas et al[101]	P	NA	NA	Male versus female (age ⩾13 years)
Acute renal failure				
Voss et al[77]	R	1·80	1·20 to 2·70	Haemodialysis
Blot et al[75]	C	1·40	1·10 to 2·00	

(continues on next page)

Table 10. Candidaemia: independent risk factors for mortality* (continued)

Risk factor	Study design	OR	95% CI	Comments
Severity of illness				
Fraser et al[6]	R	5·09	2·43 to 10·64	APACHE II, per 10-point increase
Nguyen et al[112]	P	NA	NA	Critically ill
		NA	NA	Lung involvement
Fraser et al[6]	R	7·12	2·22 to 22·77	Rapidly fatal disease
Hung et al[73]	P	NA	NA	Higher severity scores
Petri et al[78]	P	1·81	1·58 to 2·09	MOF at day 11
		4·87	1·50 to 15·80	Cirrhosis
		2·65	1·21 to 5·78	Cardiac failure
Voss et al[77]	P	10·10	2·70 to 38·60	MOF
Voss et al[77]	R	3·20	1·00 to 10·50	Abdominal surgery
		10·80	2·90 to 40·90	ARDS (ICU)
Anaissie et al[91]	R	1·05	1·03 to 1·07	APACHE III, per point increase
		6·00	3·30 to 11·00	Visceral dissemination
Nucci et al[102]	P	46·60	6·33 to 861·00	Karnowsky score
Blot et al[75]	C	1·10	1·00 to 1·20	APACHE III, per 5-point increase
Luzzati et al[66]	R	1·95	1·31 to 2·90	ICU stay
Macphail et al[67]	R	25·00	6·70 to 94·10	ICU stay
		5·90	1·70 to 21·30	Medical service
		7·20	2·60 to 20·10	Cancer
Garbino et al[69]	R	5·01	2·60 to 9·68	ICU stay
		2·64	1·12 to 5·78	Metastatic cancer
Alonso-Valle et al[71]	R	13·80	4·40 to 43·10	Sepsis syndrome
Pappas et al[101]	P	NA	NA	Intubation (age<13 years)
		NA	NA	Cancer (age ⩾13 years)
		NA	NA	APACHE II >18 (age ⩾13 years)

*Parameters associated with mortality in series where multivariate analysis has been conducted are listed. Odds ratios (and 95% CI) for death are indicated for each parameter significantly associated with mortality by multivariate analysis. †Study design: R=retrospective cohort study; P=prospective cohort study; C=matched case-control or matched historical cohort study; †Neutropenia=neutrophil counts <1000/μL^3; MOF=multiple organ failure; ARDS=acute respiratory distress syndrome; ICU=intensive care unit; CVC=central venous catheter; NA=not available in the original references.

crude mortality rate is over 50% in most series with no decrease over several decades (table 9). There are large variations in the crude mortality rate, mainly reflecting the severity of the underlying diseases.

In the early 1980s, Miller and Wenzel[175] suggested that the development of candidaemia predicted death. In a study of 1745 episodes of nosocomial bloodstream infections, candidaemia was associated with the highest mortality rate and independently predicted death (OR 1·84; 95% CI 1·22–2·76) after control for confounding factors.[176] The attributable mortality of candidaemia, defined as the proportion of deaths directly related to the infection, can be determined by simple comparison of the mortality rates between candidemic and non-candidemic in a cohort of consecutive patients. This approach might, however, overestimate the associated mortality. Case-control studies in which adjustments are made for confounding factors are considered more appropriate.[5,8,75,77,176] Wey et al established that the mortality of candidemic patients was 59% versus 19% in a group of comparable patients without candidaemia and carefully matched for confounding factors, for an attributable mortality of 38% (95% CI 26–49).[129]

Mortality rates have been reported to vary according to the type of *Candida* spp. The outcome of infections due to *C krusei* or *C glabata* has been reported to be worse than that of candidaemia caused by strains susceptible to triazole compounds.[60,70,89] This was not, however, confirmed in other series,[101] and including neonates.[79] By contrast, candidaemia due to *Candida parapsilosis* was associated with lower mortality.[101]

A large number of studies have attempted to assess risk factors that could predict a fatal outcome; a summary of the main results are presented in table 10. As shown, increased age and severity of underlying illness were associated with a

Search strategy and selection criteria

Data for this review were identified by searches of Medline, Current Contents, and references from relevant original articles published in English, French, and German between 1975 and 2003; many articles were identified through searches of the extensive files of the authors. Key word terms included "candidemia", "candidiasis", "invasive *Candida* infections", "mycosis", "fungal infections" and were combined with the "critically ill", "epidemiology", "risk factors", "guidelines", and "strategy".

worse outcome in several studies. Among parameters amenable to control, the absence of antifungal treatment[66,67,70,75,73,91] and catheter removal[66,70,73,91,112,177] were independent predictors of death from candidaemia.[6,66,73,75,143] Similarly, an increased duration of blood culture positivity predicted mortality.

In critically ill patients, Leleu et al[8] reported that the length of stay of those who survived candidaemia was prolonged from 8 to 30 days ($p<0{\cdot}0001$) with a significant increase of nursing workload. In a matched case-control study of 73 candidaemic critically ill patients, the attributable length of ICU and hospital stay was 11 days and 13 days, respectively.[75] Candidaemic patients needed a prolongation of mechanical ventilatory support of 10 days (from 19±19 to 29± 26 days, $p<0{\cdot}01$). In the study by Wey et al,[129] the length of hospital stay of the survivors was prolonged by 30 days.

Thus, candidaemia is associated with high morbidity, high mortality, and the significant use of additional resources. Preventing candidiasis would certainly improve patient safety and result in significant outcome improvement in the critically ill.

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Conflicts of interest

None declared.

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