Current Trends in Microbiology
Vol. 7, 2011

Review

Geographic distribution of *Candida* species and its correlation with blood type and biofilm formation

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ABSTRACT

Candida species are responsible for most fungal infections in intensive care units and of severe cases of nosocomial bloodstream infections in the world. Candidemia is one of the leading causes of mortality in immunocompromised hosts, diabetics, neonates and surgical patients. *Candida albicans* is regarded as the principal fungi causing infections in humans. Nevertheless, other *Candida* species such as *Candida parapsilosis*, *Candida tropicalis* and *Candida glabrata*, are increasingly being recognized as important agents of human infection. Relatively little is known about the factors that influence the variability in the frequency of the colonization by *Candida* in a particular population. Previous studies have shown the importance of elucidating the mechanisms of adhesion among the emerging species of non-*albicans Candida* which present demographic characteristics peculiar to the different geographic regions where they have been isolated. The goal of this review is to determine whether there is a correlation between the species of *Candida* and its ability to preferentially colonize one population over another. The results of this study suggest the correlation between the incidence of *Candida* species infection, their ability to form biofilms and the blood types prevalent in different countries.

KEYWORDS: *Candida* species, blood type, candidemia, biofilms

INTRODUCTION

In the last two decades, fungal infections due to *Candida* have become very important because they are the main cause of morbidity and mortality in hospitals [1]. *Candida albicans* is the yeast most frequently isolated from patients with candidemia and systemic candidiasis [2-4]. However, with the use of immunosuppressant therapies, broad-spectrum antibiotics, and antifungals [5-11], as well as the use of various diagnostic methods and invasive therapies, Non-*Candida albicans Candida* (NCAC) strains like *Candida glabrata*, *Candida parapsilosis* and *Candida tropicalis* have emerged as the second or third most common species causing candidemia in immunocompromised, surgical, diabetic, neonatal, and geriatric patients [5, 12-19].

Candidemia has a high mortality rate, estimated between 30.0-60.0% [5, 20-29]. In the last decade, it has been reported that the species of *Candida* isolated from blood cultures varies according to the geographic region [1, 7, 22, 24, 25, 27, 28, 30-36].

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C. albicans is the yeast most frequently isolated, ranging from 37.0% in Latin-America to 70.0% in Norway [5]. *C. glabrata* is the second most frequent species of *Candida* with 15.0-25.0% in the United States (USA), Canada, and some European countries [4, 18, 33, 34, 37-42]. In contrast, in some Latin American countries such as Mexico, Chile, Argentina, and Brazil, *C. glabrata* has a lower prevalence (3.0-11.0%) in blood [5, 42, 43], while *C. tropicalis* is the second most common species, causing 24.0% of all candidemias [5]. In comparison, the prevalence of *C. tropicalis* in USA and Europe is only 10.0%. *C. parapsilosis*, which has been reported as the second most frequent species in Europe (23.0%) and the USA (13.0%), ranks third in Latin America in terms of candidemias [5, 33, 34, 40, 44]. The incidence of *C. parapsilosis* has increased dramatically and it is now regarded as the second most common species isolated from blood cultures [14, 20, 45]. Fortunately, it causes a lower mortality than *C. albicans* or *C. glabrata* [46].

There are several factors that influence the variability in the frequency of the colonization by *Candida* in a particular population: a) indiscriminant use of broad-spectrum antibiotics and antifungals, b) advanced patient age, c) severity of the patient's primary disease, d) length of stay in the hospital, e) use of medical implants, f) surface proteins in the host and g) the infecting *Candida* species. In the last two decades, the high morbidity and mortality of immunocompromised and hospitalized patients associated with candidemia in nearly all regions of the world, as well as the emergence of *Candida* species other than *C. albicans* in individual hospitals, epidemiological monitoring studies, multicenter studies with patients at different stages in the progression of their disease (ICU, hospitalized, out-patient) [15, 21, 47-49] and, in studies over an extended period of time [50] have all highlighted the importance of elucidating the mechanisms of adhesion among the emerging species of non-*albicans Candida* which present demographic characteristics peculiar to the different geographic regions where they have been isolated. The goal is to determine whether there is a correlation between the species of *Candida* and its ability to preferentially colonize one population over another. This study analyses the incidence of *Candida* infection as a function of the blood types prevalent in different countries and their ability to form biofilms.

Correlation between blood type and candidemia

Candidemia is a form of systemic candidiasis which results in mortality in 30.0-60.0% of immunosuppressed hospitalized patients. In more than half of the cases of this mycosis, death occurs in the first week after the isolation of *Candida* from the patient's blood. Because of the high mortality associated with this infection and the late recognition of serious complications, it is most relevant to elucidate the mechanisms by which *Candida* species are able to colonize preferentially one or another patient in a particular population.

In the last decade it has been reported that *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* are the yeasts most frequently isolated from blood samples, surpassing *C. albicans* in some geographic areas [33, 51-55]. The variability in the incidence of *Candida* species in different geographic regions is due, on one hand, to the risk factors mentioned previously and, on the other hand, to the genotypic and phenotypic characteristics of the human hosts which may confer differential susceptibility or resistance against infectious agents. It has been reported that the incidence of candidemia varies with race and age group. People of African descent [56, 57], children less than a year old, and patients older than 65 all have a higher prevalence of the disease [56-59]. The development of candidemia from one or another species of *Candida* could be related to the host’s blood type, as in some other diseases, where the blood type is a risk factor that determines the development and progression of the disease. It has been observed that subjects with blood groups A, B, and AB are more susceptible to developing thromboembolism than those with type O [60, 61], while individuals with blood group O present more susceptibility to gastrointestinal infections caused by *Escherichia coli* O157 [62] and *Vibrio cholerae* [63, 64].

Adhesion of *Candida* to host cells is the first step in colonization and subsequent infection. This process is mediated by lectin glycoproteins which bind to various receptors on human cells, including carbohydrates, proteins, and lipids [65-67].

The proteins and the antigens on the red blood cell membrane, particularly those determined by blood group, are the molecules which enable *Candida* to adhere to these cells, spread and disseminate. These determinants are large glycoproteins which contain oligosaccharides with either five (H antigen) or six (antigen A and antigen B) sugar residues (Figure 1). In blood infections by *C. albicans*, most strains express lectin adhesion that recognizes the residues of α-fucosyl (H antigen, blood group O) in the red blood cells [68]. However, there are strains of *C. albicans* that show a preference for receptors that contain *N*-acetyl-D-glucosamine [69]. This ability of the *C. albicans* strains to recognize one or another receptor in the host is due to the antigen that each ABO group expresses. The determining receptor in persons with type A is *N*-acetyl-D-glucosamine. This antigenic determinant is not recognized by the lectin I of Europeans, which is highly specific to the H antigen of blood groups. The H and A antigens are present in the glycolipids of the buccal cells of type A individuals, but A antigen has a large number of surface cells, which does not occur with the H antigen group, a phenomenon seemingly related to cell differentiation [70]. Other receptors for adhesins of *Candida* in host epithelial cells are the Lewis blood group antigens, which also possess α-fucosyl residues. It has been reported that Lewis antigens are found in the fluids of non-secreting subjects, but when they are absorbed on the surface of epithelial cells they can function as receptors for *C. albicans* [69, 71, 72]. These results are contradictory to those described by Brassart *et al.* [73], who observed that the ability of *C. albicans* to adhere to Lewis antigens is strain-dependent [72]. While these findings are somewhat contradictory, both confirm that there is a specific receptor that recognizes the *Candida* species and indicate that blood group antigens can act as receptors for these yeasts.

Table 1 presents the incidence of candidemia over the years in various regions of the world and its relation to the predominant ABO blood group. In Europe, Asia, and America the predominant species is *C. albicans* with an incidence of 40.6-52.6%. NCAC species are nearly 50% of the total, with *C. parapsilosis* and *C. tropicalis* being the most prevalent (Figure 2). Many studies have been published which report that the blood group of a population is a function of its local geography. The observed distribution for the four blood types O, A, B, and AB, according to the bibliography, shows a predominance of blood type O over the other three. The prevalence of group O ranges from 50.4 to 73.1% in the

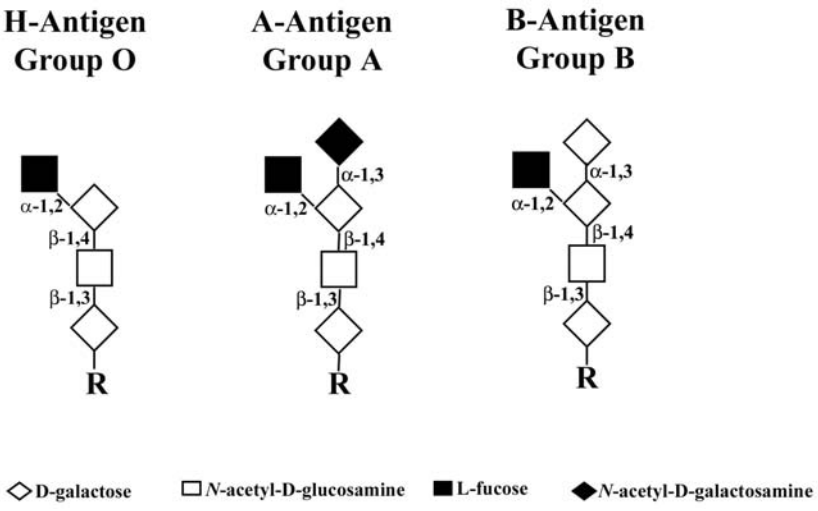

Figure 1. Structure of ABO blood group antigens. H antigen formed by the oligosaccharide precursor chains in which the terminal D-galactose is linked to *N*-acetyl-D-galactosamine residue. A antigen contains an additional *N*-acetyl-D-galactosamine group and the B antigen contains a D-galactose residue.

Table 1. Correlation between incidence of *Candida* species and blood type frequency in different regions of the world.

Region/ Country[a]	[Ref.]	Year of observation	Total number of blood isolates[b]	Incidence (%)				Blood type frequency (%) Group[c]			
				C. albicans	*C. glabrata*	*C. parapsilosis*	*C. tropicalis*	O	A	B	AB
Europe											
Belgium	[139]	2001-2005	420	59.8	22.6	9.8	4.5	45.2	39.7	10.9	4.1
	[32]	2002	211	55.0	22.0	13.0	2.8	60.0 - 70.0	25.0 - 30.0	5.0 - 10.0	-
	[140]	NR	200	56.0	19.0	10.5	9.0				
	[141]	15 month	412	47.3	25.7	8.0	6.8				
Denmark	[145]	2004-2009	2820	53.2	25.9	NR	NR	45.2	39.7	10.9	4.1
	[146]	2004-2006	1089	59.8	20.5	4.0	4.6	60.0 - 70.0	25.0 - 30.0	5.0 - 10.0	-
	[147]	2003-2004	303	63.0	20.0	4.0	4.0				
Finland	[148]	1999-2000	62	62.9	6.5	12.9	2.3	45.2	39.7	10.9	4.1
	[149]	2004-2007	603	67.0	19.0	5.0	3.0	50.0 - 60.0	25.0 - 35.0	10.0 - 15.0	-
	[150]	1987-2004	364	65.0	9.0	13.0	-				
	[151]	1995-1999	479	70.0	9.0	5.0	3.0				
France	[154]	2001-2002	57	54.2	17.0	13.5	8.5	45.2	39.7	10.9	4.1
	[31]	1998-2001	190	49.5	12.6	12.1	10.1	60.0 - 70.0	25.0 - 30.0		
	[155]	2004	193	54.9	18.7	12.7	4.7				
	[47]	2005-2006	107	57.0	16.7	7.5	4.9				
	[156]	2004 (October)	46	50.0	28.3	6.5	10.9				
	[157]	2004	29	55.0	14.0	7.0	3.5				
	[158]	1993-2003	430	61.5	16-27	14.7	9-24				
Germany	[169]	2004-2005	561	58.5	19.1	8.0	7.5	45.2	39.7	10.9	4.1
								60.0 - 70.0	25.0 - 30.0	5.0 - 10.0	-
Greece	[160]	2001-2006	140	46.0	25.0	26.0	40.0	45.2	39.7	10.9	4.1
	[161]	1994-2000	59	65.5	2.0	15.5	7.0	50.0 - 60.0	20.0 - 25.0	10.0 - 15.0	-

Table 1 continued..

	[162]	2000-2002	24	64.3	14.3	5.4	10.7							
	[163]	2001-2008	45	67.4	4.3	4.3	10.9							
Hungary	[53]	1996-2000	145	73.5	3.0	7.3	4.4	45.2		39.7		10.9		4.1
								50.0 - 60.0		30.0 - 35.0		15.0 - 20.0		-
Iceland	[51]	1980-1999	177	64.4	12.4	9.6	5.6	45.2		39.7		10.9		4.1
	[143]	1991-2006	219	61.6	13.7	8.7	9.1	70.0 - 80.0		20.0 - 25.0		5.0 - 10.0		-
***Ireland**	[133]	1984-2000	75	53.0	27.0	11.0	6.4	58.4		26.9		12.4		2.2
	[30]	1992-2003	63	50.0	18.2	21.2	6.1							
	[134]	2001-2006	151	63.5	17.2	12.0	3.3	70.0 - 80.0		15.0 - 20.0		5.0 - 10.0		-
Italy	[164]	1992-2001	370	48.1	6.6	17.9	4.7	45.2		39.7		10.9		4.1
	[15]	1999-2003	182	40.0	15.0	23.0	9.0	60.0 - 70.0		20.0 - 25.0		5.0 - 10.0		-
	[165]	1998-2004	155	45.8	4.5	35.5	4.5							
								60.0 - 70.0		30.0 - 40.0		0.0 - 10.0		-
	[2]	200-2003	94	40.4	12.8	22.3	15.9							
Netherlands	[142]	1996-2001	357	57.1	19.6	9.0	7.3	45.2		39.7		10.9		4.1
								50.0 - 60.0		25.0 - 30.0		5.0 - 10.0		-
Norway	[144]	1991-2003	1393	70.7	13.4	6.0	6.8	45.2		39.7		10.9		4.1
								60.0 - 70.0		30.0 - 35.0		5.0 - 10.0		-
Portugal	[229]	2004	97	42.3	9.3	30.9	15.5	45.2		39.7		10.9		4.1
	[159]	6 years	119	48.7	5.0	20.2	8.4	60.0 - 70.0		35.0 - 40.0		5.0 - 10.0		-
	[45]	2004	95	43.0	9.0	32.0	16.0							
Slovakia	[152]	NR	42	41.0	NR	48.0	7.0	45.2		39.7		10.9		4.1
	[153]	1990-2001	201	69.9	4.0	29.0	9.0	50.0 - 60.0		30.0 - 35.0		10.0 - 15.0		-

Table 1 continued..

	[36]	1989-1998	310	61.6	3.2	9.7	4.5				
Spain	[166]	2002-2003	24	29.0	4.0	67.0	NR	45.2	39.7	10.9	4.1
	[21]	2002-2003	345	51.0	8.0	23.0	10.0	60.0 - 70.0	25.0 - 30.0	5.0 - 10.0	-
	[22]	2009-2010	1357	44.7	11.5	29.1	8.2				
	[167]	2002-2003	339	52.0	8.6	23.0	10.0				
	[168]	2005-2006	197	49.2	13.7	17.3	15.2				
Sweden	[24]	1998-1999	191	67.0	15.7	7.3	2.0	45.2	39.7	10.9	4.1
								60.0 - 70.0	30.0 - 40.0	0.0 - 10.0	-
***Switzerland**	[8]	1991-2000	1137	66.0	15.0	1.0	9.0	64.2	29.8	5.9	-
	[28]	1989-2000	294	66.0	17.0	6.0	4.0	60.0 - 70.0	25.0 - 30.0	5.0 - 10.0	-
***United Kingdom**	[135]	2008	96	51.5	24.7	10.3	3.0	46.7 - 48.8	42.6 - 43.6	6.7 - 7.3	2.9 - 3.0
	[136]	1995-2001	128	64.3	20.0	5.4	8.5				
	[137]	2001-2004	92	46.3	24.2	10.5	5.3	60.0 - 80.0	15.0 - 30.0	5.0 - 10.0	-
	[138]	2005-2006	300	52.0	22.7	11.7	2.0				
America											
Argentina	[193]	1999-2002	46	34.8	10.9	28.3	15.0	56.5	31.1	9.9	2.5
								90.0 - 100	0.0 - 5.0	0.0 - 5.0	-
Brazil	[185]	2006	NR	52.2	6.6	22.1	14.8	56.5	31.1	9.9	2.5
	[186]	2001-2004	100	59.0	7.0	9.0	15.0	90.0 - 100	0.0 - 5.0	0.0 - 5.0	-
	[187]	2003-2004	712	40.9	4.9	20.5	20.9				
	[188]	2002-2003	120	51.6	3.3	25.8	13.3				
	[189]	1998-2004	131	45.0	6.9	24.4	15.3				
	[190]	1997-2005	25	56.0	4.0	4.0	16.0				
	[191]	2000-2002	50	28.0	4.0	36.0	16.0				
	[14]	2002-2003	282	38.0	3.0	23.0	17.0				

Table 1 continued..

	[192]	1998-2006	96	45.8	5.2	34.4	14.6									
Canada	[175]	1992-2001	623	58.9	20.1	10.3	5.9	45.2 - 54.6		35.0 - 39.7		7.9 - 10.9		2.5 - 4.1		
	[33]	NR	71	49.0	18.0	11.0	14.0	60.0 - 90.0		15.0 - 40.0		0.0 - 5.0		- -		
	[176]	1992-1996	208	65.0	11.0	11.0	11.0	45.2 - 54.6		35.0 - 39.7		7.9 - 10.9		2.5 - 4.1		
	[40]	1997-1999	161	60.0	12.0	16.0	6.0	60.0 - 90.0		15.0 - 40.0		0.0 - 5.0		- -		
	[177]	1996-1998	442	54.3	15.2	12.2	9.3									
	[41]	1997	61	52.5	11.5	22.9	8.2									
				70.1	12.3	7.0	5.2									
		1998	57													
	[178]	1992-1994	415	68.9	8.2	10.4	6.5									
Chile	[194]	NR	37	52.0	9.0	14.0	5.0	56.5		31.1		9.9		2.5		
								90.0 - 100		0.0 - 5.0		0.0 - 5.0		- -		
Colombia	[228]	2001-2007	337	43.6	9.5	13.9	23.4	56.5		31.1		9.9		2.5		
								90.0 - 100		0.0 - 5.0		0.0 - 5.0		- -		
Cuba	[183]	NR	25	54.1	8.1	NR	8.1	56.5		31.1		9.9		2.5		
								90.0 - 100		0.0 - 5.0		0.0 - 5.0		- -		
Jamaica	[184]	1998, 2002	NR	29.0	12.5	NR	75.0	56.5		31.1		9.9		2.5		
								90.0 - 100		0.0 - 5.0		0.0 - 5.0		- -		
Mexico	[179]	NR	9	77.8	11.1	NR	11.1	56.5		31.1		9.9		2.5		
	[180]	NR	NR	72.3	13.4	8.0	NR	90.0 - 100		0.0- 5.0		0.0 - 5.0		-		
	[181]	1990-1991	180	60.0	6.8	0.86	15.5									
Paraguay	[195]	1999-2001	1006	30.2	2.3	34.9	25.6	56.5		31.1		9.9		2.5		

Table 1 continued..

							90.0 - 100	0.0 - 5.0	0.0 - 5.0	-
Puerto Rico	[182]	2005-2006	85	28.0	4.0	49.0	17.0	56.5	31.1	9.9	2.5
							90.0 - 100	0.0 - 5.0	0.0 - 5.0	-
United States	[170]	1995-1998	934	53.2	19.8	9.9	12.2	45.2 - 54.6	35.0 - 39.7	7.9 - 10.9	2.5 - 4.1
	[56]	1998-2002	1143	45.0	24.0	13.0	12.0	70.0 - 100	5.0 - 25.0	0.0 - 5.0	-
	[171]	1995-2002	1890	53.8	18.8	11.4	11.1				
	[52]	1998-2001	254	58.0	20.0	7.0	11.0				
	[172]	1994-1997	98	50.0	7.0	24.0	16.0				
	[173]	1997-2001	65	48.0	2.0	25.0	11.0				
	[174]	2001-2004	157	53.5	12.7	15.9	12.7				
	[75]	1995-2004	NR	57.9	2.0	33.7	3.8				
Venezuela	[196]	2003-2005	154	18.83	7.79	25.97	38.96	56.5	31.1	9.9	2.5
							90.0 - 100	0.0 - 5.0	0.0 - 5.0	-
Asia-Pacific											
Australia	[219]	2001-2004	179	62.0	17.9	7.8	5.6	39.8	27.8	25.4	7.1
	[220]	2001-2004	1095	47.3	15.4	19.9	5.1	50.0 - 60.0	15.0 - 20.0	10.0 - 15.0	-
	[140]	NR	200	56.0	19.0	10.5	9.0				
India	[208]	2000-2001	21	33.0	9.5	9.5	33.0	39.8	27.8	25.4	7.1
	[209]	2003-2004	30	17.0	NR	23.0	60.0	50.0 - 60.0	15.0 - 20.0	20.0 - 30.0	-
	[210]	2001-2005	275	21.5	17.5	20.0	35.3				
Israel	[206]	2003-2004	142	44.3	9.8	20.4	24.6	39.8	27.8	25.4	7.1
	[207]	1995-2000	272	55.0	10.0	16.0	16.0	50.0 - 60.0	25.0 - 30.0	10.0 - 15.0	-
Japan	[221]	1993-2002	125	30.1	NR	39.2	NR	39.8	27.8	25.4	7.1

Table 1 continued..

	[222]	2001-2002	535	40.7	17.9	23.0	11.6	50.0 - 60.0	15.0 - 20.0	10.0 - 15.0	-	-
	[223]	1979-1995	642	34.9	10.1	23.2	13.6					
Korea	[217]	2004-2005	143	49.0	11.0	22.0	14.0	39.8	27.8	25.4	7.1	
	[218]	2006-2007	639	38.0	11.0	26.0	20.0	50.0 - 60.0	20.0 - 25.0	20.0 - 25.0	-	-
Saudi Arabia	[203]	1995-2000	32	19.0	3.0	44.0	25.0	39.8	27.8	25.4	7.1	
	[204]	1998-2002	83	46.0	4.8	10.8	10.8	70.0 - 80.0	15.0 - 25.0	5.0 - 15.0	-	-
Singapore	[214]	3 years	NR	36.0	16.0	16.0	27.0	39.8	27.8	25.4	7.1	
	[215]	2004-2006	279	37.0	16.0	14.0	27.0	60.0 - 70.0	15.0 - 20.0	10.0 - 15.0	-	-
	[216]	2001	72	33.3	15.3	19.4	22.2					
Taiwan	[211]	1996-1999	383	55.6	5.2	17.5	16.5	39.8	27.8	25.4	7.1	
	[212]	2002	230	48.3	13.0	13.9	21.7	60.0 - 70.0	15.0 - 20.0	20.0 - 25.0	-	-
	[213]	2003-2005	179	63.7	11.7	10.6	12.2					
Turkey	[197]	2000-2003	104	57.7	3.8	12.5	20.2	39.8	27.8	25.4	7.1	
	[198]	1997-2005	102	39.2	6.9	21.6	15.7	50.0 - 60.0	30.0 - 35.0	10.0 - 15.0	-	-
	[15]	1999-2003	182	40.0	15.0	23.0	9.0					
	[199]	2005-2009	166	34.3	NR	28.9	8.4					
	[200]	1 year	83	45.8	4.8	14.5	24.1					

Table 1 continued..

	[201]	2004-2009	118	18.6	2.5	66.1	12.7				
	[202]	1996-2007	743	45.0	3.5	26.0	7.0				
United Arab Emirates	[205]	1995-2001	60	45.0	5.0	5.0	15.0	39.8	27.8	25.4	7.1
								70.0 - 80.0	15.0 - 25.0	5.0 - 15.0	-

Ref., reference; NR, relevant data were not available.
[a]Countries which reported the incidence of candidemia by *Candida* species.
[b]It refers to the total number of *Candida* isolates from blood or to the total number of candidemia from the original study.
[c]Refers to the blood type frequency by country or approximate numbers calculated from [227] and [230].
[*]In Ireland, United Kingdom and Switzerland, the blood type frequency were calculated from [224], [225] and [226] respectively.

different populations that were studied, followed by group A with a prevalence of 19.3 to 33.3% (Figure 3). The highest rate observed for type O was in America with 73.1%, while group A is found mainly in Europe with a prevalence of 33.3%. Group B is less common in America and Europe, with 6.3 and 9.6% respectively, while in Asia it has a frequency of 20.3% (Figure 3).

The incidence of *Candida* in Europe is mainly due to *C. albicans* at 52.6%, followed by *C. glabrata* at 13.6%, *C. parapsilosis* at 13.7%, and *C. tropicalis* at 8.5% (Figure 4A, Table 1). Interestingly, in Slovakia, Portugal, Italy, and Spain the second species causing candidemia is *C. parapsilosis* with a frequency between 24.7 and 31.9%. This is not observed in the other European countries, where

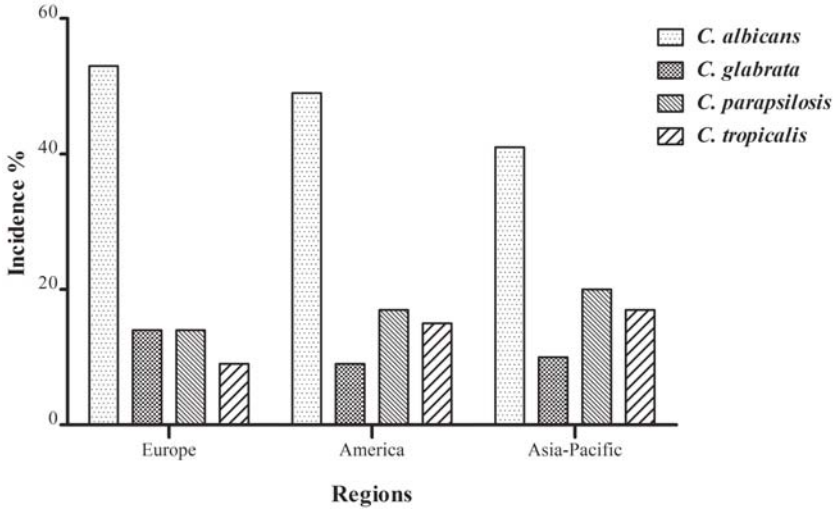

Figure 2. Species distribution of *Candida* bloodstream isolates by region.

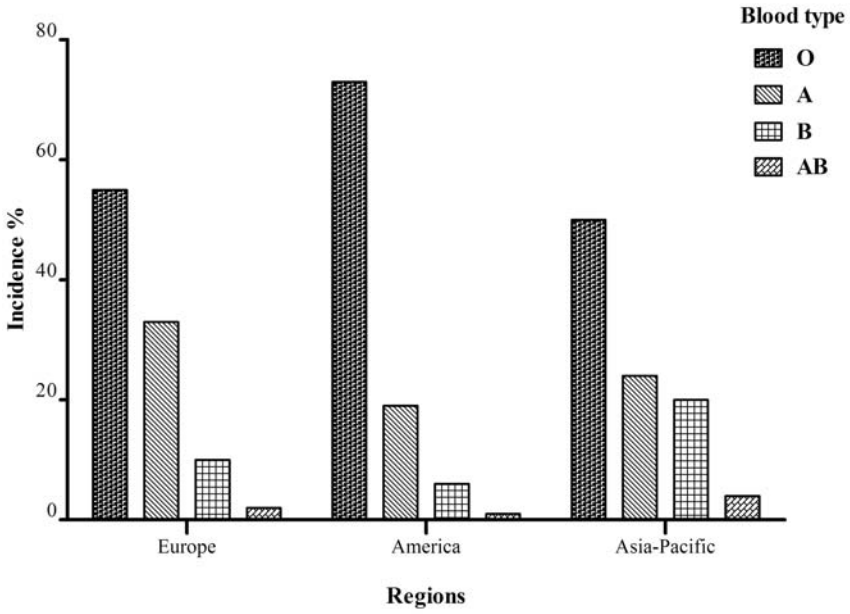

Figure 3. Regional distribution of blood type in the world.

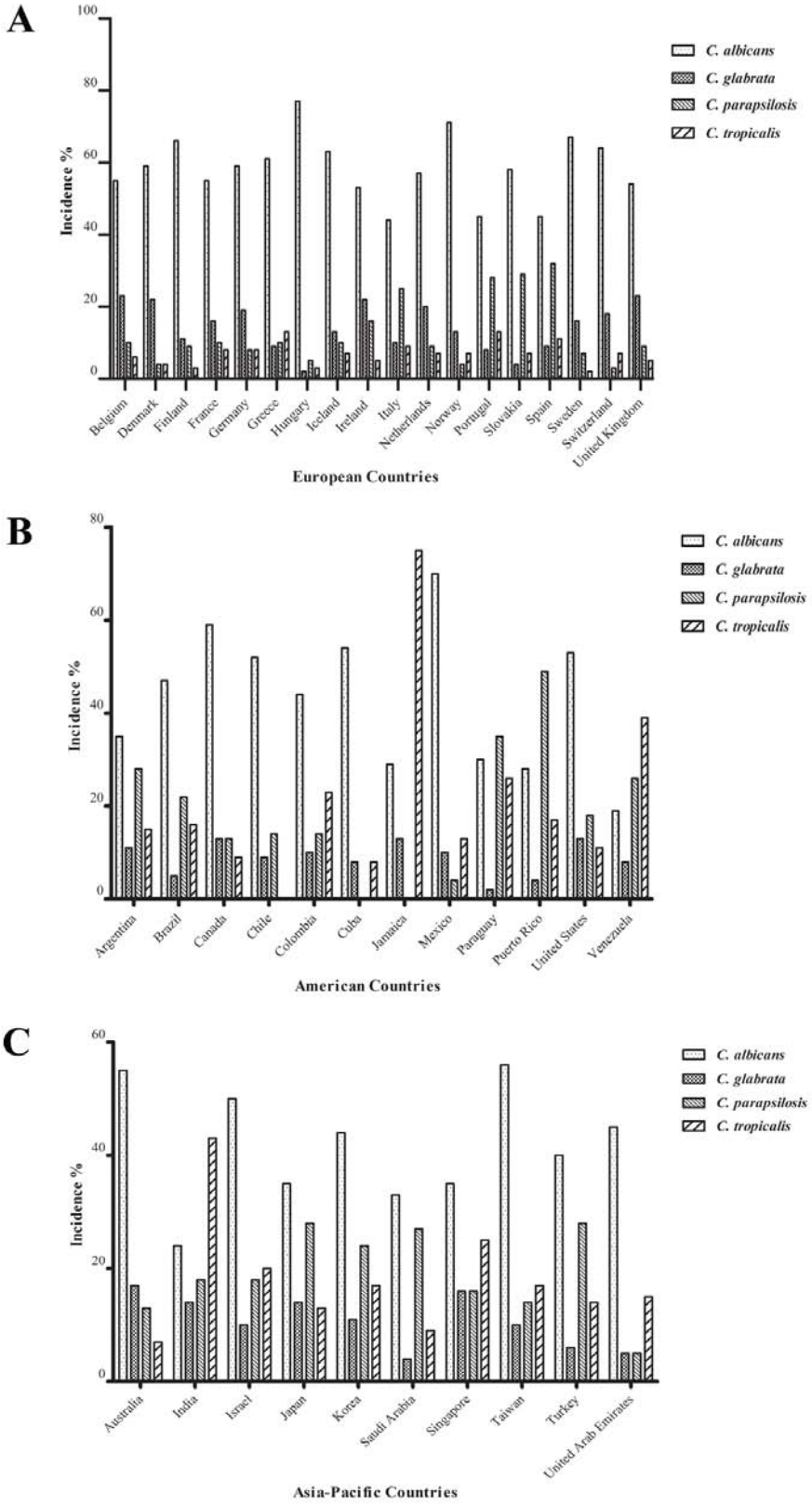

Figure 4. Incidence of *Candida* species from bloodstream isolates by country.

this fungus is third-ranked with an incidence of 4.0-10.3%. In those countries where *C. parapsilosis* is the second cause of fungemia, the prevalent ABO blood group is O, followed by type A (Table 1). This observation suggests a correlation between the ABO blood group and the prevalence of *Candida* species in these countries. However, in other European countries with a high frequency of group A, the second most dominant species of *Candida* is *C. glabrata* (Figure 5A). One possible explanation for the difference in colonization by different *Candida* species between Slovakia, Portugal, Italy, and Spain with the rest of Europe, is that even if the predominant ABO group is A in these countries, the prevalence of other antigens from different blood group classification systems (Rh, Kell, Duffy, etc.) may differ between these countries, which produces a differential in the recognition of *C. glabrata* or *C. parapsilosis*. Another possibility is that both C. *glabrata* and *C. parapsilosis* may have mutations in their genome the enable them to recognize receptors present in the host's red blood cells and cause the spread of systemic candidiasis. Mutants of *C. albicans* that lack a specific antigen factor 6, located on the yeast cell surface, are unable to adhere to the host cells [71]. In the same way, the early prophylactic use of antifungals is a prominent factor in the variations that are observed in the etiology and epidemiology of candidiasis and candidemias [35, 74].

In America, the most frequently isolated yeasts from blood after *C. albicans* (49.1%) are *C. parapsilosis* with 16.7% and *C. tropicalis* with 14.9% (Figure 2). For several decades, in USA has been reported that between 50.0-58.0% of the cases of candidiasis are caused by *C. albicans*, followed by *C. glabrata* with an incidence of 15.0-21.0% [5, 40]. The data reported from 1994-2004 in the USA (Table 1) shows that the second cause of fungemia in this country is *C. parapsilosis*, with an incidence of 17.8%, followed by *C. glabrata* (13.3%). This data are consistent with those reported previously by Pfaller *et al.* [40], who mentioned that *C. glabrata* and *C. parapsilosis* have the same incidence of 15.0%. Years later, Frindkin *et al.* [75] showed that *C. parapsilosis* emerged during the decade of 1995-2004 as the second leading cause of candidemia in the USA. In Canada, *C. glabrata* continues to be the second leading cause of infection. The appearance of this species of *Candida* as an emerging pathogen in the last decade in the USA has been mainly associated with a cross-resistance to antifungal agents, rather than the type of blood that predominates in that country. In recent years there has been a significant increase in the indiscriminate use of azole-based antifungals in USA, which has increased the development of candidemias due to *C. glabrata* that produces infections that are difficult to treat because of their innate resistance to azole compounds [76-79]. In the rest of the Americas, there have been few retrospective or prospective studies on the incidence of candidemia, although Brazil and Mexico have recently reported studies on the incidence of the prevalent *Candida* species (Table 1). Mexico is of special interest because it has a higher incidence of *C. albicans* (70.0%) than the other countries included in this study (Table 1, Figure 4B) concomitantly with a low incidence of *C. tropicalis* (13.3%), *C. glabrata* (10.4%) and *C. parapsilosis* (4.0%). This prevalence, coupled with the high frequency of group O (75.8%) in this country, suggests a possible correlation between type O and colonization by *C. albicans* (Figure 5B). In general, the H antigens (blood group O) and Lewis appear to be the prime candidates for epithelial cell receptors which contain L-fucose, which relates to a study of healthy subjects, where the individuals who were type O and non-secretors of antigens showed increased susceptibility to *C. albicans*. When comparing this result with the rest of the Americas, this correlation is not seen since in these countries the major ABO group is O. In Jamaica and Venezuela, *C. tropicalis* is the principal cause of candidemia, with an incidence of 75.0 and 38.9%, respectively. Paraguay and Puerto Rico are the only countries where *C. parapsilosis* is the leading cause of candidemia with an incidence of 34.9-49.0% (Figure 4B), while in Chile and Argentina this is the second most frequently isolated species from blood samples (14.0-28.3%). None of the countries of the Americas, with the exception of the USA, are susceptible to *C. glabrata*. Overall, these results indicate that blood type O that is dominant in America (Figure 5B), favours *Candida* species to colonize these patients. This is probably due to a

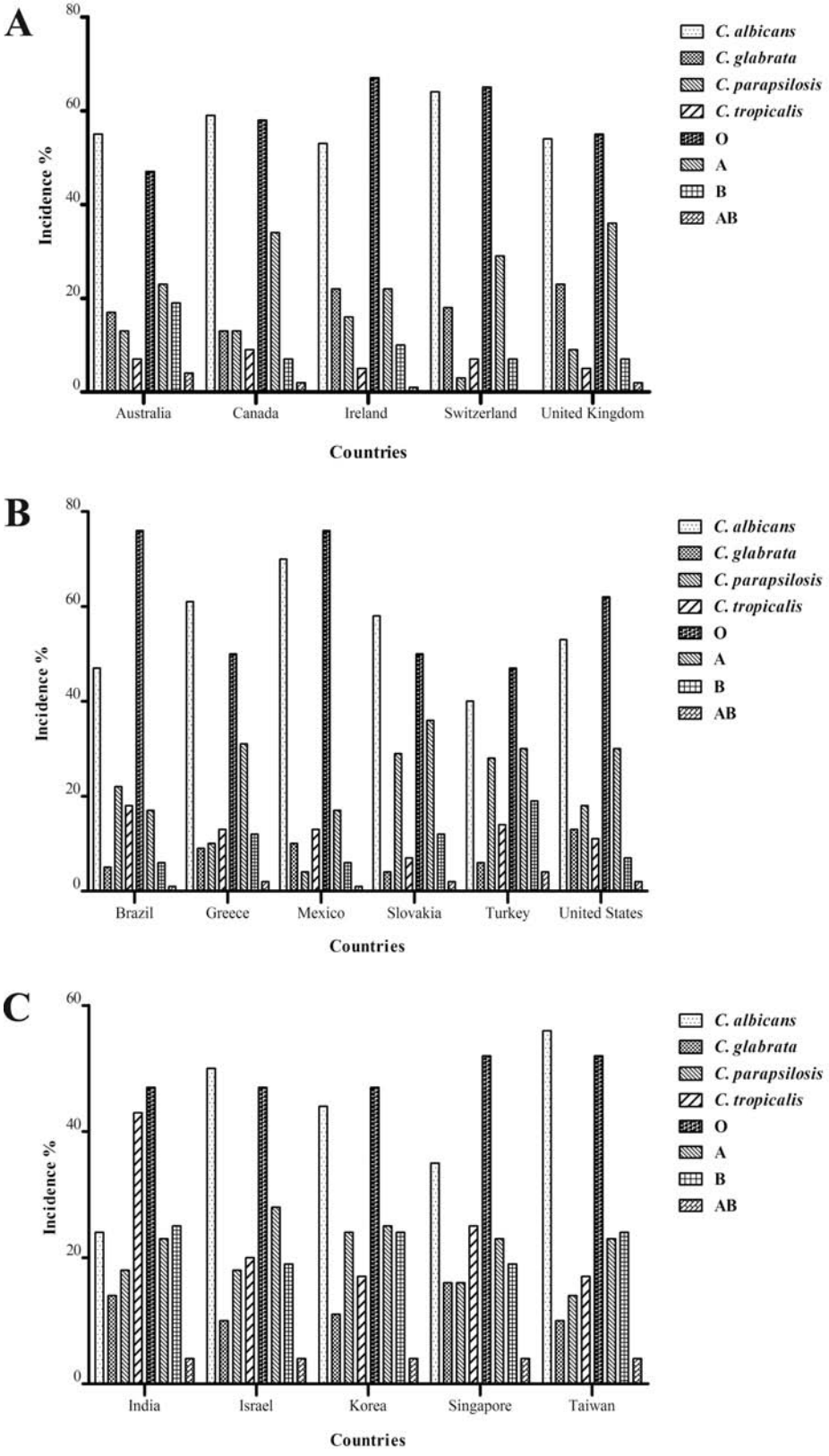

Figure 5. Correlation between distribution of *Candida* species and blood type by country.

type O phenotype that is the result of an inactivation of the gene coding for glycosyltransferase A1 and the non reduction of the ends of the corresponding glycans. As a result, the subjects of this blood group do not express transferase A/B. The biological significance of this transferase has not been fully elucidated, but it is likely that the loss of this function in persons with type O may have some adverse consequences [80], such as providing *Candida* with adequate receptors to adhere to the host blood cells. In general, the antigens of the blood group seem to be common enough to function as epithelial receptors for microorganisms, so it is likely that type O favours the adhesion of some species of *Candida*, more than any other blood type. In the future, it should be clarified whether group O promotes the adhesion of a greater number of *Candida* species than other groups in the ABO system. Asian countries, in contrast to Europe and America, have the highest prevalence of people with type B and AB (Table 1, Figure 5C). Especially in India, the ABO group that occupies the first place is B, followed by type O. This is relevant as this is the only country where it has been reported that this blood group is the most common (Table 1, Figure 5C). In India, the leading cause of candidemia is *C. tropicalis* with 42.7%, followed by *C. albicans* with 23.8% (Figure 4C). While in the United Arab Emirates, Israel, Taiwan, and Singapore, *C. tropicalis* ranks second as the cause of fungemia with a prevalence of 16.8-25.4% (Figure 4C). These countries, like India, have a high prevalence of group B (Figure 5C). These observations indicate that *C. tropicalis* can preferentially colonize the bloodstream of people with blood type B. Other countries in Asia, like Turkey, Saudi Arabia, Korea, and Japan, have a high prevalence of blood type B and the *Candida* species that has been reported as a cause of candidemia is *C. parapsilosis* (Table 1). Another characteristic of Asian countries is that *C. tropicalis* is the predominant species of candidemia. This shows that this yeast is probably eager to recognize this type of blood cells. The high frequency of group B in Asia is a consequence of natural selection to confer resistance to illness caused by pathogens. A change that is present in type B red blood cells is in the protein encoded by the complement receptor type 1 (*CR1*) gene, which is responsible for carrying the antigens of the Knops blood group. In the African population, *CR1* has three polymorphisms that result in a high molecular weight protein, high levels of expression, and increased frequency of the antigens of the Knops blood group. These changes are associated with increased resistance to severe malaria infections [81]. In contrast, Deepa *et al.* [82] showed that group O has an advantage over types A and B against *Plasmodium falciparum* and *Plasmodium vivax*. This evidence shows that the mechanism of adhesion of pathogens to host red blood cells is not fully elucidated. However, these results do not show a change in the receptors in group B red blood cells, which probably favour the development of candidemia due to *C. tropicalis* in that region of the world.

In order to evaluate whether there is a correlation between countries with similar characteristics in the incidence of *Candida* species and the ABO group, we divided these countries into three groups, as shown in Figure 5. In those countries where the predominant ABO group (after type O) is A, *C. glabrata* has the highest incidence (Figures 5A, 5B, 5C). Countries with a high frequency of group O have a high susceptibility to being colonized by *C. albicans* (Figures 5A, 5B), although it should be considered that the NCAC species, such as *C. parapsilosis* and *C. tropicalis*, are the main emerging species in America. It is likely that prospective and retrospective studies in the next decade, which should lead to a better understanding of the trends for emergent *Candida* species, as well as the development of new antifungals based on their prevalence, will contribute to an improved quality of life for patients. In those countries with the highest prevalence of blood type B, the yeast that promotes the development of candidemia is *C. tropicalis*, followed by *C. parapsilosis* (Figure 5C).

Taken together, evidences show that the increase of the species of NCAC isolated from blood during the last two decades in various regions of the world (Table 1) largely depends on the recognition of the receptors present on the host red blood cells. In the future, such studies should provide a valuable database that will help to determine each person's susceptibility to developing candidemia. However, even if ABO and Rh systems have an important role in host colonization by these

yeasts, there are other factors that influence the development of candidemia by one or another species of *Candida*. With respect to the distribution of species, increased frequency of *C. parapsilosis* is related to infections originating in venous catheters and prosthetic materials used in patients with severe conditions requiring prolonged use of these devices. Furthermore, this yeast is able to aggressively colonize pediatric patients [46, 83-85]. *C. tropicalis* is commonly found in patients with diabetes [56, 57], cancer and those who require prolonged catheterization [14, 86-88]. This species is associated with high mortality as compared with *C. albicans* and the other NCAC species [14, 89-91]. The changes observed in the distribution of species causing candidemia are caused by various factors, namely, the use of implants made from inert material promotes the incidence of *C. parapsilosis* and *C. tropicalis*; and the systematic use of antifungals based on azoles in patients with blood diseases or transplant recipients has been linked to the increase of the incidence of *C. glabrata* [52, 92]. The high incidence of NCAC species causing candidemia, in addition to the host blood group, is related to the virulence that each species presents. One of the recently described virulence factors is the formation of biofilms in inert materials as a cause of recurrent candidemias [93].

A virulence factor that promotes the development of candidemia: Biofilms

One of the risk factors in immunocompromised and hospitalized patients for developing candidemia is the formation of biofilms on internal organs and medical devices such as prosthetic devices (heart valves, knees, and larynx), implants (lens and breast), endotracheal tubes and pacemakers [94, 95]. Biofilms are one of the most common growth forms of microorganisms and are one of the most important factors in clinical infections due to their high resistance to antibiotics [96-101]. The most common device is the central venous catheter, used to administer liquids, nutrients, and medications in neutropenic or immunocompromised patients. Patients with prostheses frequently have prosthetic stomatitis [102], a condition where blood group O seems to be a predisposing factor, since certain glycoproteins present in this group are involved in the adherence of *C. albicans* to biopolymers [103]. The adhesin-mediated adherence of *Candida* to medical devices is the first step in biofilms formation. Later, during the intermediate phase, *Candida* begins to proliferate across the surface of the device through the development of hyphae and the formation of a matrix of polysaccharides, carbohydrates, proteins, and other components not yet elucidated [104]. This matrix defends *Candida* from the phagocytic cells by maintaining nutrients and acting as a barrier to the diffusion of drugs or substances toxic to these yeasts [100, 105, 106]. During the last phase, called maturation, growth continues in the formation of the biofilms and finally the fungal cells penetrate the epithelial barrier reaching the blood stream and spreading throughout the body. The *Candida* species that form biofilms on the surface of plastic catheters are *C. albicans* and *C. parapsilosis*, which explains the high level of association between these species and candidemias caused by the implantation of these devices [107]. Tumbarello *et al.* [93] analyzed the capacity for forming biofilms by the NCAC species shown in patients who received parenteral nutrition and found that *C. parapsilosis* was the most frequently species isolated from blood samples, which also showed a high capacity for forming biofilms. In the same study, they showed that *C. tropicalis* was the species with the highest percentage of positive biofilms (71.4%), while only 22.6% of those isolated from *C. albicans* could form biofilms. Specifically, this research shows that biofilms cause adverse health effects in hospitalized patients with candidemia and suggests that these devices are significant predictors of mortality. These results suggest that *C. parapsilosis* has selective advantages for growth and biofilm formation in central venous catheters over the other *Candida* species. The advantage shown by *C. parapsilosis* and *C. tropicalis* in the formation of biofilms is probably an important virulence factor which, concomitantly with host blood type, have converted these two species in the cause of the high incidence of candidemia in a vast part of the world.

Cell wall proteins involved in *Candida* biofilm formation: Adhesins

It is documented that a variety of proteins and mannoproteins are involved in the adhesion to

plastic, and their expression depends on multiple environmental factors [108]. The cell wall is the initial site of the contact between *Candida* and the host cells or the inert material, so that the outermost structure of the yeast plays a significant role in colonization, invasion of animal tissues and in adhesion to inert surfaces. The main adhesion proteins described in *C. albicans* are the mannoproteins that interact with the epithelium and macrophages in the host [109-111]. Lectins are mannoproteins that interact with specific carbohydrates of the host cells such as L-fucose and *N*-acetyl-D-glucosamine. It has been described that the binding of *C. albicans* to erythrocytes is mediated by yeast lectins that could be involved in the acquisition of iron [69, 71, 73]. Hwpl is a mannoprotein of the external surface that serves as a substrate for the transglutaminases and allow the binding of the hyphae of *C. albicans* to the host epithelial cells [112-114]. Another mannoprotein, integrin Int1p, is also involved in adhesion and virulence [115, 116]. Besides these mannoproteins, the genes of the *ALS* (agglutinin-like sequence) family of *C. albicans*, which code for glycoproteins of the cell wall such as Als1, Als2, Als3, Als4, Als5, Als6, Als7 and Als9, are also implicated in mediating adhesion to host cells [117-120]. Each *ALS* gene has a similar structure based on three domains that includes domain 5' from 1299 to 1308 pb, which is 55-90% similar among members of the family, a central domain with a variable number of repeating sequences, and domain 3' that has a variable length among the genes of this family [119, 121]. During biofilm formation by *C. albicans*, it has been shown that there is a change in the expression of the *ALS* adhesin families [100, 122-125]. Expression of the *ALS1* gene is dramatically overexpressed in all the strains of *C. albicans* capable of forming biofilms, in contrast to *ALS7* whose expression is repressed. *ALS5* and *ALS10* are not involved in biofilm formation [125]. Thus, each *ALS* family member contributes independently to biofilm formation. *ALS* gene expression during biofilm formation is transcriptionally regulated by the Bcr1p transcription factor, which forms part of the C_2H_2 zinc fingers factor. The mutants *bcr1*Δ/*bcr1*Δ form defective biofilms with less depth than expected and also present a large number of yeast cells with small hyphae. However, the cells *BCR1/BCR1* and *bcr1*Δ/*bcr1*Δ are able to produce hyphae in media that induce hyphae formation in normal growth conditions [126]. These results suggest that Bcr1p can activate the expression of genes involved in the formation of hyphae during formation of biofilms by mediating the regulation several genes which code for cell wall proteins like those of the *ALS* family [126].

The genome of *C. parapsilosis* contains five gene orthologs of *ALS* and six glycophosphatidylinositol (GPI)-anchored proteins. In this species, unlike *C. albicans*, small changes in the level of expression of this gene family have been identified during formation of biofilms. The expression levels of the genes *CPAG_05314*, *CPAG_00368*, and *CPAG_00369* remained unchanged, while the level of expression of *CPAG_05054* was induced three fold in 24 hours but not after 50 hours. The expression level of *CPAG_05056* increased slightly at 50 hours [127]. These authors concluded that it is possible that levels of expression of the *ALS* gene family vary between isolates of *C. parapsilosis*, a possibility that should be investigated in future work. However, these discrete changes in the level of *ALS* gene expression of *C. parapsilosis* compared to *C. albicans* indicate that *C. parapsilosis* probably uses other adhesins to interact with the inert biofilm material. This difference in the ability to adhere to the medical devices confers specificity between the two species, a characteristic that is also observed in binding to the host erythrocytes. The genome of *C. glabrata* contains a family of at least 23 homologous *EPA* genes (epithelial adhesins), that code for cell wall proteins. The structure of these Epa proteins is similar to the *ALS* proteins of *C. albicans*. However, of all *EPA* genes, only *EPA1* expresses *in vitro* and mediates adhesion to mammalian epithelial cells [128]. The absence of expression of other *EPA* genes is partly due to the fact that most of these are subjected to subtelomeric silencing. They are not expressed because of the repressive structure of chromatin [129, 130]. The proteins involved in subtelomeric silencing in *C. glabrata* are Rap1, Sir2, Sir3, Sir4, yKu70, yKu80 and Rif1 [129-131]. Mutations of *C. glabrata* in any of these genes relax chromatin allowing various *EPA* genes under subtelomeric silencing to be expressed. These mutants are

hyperadherents. Interestingly, it was determined that Epa6 is the principal adhesin involved in the formation of biofilms [132]. In *C. tropicalis*, 3 orthologous genes of the *ALS* families have been identified by southern and western blot analysis with anti-ALS antibodies. However, it has not been determined whether these genes are involved in biofilm formation.

It has been suggested that *ALS* genes in the genome of *C. albicans, C. tropicalis, C. parapsilosis* and *C. glabrata* (*EPA*) have been preserved because they confer advantages to these *Candida* species over other microorganisms to aggressively colonize host cells and inert materials [119]. Differences in the pattern of expression of these orthologous genes between species of *Candida* may be due to genetic variability, which gives each one of these species an interval to adhere to their host. The existence in each *Candida* species of gene paralogs for adhesins probably helps them to respond differentially to environmental signals and thus colonize and invade different niches and physiological tissues such as epithelial, endothelia, erythrocytes, and medical devices during infection.

CONCLUSIONS AND PERSPECTIVES

This study analyses the incidence of *Candida* infection as a function of the blood types prevalent in different countries and their ability to form biofilms. In the last decade it has been reported that *C. tropicalis, C. parapsilosis*, and *C. glabrata* are the yeasts most frequently isolated from blood samples, surpassing *C. albicans* in some geographic areas [33, 51-55]. The variability in the incidence of *Candida* species is due to the risk factors mentioned previously and to the genotypic and phenotypic characteristics of the human hosts which may confer differential susceptibility or resistance against infectious agents. Several global studies [227, 230] show a predominance of blood type O over the other three (A, B and AB).

The proteins and the antigens on the red blood cell membrane, particularly those determined by ABO blood group are the molecules which enable *Candida* to adhere to these cells, spread and disseminate, however Lewis antigens also have been proposed as receptors specific for different strains of *Candida* [69, 71, 72, 73].

The results of this study suggest that there is a correlation between countries with similar characteristics in the incidence of *Candida* species and the host's blood type. Countries with a high frequency of group O have a high susceptibility to being colonized by *C. albicans*. In those countries where the predominant ABO group (after type O) is A, *C. glabrata* has the highest incidence and regions with highest prevalence of blood type B and AB present more susceptibility to candidemia by *C. parapsilosis* and *C. tropicalis*. These latter are the main emerging species in America.

In the future, it should be clarified whether group O promotes the adhesion of a greater number of *Candida* species than other groups in the ABO system, the role of glycolipids of Lewis system in recognition of *Candida* and the correlation between biofilm formation with blood types.

It is likely that prospective and retrospective studies in the next decade, which should lead to a better understanding of the trends for emergent *Candida* species, as well as the development of new antifungals based on their prevalence, will contribute to an improved quality of life for patients.

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