Malassezia spp: ruolo nei disordini cutanei e nelle infezioni fungine invasive

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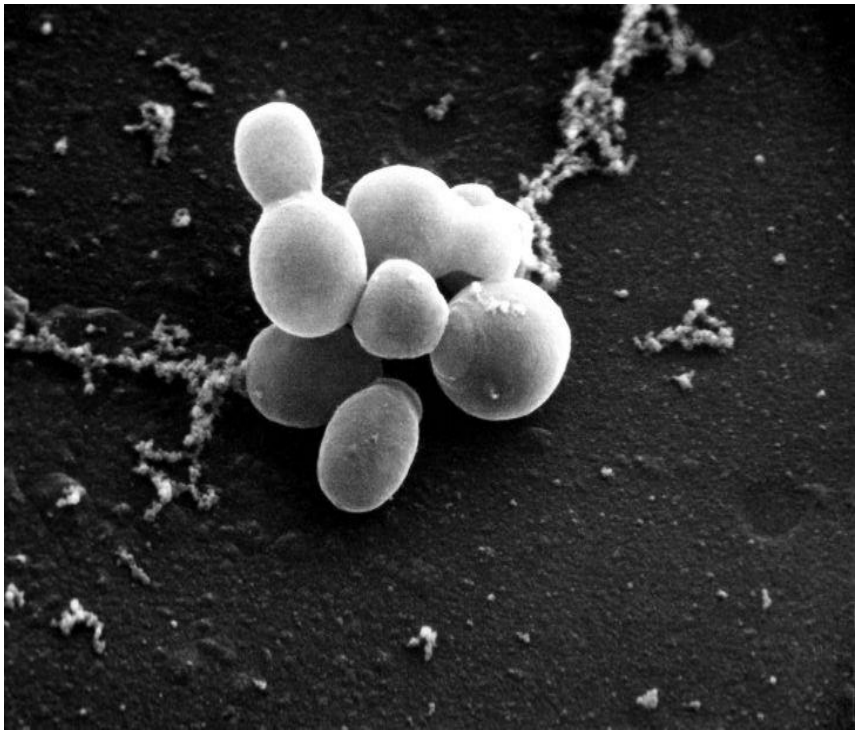

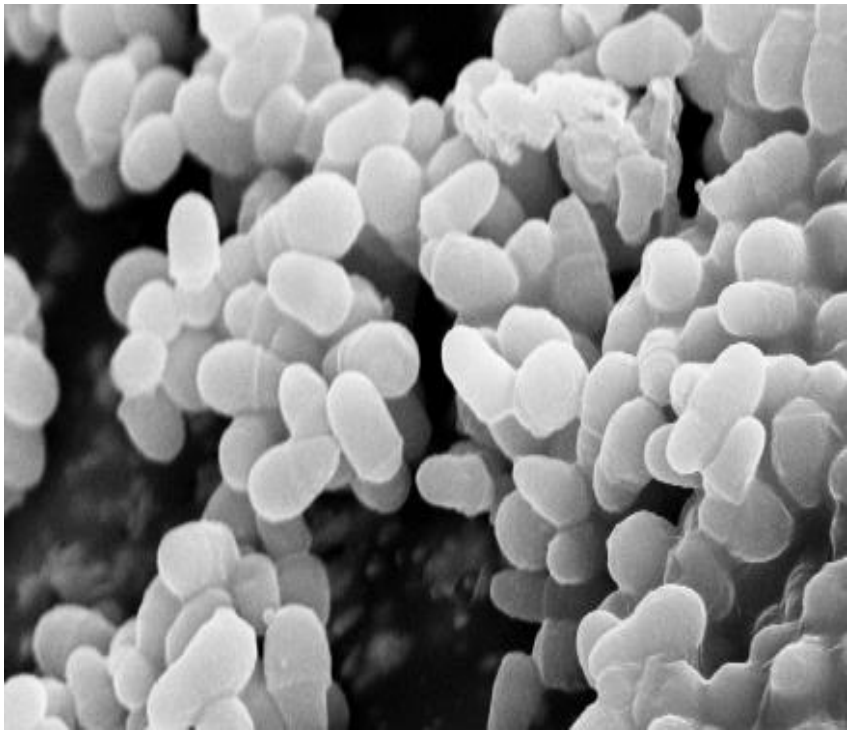

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- 18 specie lipidopendenti con patologia e distribuzione variabili su diversi ospiti
- Non esiste una reale ospite specificità
- Alcune specie sembrano avere ospiti specifici (*M. caprae, M. cuniculi, M. pstittaci, M. equina, M. vespertilionis*)
- Altre specie hanno un ampia gamma di ospiti (*M. furfur, M. globosa, M. pachydermatis*)

TABLE 1 | *Malassezia* species and main mammalian hosts.

Malassezia species	Synonyms	Presence on healthy skin	Presence in lesions
M. furfur	*Pityrosporum ovale*	In humans Sometimes in animals	In humans (PV, FG)
M. pachydermatis	*P. pachydermatis*, *P. canis*	In dogs, cats, many others (mostly canids) Sometimes in humans (dog contact)	In dogs, cats, others (SD, OT) Sometimes in humans (FG)
M. sympodialis	*M. furfur* serovar A	In humans and animals	In humans (AD, SD) Sometimes in cats (OT)
M. globosa	*P. orbiculare* *M. furfur* serovar B	In humans and animals	In humans (PV, SD, AD) Sometimes in cats (OT)
M. obtusa		In humans	In humans
M. slooffiae		In pigs, cats (claws) In humans	In humans
M. restricta	*M. furfur* serovar C	In humans	In humans (SD)
M. dermatis		In humans	In humans (AD)
M. japonica		In humans	In humans (AD, SD)
M. nana		In cats, horses	In cats, cattle (OT)
M. yamatoensis		In humans	In humans (SD)
M. caprae		In goats	
M. equina	*M. equi*	In horses	In horses
M. cuniculi		In rabbits	
M. arunalokei		In humans	In humans
M. brasiliensis		In parrots	–
M. psittaci		In parrots	–
M. vespertilionis		In hibernating bats	–

–, not reported; PV, pityriasis versicolor; FG, fungaemia; AD, atopic dermatitis; SD, seborrheic dermatitis; OT, otitis.

Guillot and Bond ,2020

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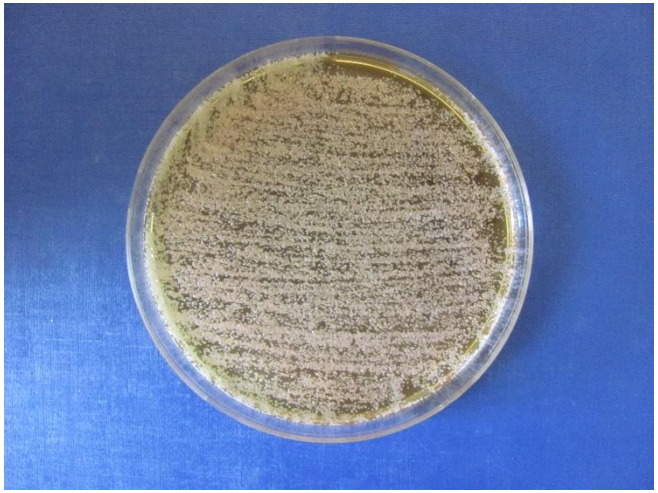
Table 1
The compositions of media commonly used for the culturing of *Malassezia*.

Medium	Composition (per litre of distilled water)	References
Dixon's agar medium	36 g malt extract, 6 g peptone, 20 g bile, 10 mL Tween 40, 2 mL glycerol, 2 mL oleic acid and 12 g agar	[5,26]
Leeming-Notman agar medium	10 g peptone, 5 g glucose, 0.1 g yeast extract, 4 g bile, 1 mL glycerol, 0.5 g glycerol monostearate, 0.5 mL of Tween 60, 10 mL milk and 12 g agar	[27]
Ushijima's medium A (for *M. pachydermatis*)	10 g trypticase peptone (BBL), 5 g yeast extract (BBL), 3 g glucose, 2 g NaCl, 12 g KH2 PO4 (anhydrous), 15 g agar, 0.1 g ampicillin, and 0.25 g cycloheximide; adjust pH to 5.5	[28]
Modified CHROMagar *Candida*	47.5 g of CHROMagar *Candida* (=10 g peptone, 22 g special chromgen mixture, 0.5 g chroramphenicol and 15 g agar), 8 g ox bile (Oxoid), 1 mL glycerol monostearate and 0.5 mL Tween 60	[30]
Modified CHROMOagar	56.3 g of CHROMagar *Malassezia* basal medium and 10 mL of Tween 40	[31]



Cafarchia et al. Mol Cell Probes 2011; 25:1-7

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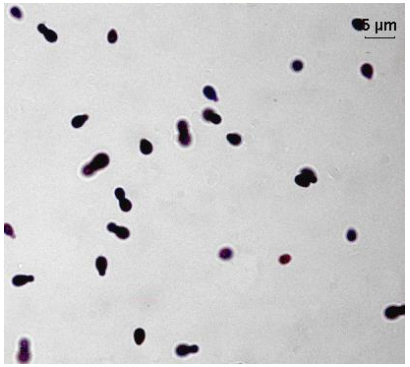
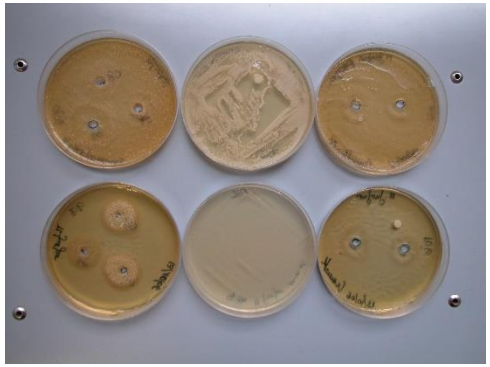
Table 2
Morphological, physiological and biochemical characteristics of the 14 currently recognized species of *Malassezia*.

Species	Morphology	SDA (32 °C)	TDT using Tween				Chremophor EL	Catalase	Tryptophan	β-glucosidase	Growth on Dixon's agar at		
			20	40	60	80					32 °C	37 °C	40 °C
M. furfur [5]	G E C	−	+ [−]	+ [−]	+ [−]	+ [−]	+ [−]	+ [−]	+	− or ±	+	+	+
M. obtusa [5]	E C	−	−	−	−	−	−	+	−	+	+	− or ±	−
M. globosa [5]	G	−	−	−	−	−	−	+	−	−	+	− or ±	−
M. slooffiae [5]	E C	−	+ or ± [−]	+	+	−	−	+	−	−	+	+	+
M. sympodialis [5]	E	−	− or ±	+	+	+	− or ±	+	−	+	+	+	+
M. restricta [5]	G E	−	−	−	−	−	−	−	−	−	+	+ or −	−
M. dermatis [13]	G E	−	+	+	+	+	± or +	+	?	−	+	+	+
M. japonica [14]	G	−	−	±	+	−	?	+	?	?	+	+	−
M. nana [16]	E	−	v	+	+	±	−	+	?	−	+	+	+ or −
M. yamatoensis [15]	E	−	+	+	+	+	?	+	?	?	+	+	−
M. equina [17]	G E	−	±	+	+	+	−	+	?	− [+]	+	±	−
M. caprae [17]	G E	−	−	+	+	+ [−]	−	+	?	+ [−]	+	− or ±	−
M. cuniculi [18]	G	−	−	−	−	−	−	+	?	+	− or ±	+	+
M. pachydermatis[5]	E	+ or ±	+	+	+	+	+	+ or ±	−	+ [−]	+	+	+

Globose (G); ellipsoidal (E); cylindrical (C); Sabouraud dextrose agar (SDA); weakly positive (±); rare deviation from usual pattern ([]); unknown (?). Tween diffusion test (TDT); Tryptophan consumption; Chremophor EL; Catalase; Tryptophan; β-glucosidase [34–37].





Cafarchia et al. Mol Cell Probes 2011; 25:1-7

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Numerosi genotipi di *Malassezia* all'interno della stessa specie, associate

- ospite,
- area geografica,
- manifestazioni cliniche.

Table 3
Molecular tools established and utilized for the identification and differentiation of species of *Malassezia* and/or the detection of intraspecific genetic variation.

Molecular tools	DNA regions	*Malassezia* spp. studied	Relevant information	Selected references
Direct DNA sequencing	ITS-1	*M. furfur*, *M. globosa*, *M. restricta*, *M. sympodialis*, *M. pachydermatis*, *M. slooffiae*, *M. obtusa* and *M. nana*.	Strains of *M. nana* from Japan were distinct from those from Brazil. All species were identified. Seven sequence types for *M. furfur*. Eight sequence types in *M. pachydermatis* linked to the presence of lesions and sampling sites. Five sequence types for *M. globosa* with one associated with extensive pityriasis versicolor.	[16] [50] [62] [69]
	LSU	*M. furfur*, *M. globosa*, *M. restricta*, *M. sympodialis*, *M. pachydermatis*, *M. slooffiae*, *M. obtusa* and *M. nana*.	Three different genotypes in *M. pachydermatis* related to the presence of skin lesions. Four different variants within *M. sympodialis* linked to host species. Eight sequence types for *M. pachydermatis* from dogs, cats and humans. Samples from humans identical genetically to those from other animals. All species identified and differentiated.	[22,62] [51] [58] [59]
	chs-2	*M. furfur*, *M. globosa*, *M. restricta*, *M. sympodialis*, *M. pachydermatis*, *M. slooffiae* and *M. obtusa*.	Three genetic variants of *M. pachydermatis* from dogs linked to skin lesions. All species identified and differentiated. Four *chs*-2 genetic variants within *M. pachydermatis* of animal origin, linked to skin lesions or otitis.	[22,62] [60] [61]
	ITS-2 IGS-1	*M. furfur*, *M. japonica*. *M. globosa*, *M. restricta* and *M. pachydermatis*.	Nucleotide differences of 15.6–17.9% between *M. furfur* and *M. japonica*. *M. globosa* and *M. restricta* grouped according to their occurrence on skin with seborrhoeic, atopic dermatitis and healthy skin. Remarkable intraspecific diversity within *M. pachydermatis*. Absence of intraspecific polymorphism within *M. nana* from various geographical origins.	[14] [53] [56] [57]
PCR-based restriction fragment length polymorphism (PCR-RFLP)	ITS-1, ITS-2 and LSU	*M. furfur*, *M. globosa*, *M. restricta*, *M. sympodialis*, *M. pachydermatis*, *M. slooffiae*, *M. obtusa*, *M. nana*, *M. japonica*, *M. yamatoensis* and *M. dermatis*.	*M. furfur* strains from distinct geographical regions in Europe display an absence/presence of a cleavage site in the ITS-2 region for the endonuclease *Bsm*I. All species were identified and differentiated using the endonucleases *Cfo*I and *Bsm*I.	[46] [64]
PCR-based single strand conformation polymorphism (PCR-SSCP) analysis	ITS-1 and *chs*-2	*M. globosa*, *M. sympodialis* and *M. pachydermatis*.	*M. pachydermatis* represented at least three genotypes based on PCR-SSCP analyses of *chs*-2 and ITS-1. *M. sympodialis* displays a uniform ITS-1 PCR-SSCP profile.	[22] [69]
Real-time PCR	ITS-1 and ITS-2	*M. globosa*, *M. restricta*, *M. sympodialis* and *M. pachydermatis*.	*M. restricta* and *M. globosa* were the most prevalent species from both healthy subjects and from patients with psoriasis, atopic dermatitis, and pityriasis versicolor.	[55,72–74]
Random amplification of polymorphic DNA (RAPD)	Total genomic DNA	*M. furfur*, *M. globosa*, *M. restricta*, *M. sympodialis*, *M. pachydermatis*, *M. slooffiae* and *M. obtusa*.	Polymorphic profiles for *M. furfur* linked to pityriasis versicolor or seborrhoeic dermatitis. Intraspecific variation in DNA patterns for *M. furfur*, *M. slooffiae* and *M. pachydermatis* and presence of specific genetic-types linked to host and/or sampling sites. Polymorphic profiles for all *Malassezia* species without clinical association.	[39] [41,81] [49]
Amplified fragment length polymorphism (AFLP)	Total genomic DNA	*M. furfur*, *M. globosa*, *M. restricta*, *M. sympodialis*, *M. pachydermatis*, *M. slooffiae*, *M. obtusa* and *M. dermatis*.	All species were identified and differentiated. Specific genotypes of *Malassezia furfur* linked to geographical origin.	[45]
Denaturing gradient gel electrophoresis (DGGE)	SSU	*M. furfur*, *M. globosa*, *M. restricta*, *M. sympodialis*, *M. pachydermatis*, *M. slooffiae* and *M. obtusa*.	All species of *Malassezia* identified and differentiated. No intraspecific variation detected.	[49]
Pulsed field gel electrophoresis (PFGE)	Chromosomal DNA	*M. furfur*, *M. globosa*, *M. restricta*, *M. sympodialis*, *M. pachydermatis*, *M. slooffiae* and *M. obtusa*.	All species of *Malassezia* identified and differentiated. Intraspecific variation detected only within *M. furfur*.	[47]

Internal transcribed spacer 1 of rDNA (ITS-1); internal transcribed spacer 2 of rDNA (ITS-2); large subunit of rDNA (LSU); chitin synthase-2 (*chs*-2); first intergenic spacer (IGS-1); small subunit of rDNA (SSU).

Cafarchia et al. Mol Cell Probes 2011; 25:1-7

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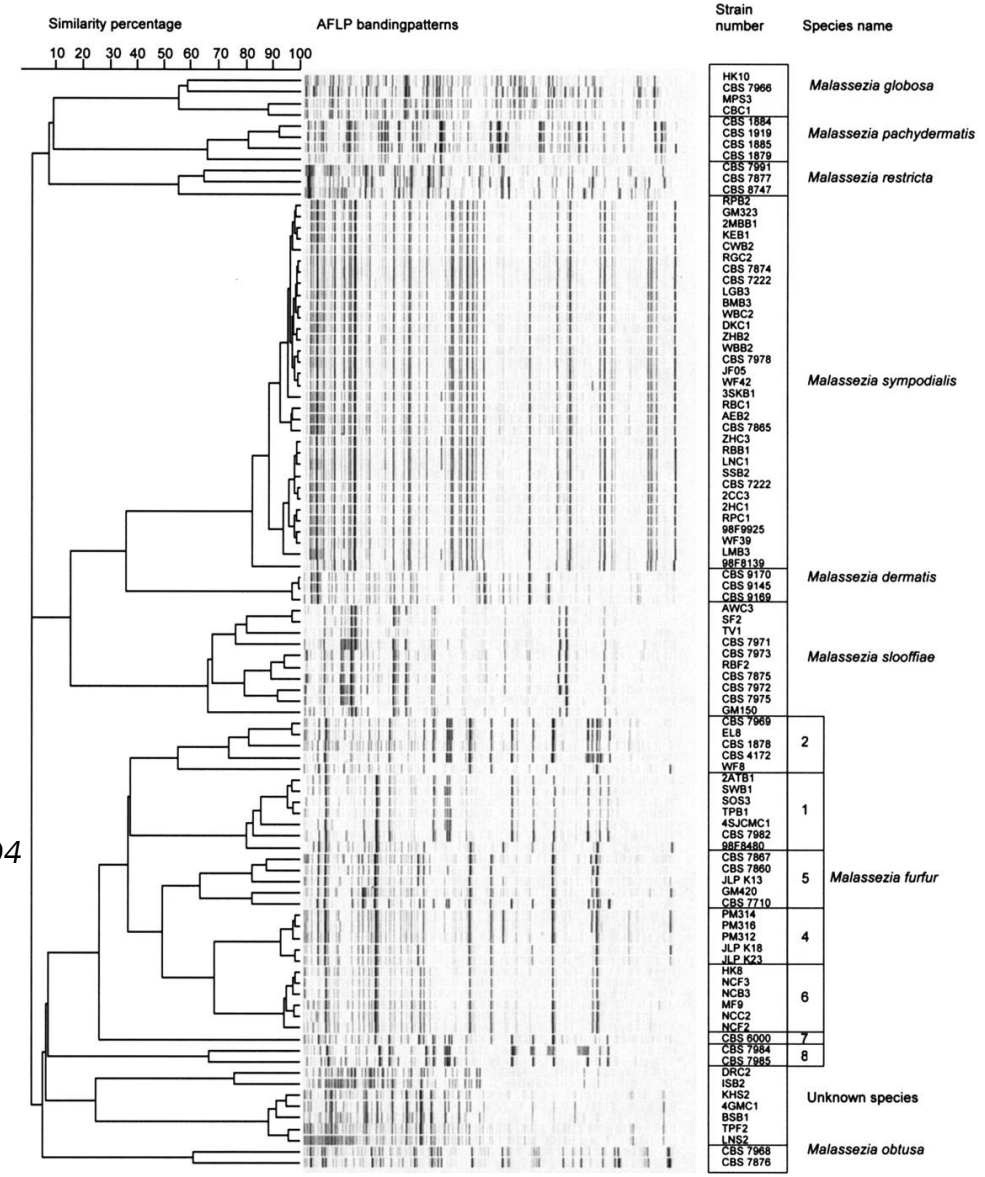
- *M. furfur* dall'Ontario, Canada, raggruppato separatamente dai ceppi europei
- *M. furfur* notevole diversità genetica con otto sottotipi ben distinti
- Sottotipo 4 e Sottotipo 5 da siti corporei interni di ospiti e / o malattie sistemiche.

Gupta et al., JCM 2004



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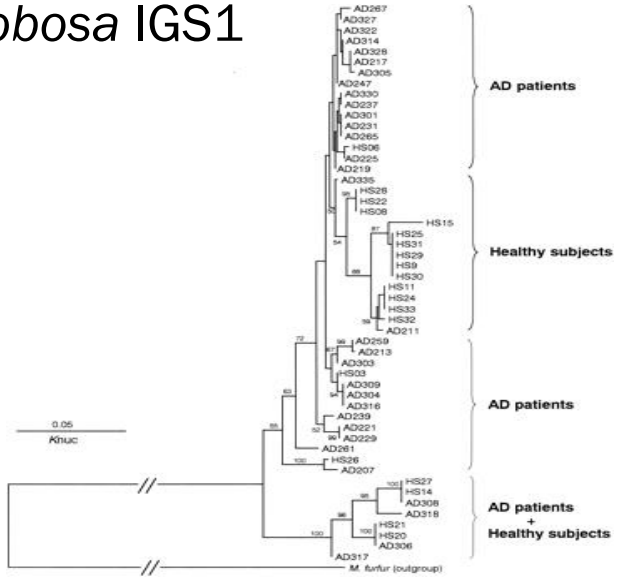
IGS1 distingue varianti specifiche di *M.* globosa, *M. restricta* e *M. pachydermatis* nella dermatite seborroica, nell'eczema atopico e sulla pelle sana di esseri umani e animali (*Sugita et al., 2004; Gupta et al. 2004*)

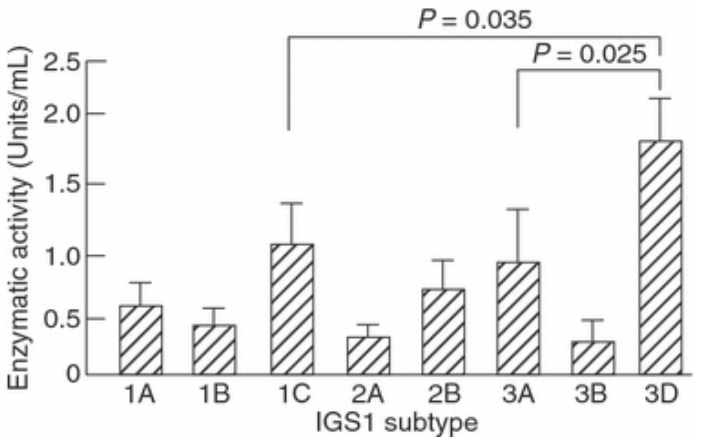
M. pachydermatis 8 sottotipi IGS1 con sottotipo 3D principalmente associato a lesioni cutanee (*Kobayashi et al., 2011*)

Le analisi di sequenza dell'rDNA della LSU hanno mostrato *Malassezia* spp. sottotipi su diverse specie ospiti (*Gaitanis et al., 2012*)

M . globosa IGS1



M . pachydermatis IGS1



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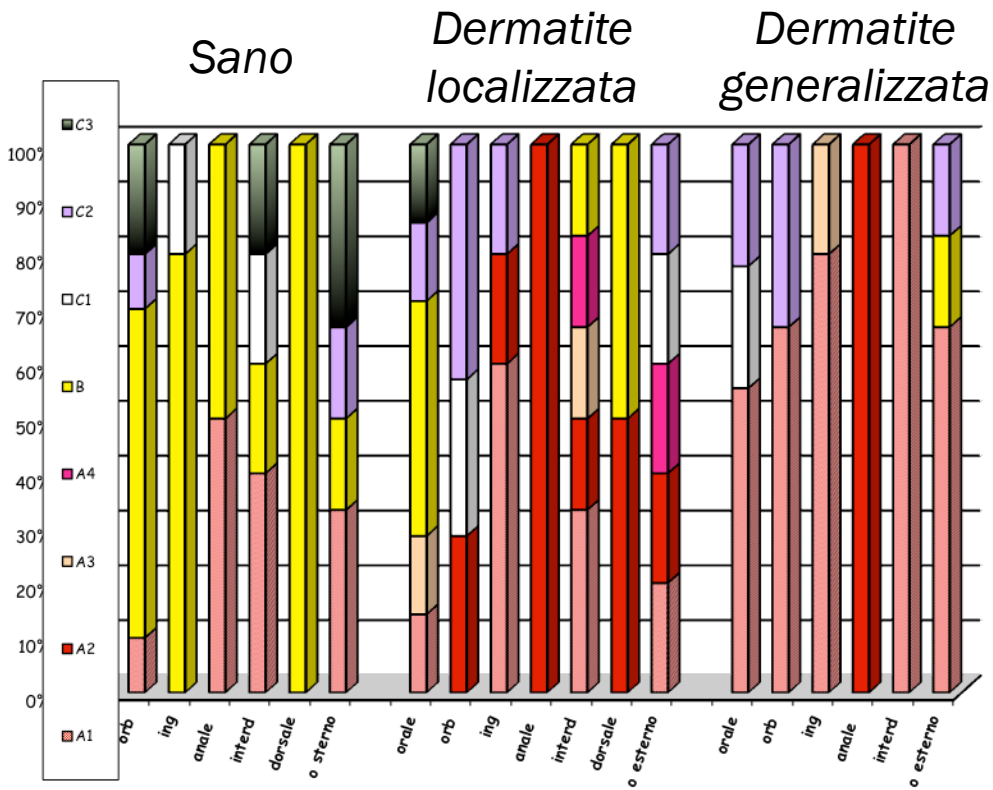
- Il genotipo B è principalmente isolato da cute sana.
- I genotipi A e C associati a lesioni cutanee
- Sub-genotipo CI_2 è per lo più legato ad una particolare posizione.
- Il microclima cutaneo potrebbe selezionare la popolazione genetica dei lieviti del genere *Malassezia*

Malassezia pachydermatis ITS1 sub-genotipo del cane



Cafarchia et al, FEMS Yeast Res. 2008; 8:451-9

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Malassezia furfur **from skin lesions (SL) and Blood Stream Infection (BSI): Range of MIC Values and MIC90 or MIC50 *in bracket of Fluconazole (FLZ), ketoconazole (KTZ), itraconazole (ITZ) posaconazolo (POS), terbinafine (TER) and amphotericin B (AmB) obtained with modified CLSI protocols**

References	N. isolates/host	FLZ	KTZ	ITZ	VRZ	POS	TER	AMB	MEDIA	T°C/reading time
Rojas et al., 2016	30/Human SL	0.5-128 (32)	0.03-0.125 (0.03)	0.03 0.125 (0,.03)	0.03-0.5 (0.25)	ND	0.125-32 (16)	0.25-16 (8)	Modified RPMI	32°C/48h
Cafarchia et al., 2015	60/Human BSI	8-128 (128)	ND	0.032-8 (1)	0.064-8 (2)	0.016-8 (0.5)	ND	ND	SAB+1% tween 80	32°C/48h
Cafarchia et al., 2015	18/Human SL	8-128 (>128)	ND	0.064-16 (0.5)	0.064-8 (2)	0.032-0.25 (0.25)	ND	ND	SAB+1% tween 80	32°C/48h
Iatta et al., 2014,	16/Humans BSI	16– >128 (128)	ND	0.03–8 (0.5)	0.06–2 (1)	0.016–0.25 (1)	ND	16	SAB+ 1% tween. 80	32°C/ 48h
Iatta et al., 2014	16/Humans BSI	16– >128 >128	ND	0.125–1 (1)	0.125–4 (4)	0.125–0.5 (0.5)	ND	16	Modified RPMI	32°C/48-72h
Rojas et al., 2014	39/ Human SL	≤0.125–>64 (16)	≤0.03–0.25 (0.06)	≤0.03–0.125 (0.06)	≤0.03–0.5 (0.25)	ND	ND	0.25-4 (2)	RPMI	32°C/72h
Carrillo-Munoz et al., 2013	20/Human SL	38.5*	0.01*	0.01*	0.03*	0.02*	1*	Nd	RPMI	32°C/27h
Miranda et al., 2007	74 /Human SL	8	0.25	0.25	0.5	ND	ND	ND	Modified Leeming–Notman	32°C/72h
Rincon et al., 2006	52/human SL	ND	0.03-1 (0.5)	0.03-0.5 (0.25)	0.03-1 (0.5)	ND	ND	ND	Modified RPMI	32°C/72h
Sugita T at al., 2005	12/human SL	ND	0.016-0.125 (.0.03)	0.016-0.125 (0.03)	ND	ND	ND	ND	Leeming–Notman	32°C/7days
Velegraki et al., 2004	12 /Human SL	0.5-32 (8)	0.3-1 (0.25)	0.03-0.06 (0.06)	0.03-16 (1)	0.03-32(2)	0.03-50 (12)	0.12-16 (1)	Modified RPMI	32°C/ 48 h
Garau et al., 2003	24 Human SL	2-4 (4)	≤0.03	≤0.03-0.06	≤0.03-0.12 (0.06)	ND	ND	≤0.06	Modified RPMI	32°C/72h
Gupta et al., 2000	20 Human SL	ND	≤0.03-0.125 (≤0.03)	≤0.03-0.125 (≤0.03)	0.03-0.125 (0.06)	ND	0.03-32 (16)	ND	Leeming–Notman	35°C/48h

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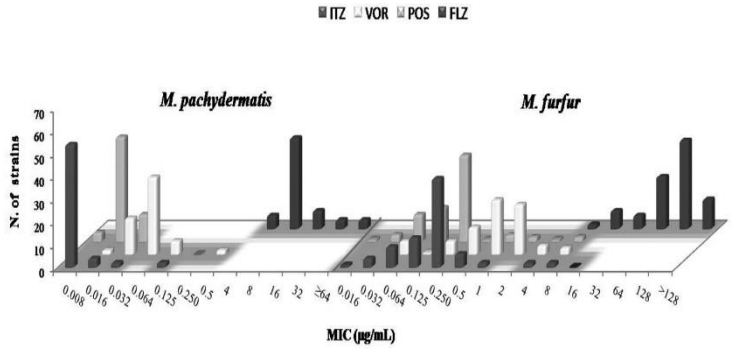
- Il profilo di suscettibilità antifungina contro azoli, AMB e TER varia a seconda della specie *Malassezia*, indipendentemente dal mezzo o da altre condizioni impiegate;
- *Malassezia sympodialis* e *M. pachydermatis* sono le specie più sensibili e *M. furfur* e *M. globosa* le specie meno sensibili
- ITZ e KTZ sono i farmaci più attivi, FLZ, VOR e AmB i meno attivi

Malassezia spp	N. isolates/host	Low active drugs	Media	T°C/Reading time	References
	241/ Human SL	FLZ	Christensen´s urea broth	32°C/96h	Sharma, 2017
	30/Human SL	FLZ ,TER, AmB	Modified RPMI	32°C/48h	Rojas et al., 2016
	60/Human BSI	FLZ, VOR	SAB+1% tween 80	32°C/48h	Cafarchia et al., 2015
	18/Human SL	FLZ, VOR	SAB+1% tween 80	32°C/48h	Cafarchia et al., 2015
	16/Human BSI	FLZ, AmB	SAB+ 1% tween 80	32°C/ 48h	Iatta et al., 2014
	39/ Human SL	FLZ, AmB	RPMI	32°C/72h	Rojas et al., 2014
M. furfur	20/Human SL	FLZ, TER	RPMI	32°C/27h	Carrillo-Munoz et al., 2013
	74/Human SL	FLZ	Modified Leeming–Notman	32°C/72h	Miranda et al., 2007
	52/Human SL	KTZ	Modified RPMI	32°C/72h	Rincon et al., 2006
	12/Human SL	Low MIC for all drugs	Leeming–Notman	32°C/7days	Sugita et al., 2005
	12/Human SL	FLZ,VOR, AmB	Modified RPMI	32°C/ 48 h	Velegraki et al., 2004
	24/Human SL	FLZ	Modified RPMI	32°C/72h	Garau et al., 2003
	20/Human SL	FLZ, VOR, AmB	Leeming–Notman	35°C/48h	Gupta et al., 2000
M. sympodialis	10 /Human SL	FLZ, AmB	Modified RPMI	32°C/72h	Rojas et al., 2016
	20/ Human SL	FLZ, AmB	Modified RPMI	32°C/72h	Rojas et al., 2014
	8 /Human SL	FLZ	Modified RPMI	32°C/72h	Velegraki et al., 2004
M pachydermatis	22/Dogs	FLZ,KTZ, AmB	SAB+1% tween 80	35°C/48h	Brilhante et al. 2018
	216/Dogs	FLZ, VOR	SAB+1% tween 80	32°C/48h	Álvarez-Pérez et al., 2016
	62/Dogs	FLZ	SAB+1% tween 80	32°C/48h	Cafarchia et al., 2012, 2015
	40/Dogs	Low MIC for all drugs	Modified RPMI	35°C/ 48-72h	Weiler et al., 2013
	20/Dogs	FLZ	RPMI	32°C/48h	Brito et al., 2009
	50/Dogs	FLZ, AmB	Modified RPMI	32°C/48h	Prado et al., 2008
	24/ Dogs, cats	FLZ	RPMI	32°C/48h	Nascente et al., 2003
	10/Dogs	FLZ	RPMI	32°C/48h	Garau et al., 2003
	82/Dogs, cats	FLZ	RPMI	35°C/48h	Eichenberg et al., 2003



The MIC data for all azoles of *M. pachydermatis* were at least four two-fold dilutions lower than those registered for *M. furfur*

Rojas et al., Med Mycol. 2014 ;*Cafarchia et al, Med Mycol. 2015;*

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Table 4 Number and percentage (in bracket) of *Malassezia pachydermatis* strains with genotype A, B and C resulting susceptible (S), intermediary susceptible (I) and resistant (R) to ketoconazole (KTZ), itraconazole (ITZ), voriconazole (VOR), posaconazole (POS) and fluconazole (FLZ). Statistically significant differences were marked with same superscript letter.

	A = 36			B = 12			C = 14			Total = 62		
Antif. agents	S	I	R	S	I	R	S	I	R	S	I	R
KTZ	32 (88.9)^{a}	1 (2.8)^{a}	3 (8.3)^{a}	10 (83.3)^{b}	2 (16.7)^{b}	0 (0)^{b}	9 (64.3)	3 (21.4)	2 (14.3)	51 (82.3)	6 (9.7)	5 (8.0)
ITZ	33 (91.7)^{c}	0 (0)^{c}	3 (8.3)^{c}	12 (100)^{d}	0 (0)^{d}	0 (0)^{d}	13 (92.8)	0 (0)	1 (7.1)	58 (93.6)	0 (0)	4 (6.4)
VOR	33 (91.7)^{ck}	2 (5.5)^{e}	1 (2.8)^{e}	11 (91.7)^{fk}	1 (8.3)^{f}	0 (0)^{f}	9 (64.3)^{k}	4 (28.6)	1 (7.1)	53 (85.5)	7 (11.3)	2 (3.2)
POS	32 (88.9)^{g}	3 (8.3)^{g}	1 (2.8)^{g}	11 (91.7)^{h}	1 (8.3)^{h}	0 (0)^{h}	11 (78.6)	2 (14.3)	1 (7.1)	54 (87.1)	6 (9.7)	2 (3.2)
FLZ	30 (83.3)^{il}	5 (13.9)^{im}	1 (2.8)^{i}	2 (16.7)^{jl}	8 (66.7)^{jm}	2 (16.7)^{j}	7 (50.0)^{l}	5 (35.7)^{m}	2 (14.3)	37 (59.7)	18 (29.0)	7 (11.3)

$S = MIC\ sample \leq MIC_{50}$; $I = MIC_{50} < MIC\ sample \leq MIC_{90}$; $R = MIC\ sample > MIC_{90}$. $^{a-m}$: Statistically significant differences ($P < 0.05$, Chi-squared test).

La sensibilità antifungina varia a seconda del genotipo : diversi ceppi resistenti tra gli isolati con genotipo A e C.

Il microclima cutaneo potrebbe selezionare i lieviti del genere *Malassezia* con diversi profili antifungini.

Cafarchia et al, FEMS Yeast Res. 2008; 8:451-9

EPIDEMIOLOGIA

- I lieviti del genere *Malassezia* sono commensali della cute degli animali.
- *M. pachydermatis* è stato isolata dalla cute di div. spp animali, ad eccezione di capre e conigli.
- Differenti *Malassezia spp.* sono isolate dalla cute degli animali (es. *M. furfur*, *M. globosa* e *M. sympodialis*)
- NGS Cani: *M. restricta* pelle sana e *M. pachydermatis* lesioni
- NGS Gatti; *M. restricta* e *M. globosa* più abbondanti con altre spp. antropofile.
- Prevalenza di *Malassezia* spp. è superiore in animali con lesioni cutanee rispetto a quelli sani

ANIMAL SPECIES	ANIMAL WITH LESION		ANIMAL WITHOUT LESION		REFERENCES
	PREVALENCE	*Malassezia* species	PREVALENCE	*Malassezia* species	
Dogs	23 - 80%	*M. pachydermati; M. furfur.*	3 - 36%	*M. pachydermatis.*	Brito et al., 2009. *Vet J.* **182:** 320–326; Cafarchia et al., 2005. *J Vet Diagn Invest.* **17:** 316–322; Cafarchia et al., 2011. *Med Mycol.* **49:** 365-374; Campbell et al., 2010. *Vet Dermatol.* **21:** 619–625; Newbold et al., 2014. *J Am Vet Med Assoc.* **244:** 1304-1308; Prado et al., 2004. *Vet Microbiol.* **100:** 115–120; Prado et al., 2008. *J Vet Diagn Invest.* **20:** 197–202.
Cats	75 - 89%	*M. pachydermatis; M. sympodialis; M. furfur; M. globosa; M. slooffiae; M. obtusa; M. restricta; M. nana.*	10 - 28%	*M. pachydermatis; M. sympodialis; M. obtusa; M. furfur; M. slooffiae; M. nana; M. globosa.*	Cafarchia et al., 2005. *J Vet Diagn Invest.* **17:** 316–322; Dizotti & Coutinho. *2007. Acta Vet Hung.* **55:** 471–477; Shokri et al., 2009. *J Vet Med Sci.* **72:** 293–296; Volk et al., 2010. *J Feline Med Surg.* **12:** 917-922.
Horses	60%	*M. pachydermatis; M. furfur; M. sympodialis; M. slooffiae; M. obtusa; M. globosa; M.restricta.*	54%	*M. equi; M. slooffiae.*	Cafarchia et al., 2013. *Vet Microbiol.* **167:** 215–234; Crespo et al., 2002. *Mycoses.* **45:** 333–337; White et al., 2006. *J. Vet Intern Med.* **20:** 395–398.
Sheep	28%	*M. sympodialis; M. globosa; M. restricta.*			Crespo et al., 2002. *Mycoses.* **45:** 333–337.
Cows	58 - 64%	*M. slooffiae; M. furfur; M. sympodialis; M. globosa; M.restricta; M. obtusa; M. pachydermatis.*	39%	*M. slooffiae, M. furfur, M. sympodialis, M. globosa, M.restricta; M. obtusa; M. pachydermatis.*	Crespo et al., 2002. Mycoses. **45:** 333–337; Duarte et al., 2003. *Med Mycol.* **41:** 137–142.
Goats	21 - 44%	*M. pachydermatis; M. furfur; M. sympodialis, M. obtusa; M. globosa; M.restricta.*			Crespo et al., 2002. *Mycoses.* **45:** 333–337; Eguchi-Coe et al., 2011. *Vet Dermatol.* **22:** 497–501.
Pigs			22 - 73%	*M. pachydermatis; M. sympodialis; M. furfur; M. slooffiae.*	Garau et al., 2005. *Mycoses.* **48:** 17-20; Nardoni et al., 2010. *Vet. Microbiol.* **141:** 155–158.
Birds	35%	*M. sympodialis.*	2%	*M. furfur.*	Grunder et al., 2005. *Mycoses.* **48:** 114-119; Mendes et al., 2014. *Rev Inst Med Trop Sao Paulo.* **56:** 525-528.
Rabbits			18%	*M. cuniculi.*	Cabañes et al,. 2011. *Med Mycol.* **49:** 40-48.

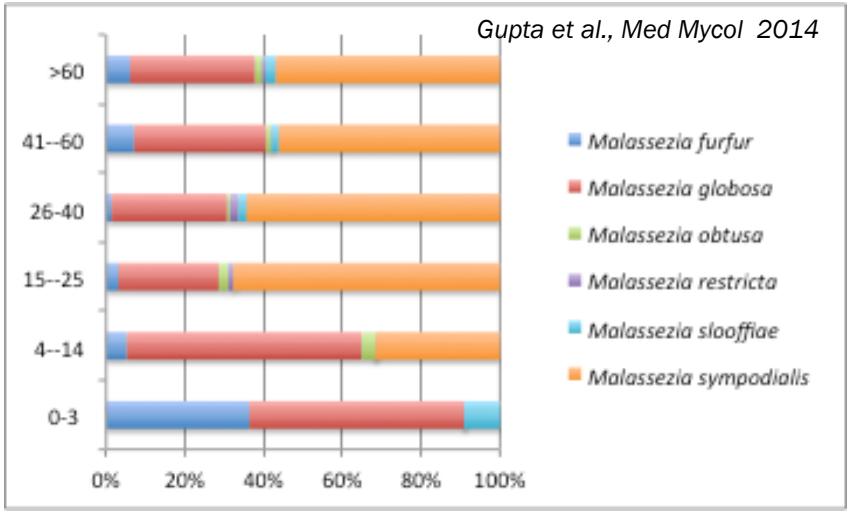
EPIDEMIOLOGIA

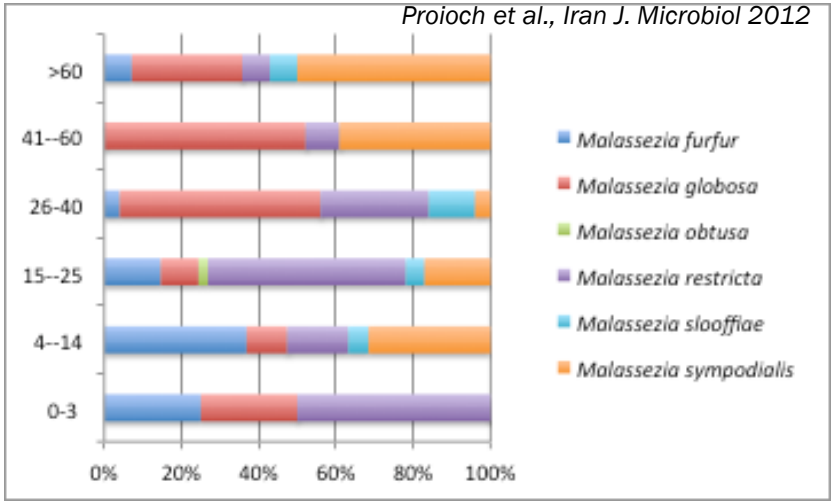
Organismi commensali: 50-80% del micobioma cutaneo totale;

La colonizzazione della cute umana inizia immediatamente dopo la nascita e rimane bassa fino alla pubertà.

La distribuzione delle specie *Malassezia* varia con l'età con *M. furfur, M. restricta* e *M. globosa* isolati più frequentemente nei bambini e negli adolescenti.

Distribution of Malassezia species in individuals from different age groups





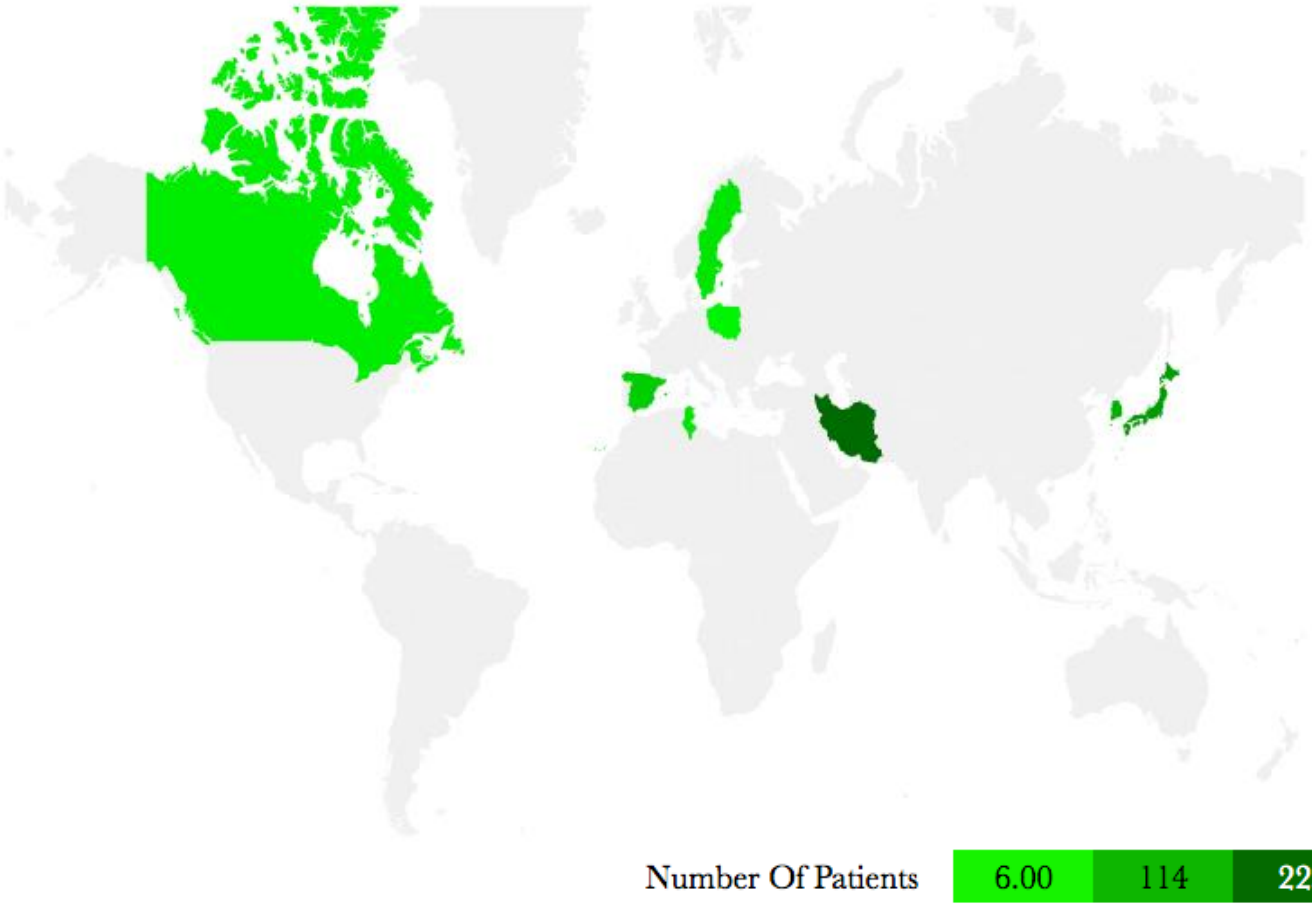
Findley et al., Nature 2013; *Nagata et al., Pediatr Int. 2012*

EPIDEMIOLOGIA

Malassezia spp. pazienti sani

(Phrohic et al., Int J Dermatol. 2016)

Spain	*M. sympodialis* (91.7)
Poland	*M. sympodialis* (46)
Sweden	*M. sympodialis* (69)
Canada	*M. sympodialis* (47.2)
Japan	*M. restricta* (61.1)
South Korea	*M. restricta* (31.6)
Japan	*M. globosa* (22)
Iran	*M. globosa* (42)
Tunisia	*M. globosa* (7.8)
Iran	*M. globosa* (68.1)
Japan	*M. globosa* (86.7)
South Korea	*M. restricta* (32)
India	*M. sympodialis* (47.6)
B&H	*M. sympodialis* (30)
	M. restricta (33)

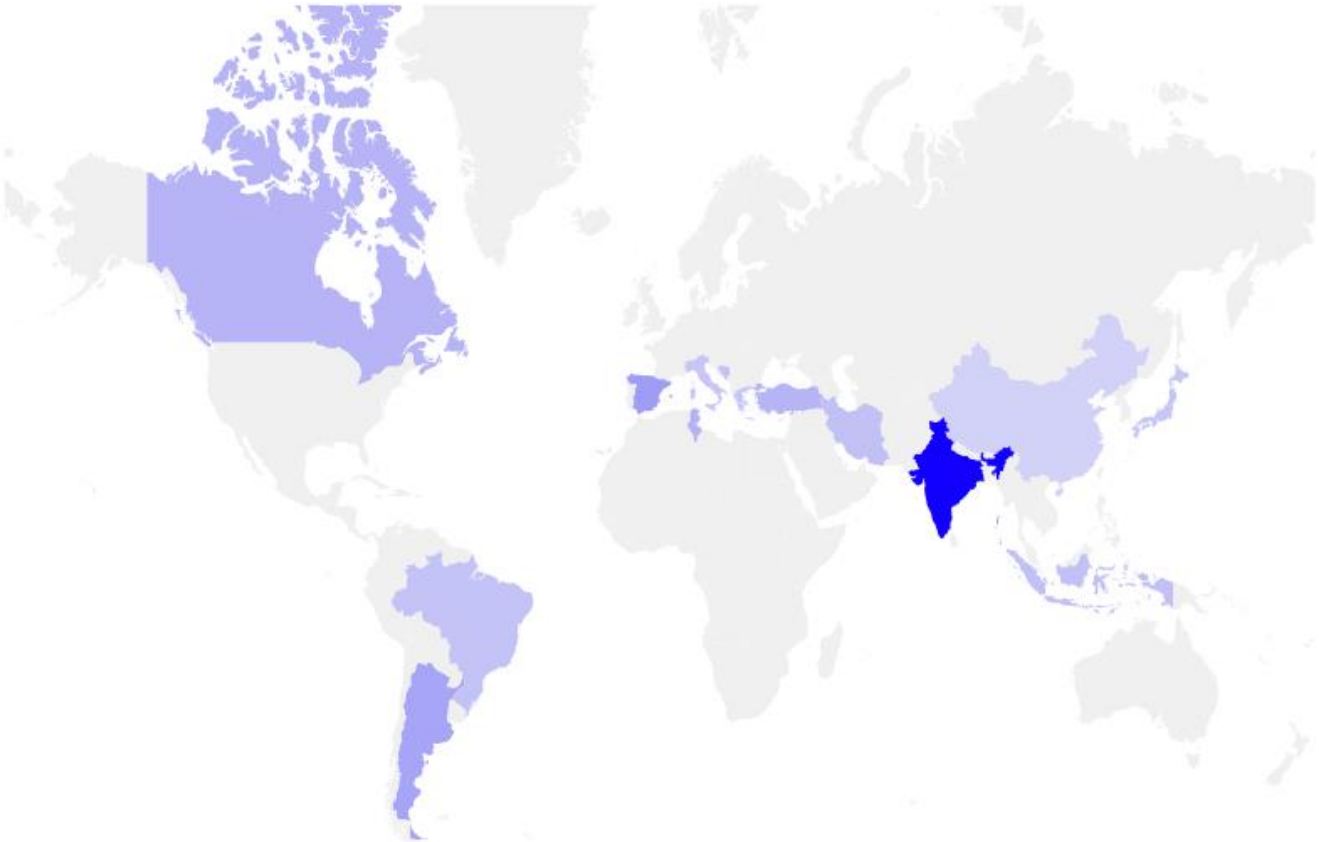


EPIDEMIOLOGIA

Malassezia spp. e *Pityriasis versicolor* , M. follicolite, psoriasi, dermatite seborroica

(*Phrohic et al., Int J Dermatol. 2016*)

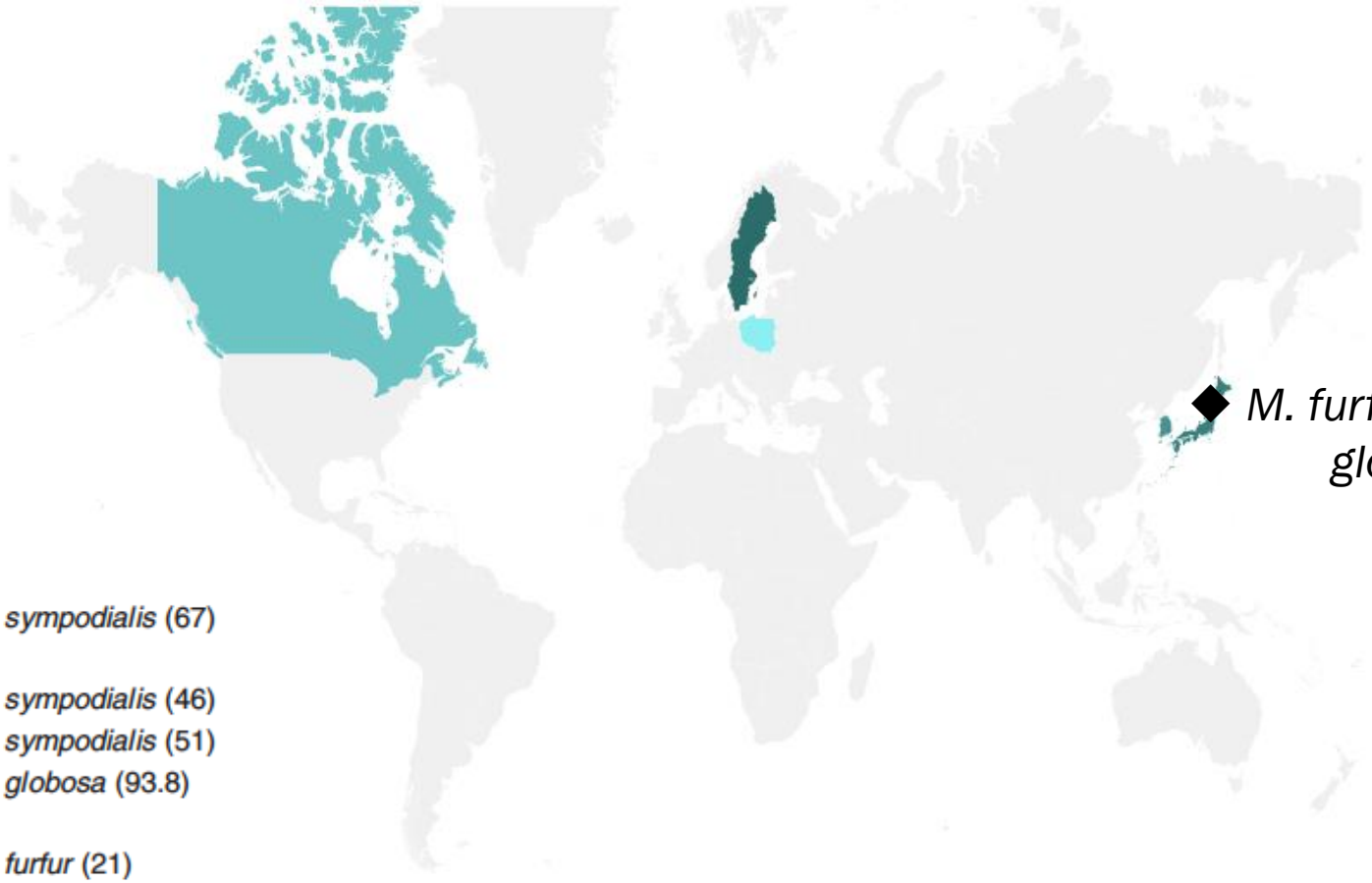
Spain	*M. globosa* (84)
Canada	*M. sympodialis* (62.7)
Japan	*M. globosa* (55)
Iran	*M. globosa* (53)
Tunisia	*M. globosa* (47)
India	*M. globosa* (51.8)
Spain	*M. globosa* (97)
Spain	*M. globosa* (90)
India	*M. globosa* (64)
Greece	*M. globosa* (77)
Japan	*M. globosa*, *M. restricta* (93.9)
B&H	*M. globosa* (63)
Tunisia	*M. globosa* (76.2)
India	*M. globosa* (50.3)
Italy	*M. globosa* (60.3)
China	M. globosa (95.8)
Turkey	*M. globosa* (65.1)
Canada	*M. sympodialis* (59.5)
Argentina	*M. sympodialis* (37.7)
Brazil	*M. sympodialis* (30)
Indonesia	*M. furfur* (42.9)



EPIDEMIOLOGIA

Malassezia spp. e dermatite atopica

(*Phrohic et al., Int J Dermatol. 2016*)



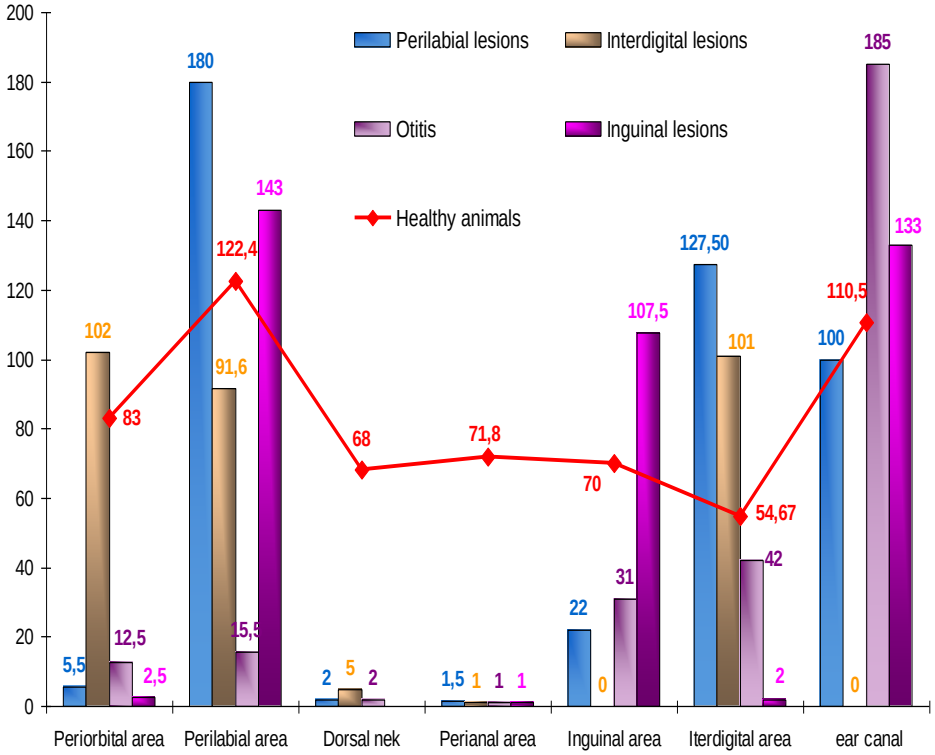
Poland	*M. sympodialis* (67)
Sweden	*M. sympodialis* (46)
Canada	*M. sympodialis* (51)
Japan	*M. globosa* (93.8)
Japan	*M. furfur* (21)
Japan	*M. globosa* (100)
South Korea	*M. sympodialis* (16.3)

EPIDEMIOLOGIA

- La carica del lieviti è maggiore nelle aree con lesioni rispetto a quello senza lesioni

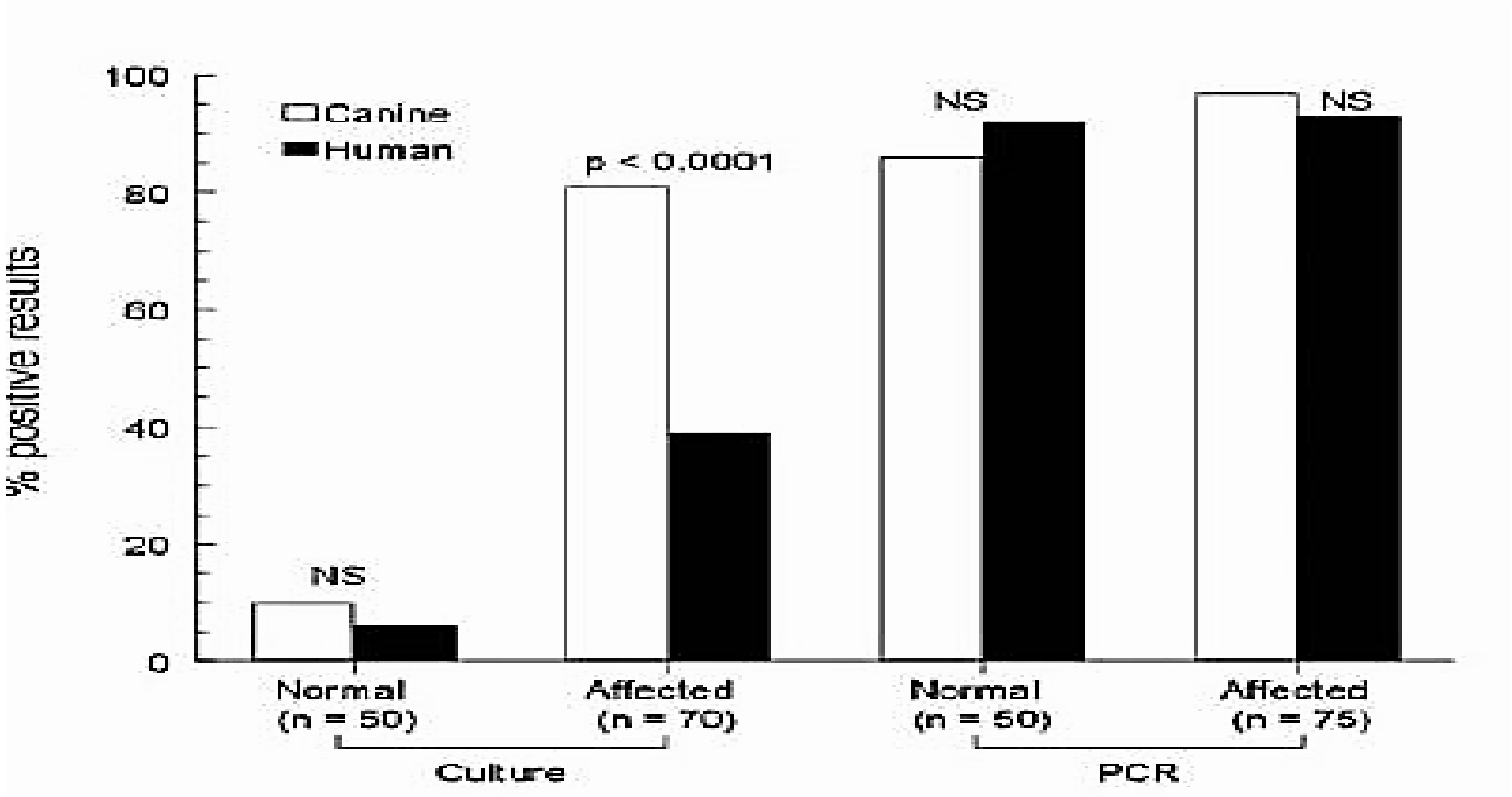
- La carica può essere maggiore anche in aree senza lesioni a causa del grattamento indotto dal prurito.

Densità di popolazione di M. pachydermatis nei cani



Cafarchia et al, J Vet Diagn Invest. 2005;17:316-22

EPIDEMIOLOGIA



Malassezia yeasts might be mechanically transferred from dogs to pet owners

Morris et al., Emerg Infect Dis. 2005 11(1):83-8

EPIDEMIOLOGIA

REFERENCES	SAMPLE	*M. pachydermatis* Prevalence (%)	ID METHOD
Guheo et al., 1987	Blood of hospitalized patients	12.5	Fungal culture / G-C content
Larocco et al., 1988	Blood of hospitalized patients	1.6	Fungal culture
Mickelsen et al., 1988	Blood of hospitalized patients	33	Fungal culture
Welbel et al., 1994	Blood of hospitalized patients	5	Fungal culture
van Belkum et al., 1994	Blood of hospitalized patients, incubators and dogs	25	Fungal culture/PCR Finger-printing
Chang et al., 1998	Blood of hospitalized patients, dogs, dogs owers	3.9 (patients) 31 (dogs) 11 (dog owners)	Fungal culture /PFGE
Chrysanthou et al., 2001	Blood of hospitalized patients	8	Fungal culture RAPD

PATOGENESI

I cambiamenti nei meccanismi chimici o immunologici della cute, possono modificare la composizione della parete cellulare della *Malassezia* o il metabolismo della Malassezia.

Fattori di virulenza

- Formazione di biofilm
- Composizione della parete cellulare
- Produzione di enzimi
- Produzione di metaboliti

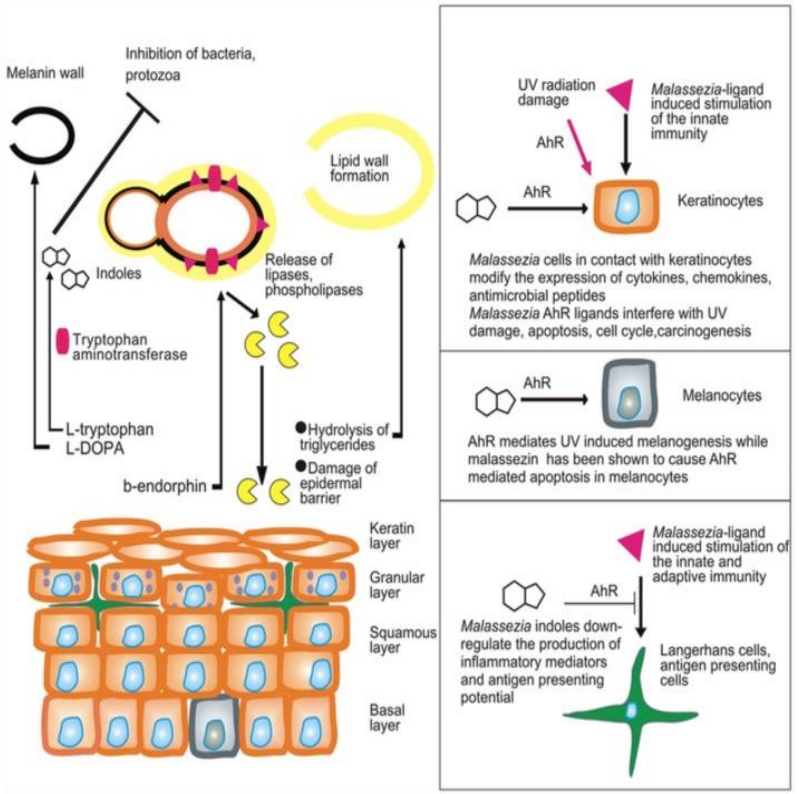


Fig. 1. Model showing the putative interactions of *Malassezia* yeasts with the skin. *Malassezia* yeasts take up nutrients as well as sebum lipids that are used to form the outer layer of the yeast or amino acids that are needed for the formation of melanin or the synthesis of AhR indolic ligands. In parallel they modify the expression of lipases and phospholipases under the action of β-endorphin. Cellular components (enzymes, proteins, glyceroglycolipids, and mannosyl fatty acids) are recognized by the innate and adaptive immune system and alter its function. AhR ligands potentially down-regulate immune stimulation, modify the function of epidermal cells, interfere with AhR-induced ultraviolet (UV) damage and melanogenesis, and probably inhibit antagonist microbes.
doi:10.1371/journal.ppat.1004523.g001

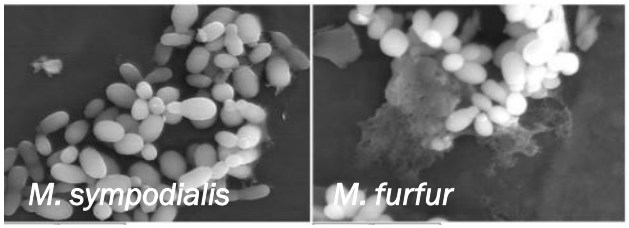
Velegraki et al., PLoS Pathog. 2015 8;11:e1004523

PATOGENESI

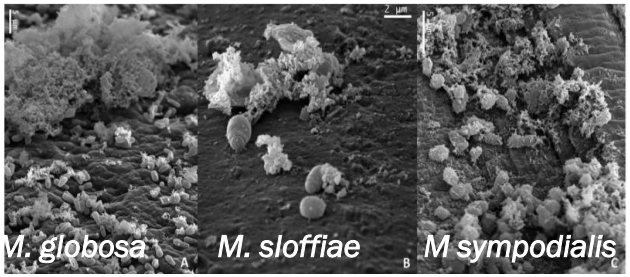
- *M. furfur, M. sympodialis, M. pachydermatis, M. sloffiae e M. globosa* sono in grado di formare biofilm

- La formazione del biofilm dipende dalla specie e dal ceppo: *M. furfur* produce maggiore ECM rispetto *a M sympodialis, M. sloffiae*

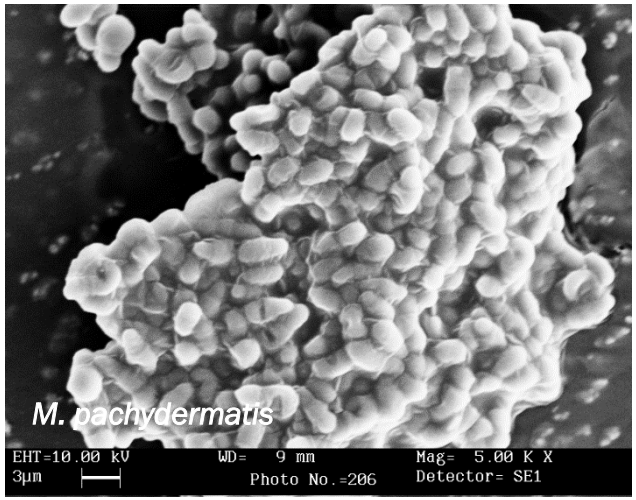
- Una maggiore produzione di biofilm è stata registrata nei ceppi di *Malassezia* da ospiti con lesioni cutanee



Pedrosa et al., Mycoses 2019



Angiolella et al., Med Myc. 2020



Figueredo et al., Vet Microbiol. 2012

PATOGENESI

La formazione del biofilm di *M. pachydermatis* è associata a resistenza antifungina

Table 2 Number of *Malassezia pachydermatis* isolates from dogs without (Group A), and with skin lesions (Group B) susceptible (S), susceptible dependent upon dose (SDD), and resistant (R) to ketoconazole (KTZ), itraconazole (ITZ), posaconazole (POS), terbinafine (TER), voriconazole (VOR), and fluconazole (FLZ). Categorical agreement among MICs of sessile and planktonic cells is reported.

	Isolates from dogs without skin lesion (Group A) = 31						Isolates from dogs with skin lesions (Group B) = 29						All isolates = 60						
	Sessile			Planktonic			Sessile			Planktonic			Sessile			Planktonic			
Antifungal agents	S	SDD	R	S	SDD	R	S	SDD	R	S	SDD	R	S	SDD	R	S	SDD	R	CA (%)
KTZ	0	0	31	27	2	2	1	1	27	25	4	0	1	0	59	52	3	5	8.3
ITZ	0	0	31	31	0	0	3	0	26	26	3	0	3	0	57	57	3	0	1.7
POS	0	0	31	29	0	2	2	2	25	24	4	1	2	2	56	53	5	2	5
TER	0	1	30	21	10	0	0	1	28	23	6	0	1	1	58	33	27	0	1.7
VOR	2	1	28	27	4	0	3	0	26	25	3	1	5	1	54	52	7	1	6.7
FLZ	2	1	28	18	12	1	2	2	25	22	5	2	4	2	54	40	16	4	10

S = MIC sample ≤ MIC50, SDD = MIC50 < MIC sample ≤ MIC90, and R = MIC sample > MIC90. CA, Categorical Agreement – Percentage of isolates classified in the same category (S, SDD, R) using sessile and planktonic cells.

Figueredo et al., Med Mycol. 2013

La formazione del biofilm delle cellule di *M. furfur* e *M. pachydermatis* è ben correlata con l'idrofobicità, l'aderenza e la produzione di fosfolipasi

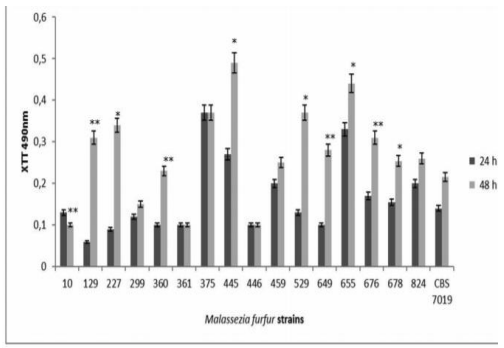


Table 2. Hydrophobicity and adherence in *M. furfur* clinical isolates.

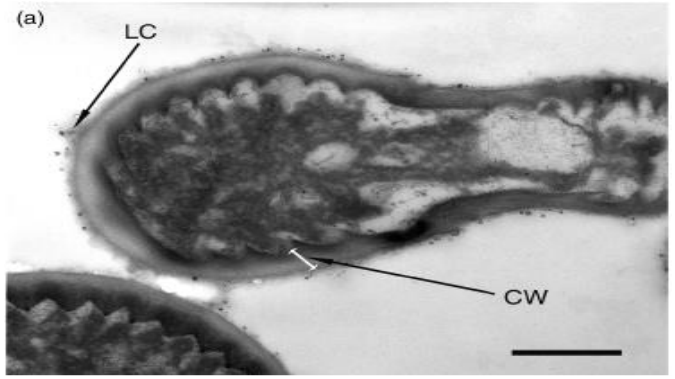
Strains	% Hydrophobicity	% Adherence
IMR-M 010	81.9 ± 5.5	76.7 ± 5.7
IMR-M 129	24.8 ± 1.1	45.0 ± 7.0
IMR-M 227	49.1 ± 5.2	58.4 ± 2.3
IMR-M 299	1 ± 0.1	49.0 ± 6.5
IMR-M 360	39.4 ± 4.8	40.8 ± 0.3
IMR-M 361	47.9 ± 2.2	40.7 ± 6.4
IMR-M 375	50.1 ± 5.6	51.6 ± 6.2
IMR-M 445	33.1 ± 2.5	78.7 ± 2.3
IMR-M 446	70.2 ± 20.7	57.9 ± 19.9
IMR-M 459	46.8 ± 8.9	54.9 ± 8.7
IMR-M 529	53.5 ± 0.1	48.6 ± 9.8
IMR-M 649	76.6 ± 27.4	39.8 ± 0.28
IMR-M 655	83.3 ± 14.6	46.4 ± 3.4
IMR-M 676	58.6 ± 11.3	38.8 ± 3.2
IMR-M 678	60.3 ± 8.5	30.7 ± 3.3
IMR-M 824	57.6 ± 3.2	29.2 ± 1.1
CBS 7019	41.6 ± 3.8	64.5 ± 4.5

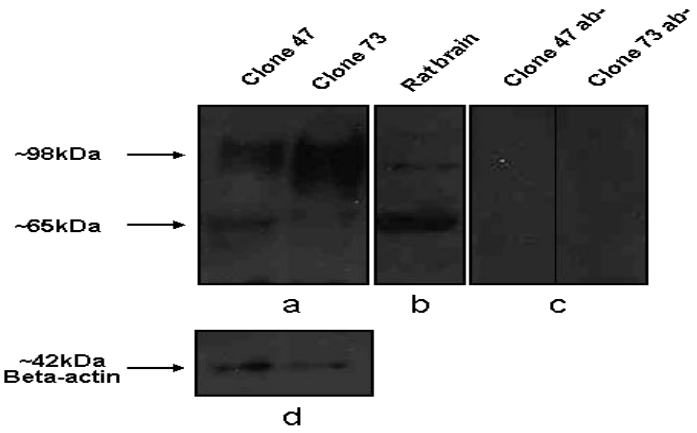
Percentage of plastic adherent cells and cell surface hydrophobicity values measured with a two phase system. Mean values of % hydrophobicity and adherence ± SD of three independent experiments.

Angiolella et al., *Med Mycol. 2018*

PATOGENESI

- ZIMOGENO: attivazione del complemento per via alternativa provocando una risposta infiammatoria.
- STRATO LIPIDICO: modula la produzione di citochine da cheratinociti.
- PRESENZA DI RECETTORI MOR-OPPIOIDI: ruolo nel modulare la produzione di fosfolipasi.

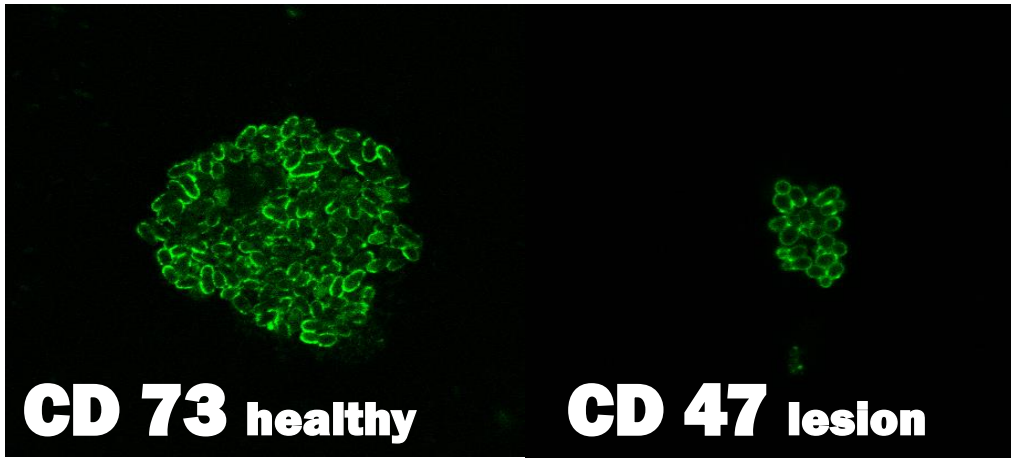




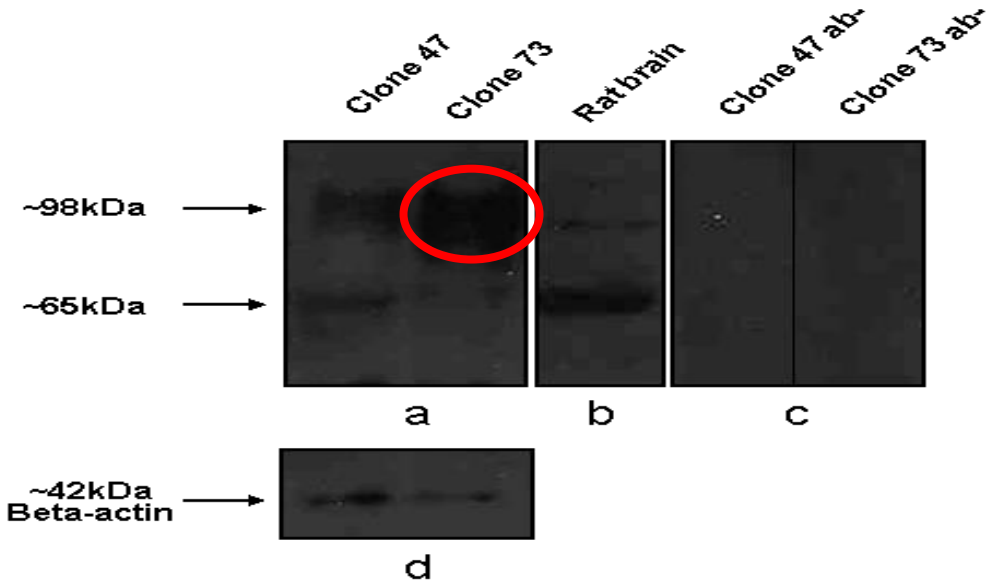
Thomas et al, FEMS Immunol Med Microbiol.2008;54:203-14
Cafarchia et al, Med. Mycol. 2010;48:73-78

PATOGENESI

Localizzazione immunocitochimica dei MOR con microscopia laser confocale



Analisi Western blot dei MOR delle cellule di *Malassezia* CD47 e CD73.



Cafarchia et al, Med. Mycol. 2010;48:73-78

PATOGENESI

Dermatology

Dermatology 2005;210:91–99
DOI: 10.1159/000082563

Changes of Epidermal Mu-Opiate Receptor Expression and Nerve Endings in Chronic Atopic Dermatitis

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Key Words
μ-Opiate receptor internalization · Epidermis · Atopic dermatitis · Peripheral nerve endings · Pruritus · Itch

Abstract
There is increasing evidence that neuropeptides such as a substance P, neurotrophins or β-endorphin, an endogenous agonist for μ-opioid receptor, are involved in the pathogenesis of atopic dermatitis in which mental stress and scratching deteriorate the disease. μ-Opioid receptor, a G-protein-coupled receptor, can be downregulated and internalized by agonists and other factors in vitro. In this study, we investigated the regulation of μ-opioid receptor and nerve endings in atopic dermatitis patients. Skin biopsies from atopic dermatitis patients revealed a significant downregulation of μ-opiate receptor expression in epidermis of atopic dermatitis. Permeabilization of the skin showed that the receptor in keratinocytes from atopic dermatitis is internalized. The mRNA expression pattern of the μ-opiate receptor is different in epidermis taken from patients with chronic atopic dermatitis compared to normal skin. In atopic dermatitis, the mRNA is concentrated in the subcorneal layers of the epidermis and in normal skin in the suprabasal layers. Staining of the nerve endings using protein gene product 9.5 shows a different pattern of epidermal nerve endings in normal skin compared to atopic dermatitis. In normal skin, the epidermal nerve endings are rather thick. However, in atopic dermatitis, the epidermal nerve endings are thin and run straight through the epidermis. Based on these observations and combining the 'intensity' and 'pattern' hypothesis, we propose a new theory especially for histamine-unrelated, peripheral induction of chronic pruritus. We suggest that 'itch' is elicited in the epidermal unmyelinated nerve C-fibers and 'pain' in the dermal unmyelinated nerve fibers. The downregulation of the opioid receptor in the epidermis contributes to the chronic itching. We call this new hypothesis the 'layer hypothesis'.

Introduction

The μ-Opiate receptor is expressed and its endogenous ligand β-endorphin is synthesized in cells of the immune system [1], keratinocytes and peripheral nerve endings [2]. We have previously demonstrated that human epidermal keratinocytes express the μ-opiate receptor at both

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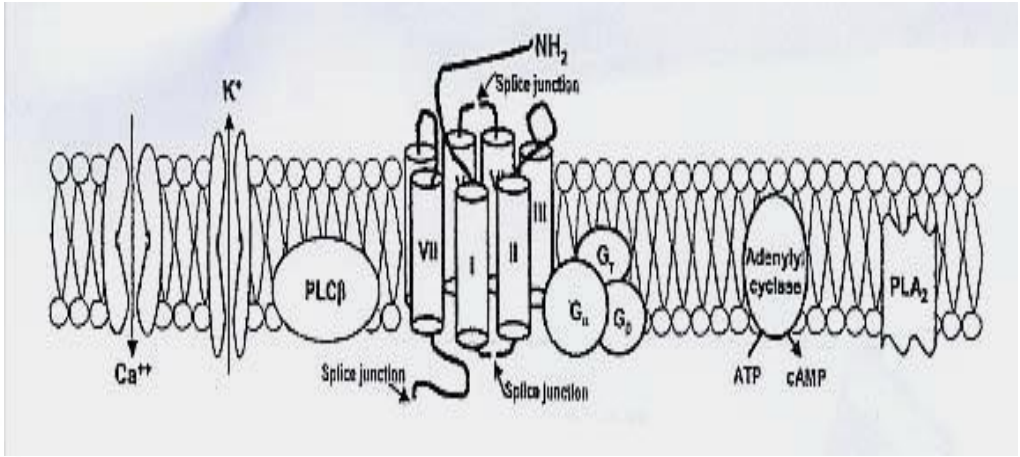
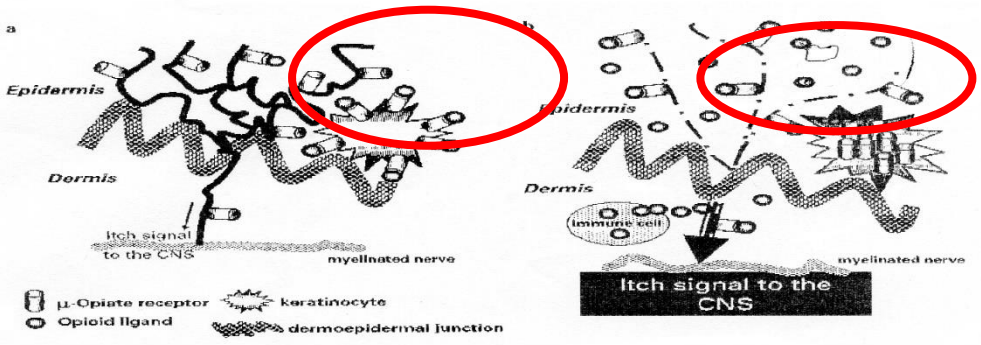




Pan YX. DNA Cell Biol 2005; 24: 736-750

PATOGENESI

Table 1 Effects of different β-endorphin concentrations on number and on phospholipase activity (expressed as the mean Pz value) of *Malassezia* strains from lesional skin of dogs with dermatitis localized in one anatomical site (Group A) and healthy skin sites of dogs with localized skin lesion (Group B) and healthy dogs (Group C) that yielded phospholipase activity. Standard deviation (in brackets) is also reported

Isolates	Sampling sites	β-endorphin concentration (pM)											
		Control		600		300		60		6		0.6	
		Pos/Tot	Pz (SD)	Pos/Tot	Pz (SD)	Pos/Tot	Pz (SD)	Pos/Tot	Pz (SD)	Pos/Tot	Pz (SD)	Pos/Tot	Pz (SD)
Group A	Lesional skin of dogs with dermatitis localized in one anatomical site	48/48[a]	0.72 (0.12)[m]	48/48[o]	0.62 (0.12)[mno]	42/48[o]	0.66 (0.12)[no]	42/48[o]	0.67 (0.12)	28/48[abcdef]	0.75 (0.15)[n]	28/48[abcdef]	0.72 (0.10)[l]
Group B	Healthy skin sites of dogs with localized skin lesion	0/72[efghi]	1 (0.00)[pqrst]	26/72[e]	0.68 (0.12)[p]	24/72[f]	0.74 (0.11)[q]	18/72[gl]	0.76 (0.09)[r]	12/72[h]	0.72 (0.01)[s]	12/72[i]	0.75 (0.06)[t]
Group C	Skin sites of healthy dogs	0/24[l]	1[u]	6/24[l]	0.62 (0.16)[u]	0	1	0	1	0	1	0	1

[a–l] Chi-square test: statistically significant differences ($p < 0.05$) are marked with the same letters.
[m–q] ANOVA (Tukey post-hoc test): statistically significant differences ($p < 0.01$) were marked with the same letters.

β-endorfina può svolgere un ruolo importante nell'indurre la differenziazione cellulare di *M. pachydermatis* verso la produzione di fosfolipasi

Cafarchia et al, Med. Mycol. 2010;48:73-78

PATOGENESI

- **FOSFOLIPASI**: svolge un ruolo nella comparsa delle lesioni cutanee nel cane
- **LIPASI:** utile per il metabolismo lipidico e per l'inibizione dei microrganismi competitivi della cute
- **PROTEASI**: utile per il metabolismo ed è un mediatore del prurito

TABLE 1. Dogs presenting at least one isolate with phospolipase activity (P_Z) and numbers and percentages of *M. pachydermatis* isolates from different sites

Isolate group[a]	No. of dogs with positive isolates/ no. studied (%)[b]	No. of positive isolates/no. studied (%)[b]	P_Z range[c]	P_Z value, mean (SD)[b,c]
A	33/33 (100)a	62/66 (93.9)b	0.46–1	0.72 (0.13)c
B	28/33 (84.8)a	51/122 (41.8)b	0.48–1	0.89 (0.15)c
C	5/11 (45.5)a	7/66 (10.6)b	0.43–1	0.97 (0.10)c
Total		120 (47.2)		

[a] Group A, isolates collected directly from lesional skin; group B, isolates collected from healthy skin sites of the same dog (group A) with localized lesions; group C = isolates collected from skin sites of healthy dogs.

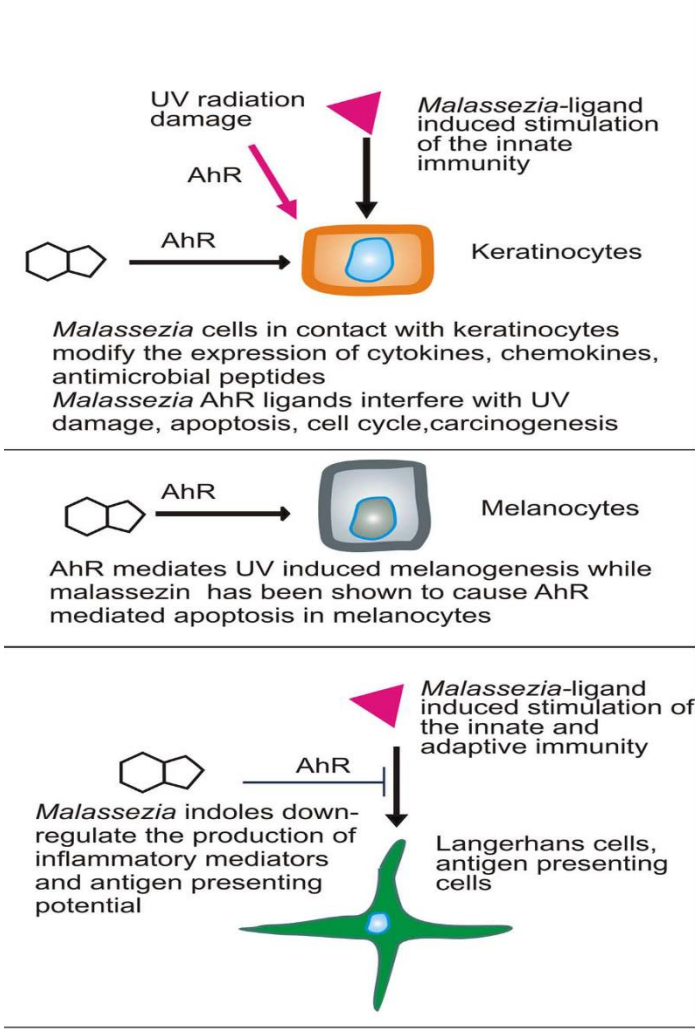
[b] a and b, statistical differences ($P < 0.05$) using chi-square test; c, statistical differences ($P < 0.05$) using Student's t test; positive, phospholipase activity detected.

[c] P_Z, production of phospholipase expressed as a ratio of colony diameter to total diameter of the colonies and zone of precipitation. SD, standard deviation.

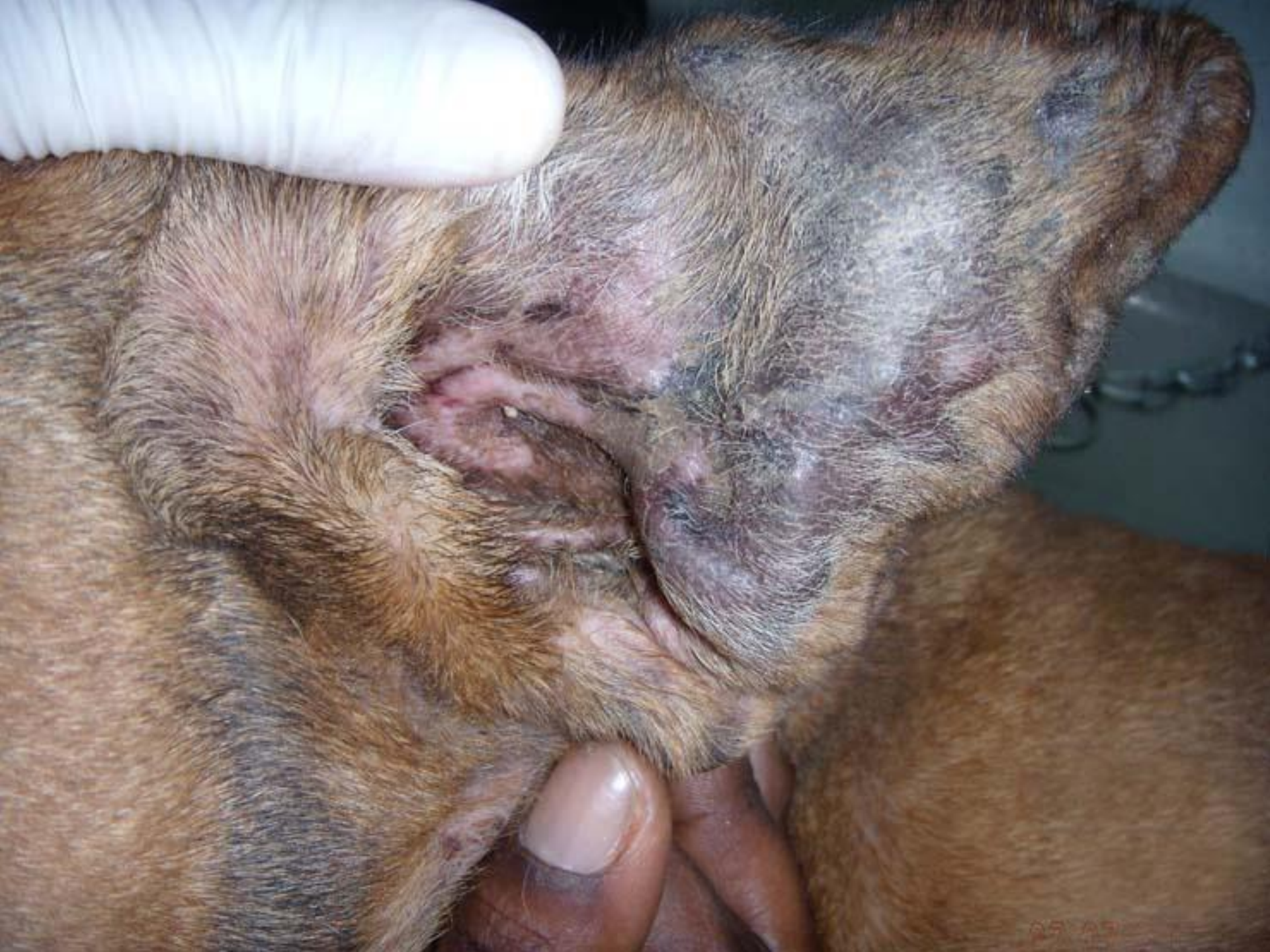
Mancianti et al., 2001, Mycopathologia 149: 131-5
Coutinho & Paula 2000, Med Mycol 38: 73-6
Cafarchia & Otranto, J Clin Microbiol. 2004;42:4868-9.

PATOGENESI

- L ’ INDOLO SI LEGA AGLI ARYL HYDROCARBON RECEPTOR (AHR)
- **Malassezin, Indirubin:** apoptosi dei melanociti o altre cellule.
- **Indole [3,2-b] carbazole (ICZ)**: Aumento del livello di espressione del BCRP mRNA.
- **Pityriarubins**: attività inibitoria contro i granulociti

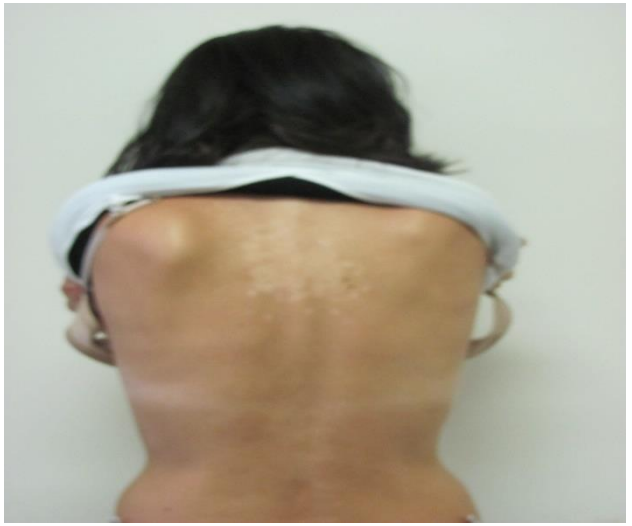


Velegraki et al., PLoS Pathog. 2015 8;11:e1004523

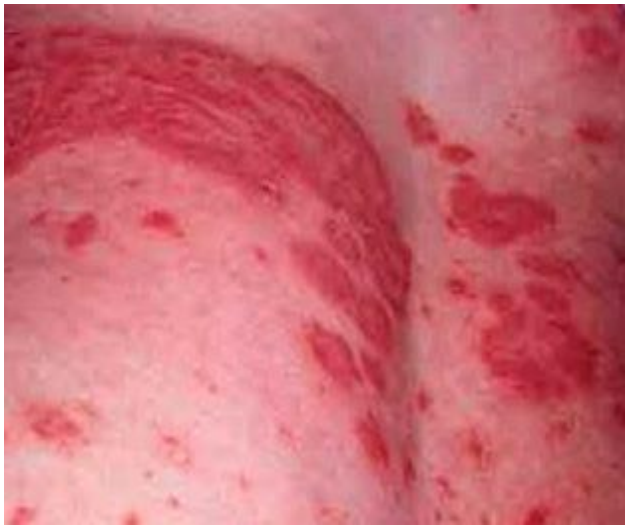


SINTOMATOLOGIA

Dermatite senza infiammazione (i.e., *Pityriasis versicolor*)



Dermatite con infiammazione (i.e., dermatite seborroica, dermatite atopica, follicolite e psoriasi)



SINTOMATOLOGIA

- Ventilazione meccanica
- Durata della permanenza in ospedale
- Cateterizzazione venosa centrale
- Terapia antibiotica/antifungina

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2014, 00, 1–6
doi: 10.1093/mmy/myt004
Advance Access Publication Date: 0 0000
Original Article

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Bloodstream infections by *Malassezia* and *Candida* species in critical care patients

Roberta Iatta[1,2,*], Claudia Cafarchia[1], Teresa Cuna[2], Osvaldo Montagna[3], Nicola Laforgia[2], Ottavio Gentile[4], Antonino Rizzo[4], Teun Boekhout[5,6,7], Domenico Otranto[1] and Maria Teresa Montagna[2]

[1]Dipartimento di Medicina Veterinaria, Università degli Studi "Aldo Moro," Valenzano, [2]Dipartimento di Scienze Biomediche e Oncologia Umana, Università degli Studi "Aldo Moro, [3]Reparto di Neonatologia e Terapia Intensiva Neonatale, Azienda Ospedaliero-Universitaria Policlinico, [4]Reparto di Chirurgia Pediatrica, Azienda Ospedaliero-Universitaria Policlinico, Bari, Italy, [5]Centraalbureau voor Schimmelcultures Fungal Biodiversity Centre (CBS-KNAW), [6]Department of Internal Medicine and Infectious Diseases, University Medical Center, Utrecht, the Netherlands and [7]Department of Dermatology, Shanghai Key Laboratory of Molecular Medical Mycology, Institute of Dermatology and Medical Mycology, Changzheng Hospital, Second Military Medical University, Shanghai, People's Republic of China.

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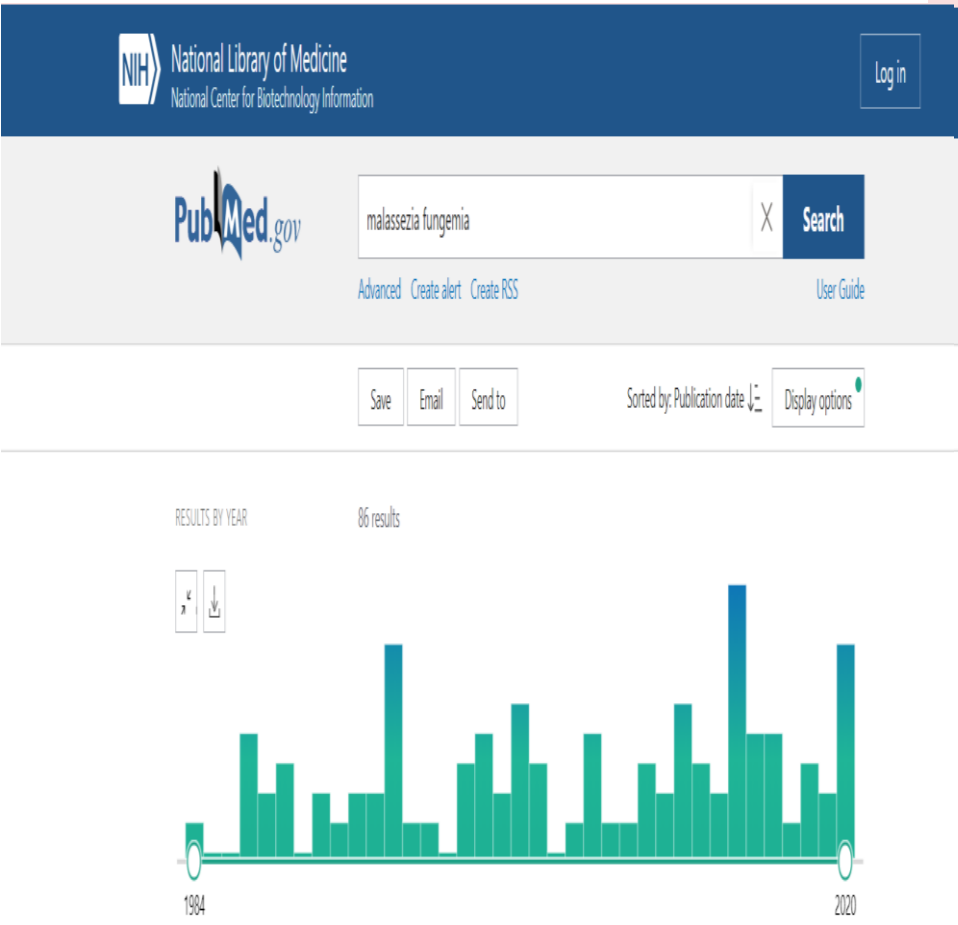
Received 6 May 2013; Revised 20 September 2013; Accepted 29 October 2013

MALASSEZIA E SANITA' PUBBLICA



MALASSEZIA E SANITA' PUBBLICA

OBSERVATION

Granulomatous Skin Infection Caused by *Malassezia pachydermatis* in a Dog Owner

Yi-Ming Fan, MD; Wen-Ming Huang; Shun-Fan Li; Guo-Feng Wu, MM; Kuan Lai, MM; Rong-Yi Chen, MM

Background: *Malassezia pachydermatis* is part of the normal cutaneous microflora of dogs and many other mammals. *M pachydermatis* has not yet been reported as an agent that causes skin infection in humans, although it has been found to cause fungemia and other nosocomial infections in preterm newborns and immunocompromised adults.

Observations: *Malassezia pachydermatis* was isolated from the facial granuloma of a healthy woman and her dog's skin scrapings and cerumen. The yeast identity was established by standard methods and scanning electron microscopy. A skin biopsy specimen showed chronic inflammatory granuloma, numerous purple-red round or ovoid spores in the superficial necrotic tissue, and sparse red spores in the dermis. The skin lesions healed after oral fluconazole and cryotherapy.

Conclusions: Definite diagnosis of *M pachydermatis*–induced skin infection principally depends on the results of fungal culture and histologic examination, and the combination of oral fluconazole and adjunctive cryotherapy seems to be an effective therapeutic regimen.

Arch Dermatol. 2006;142:1181-1184

THE GENUS MALASSEZIA, comprising 10 distinct species, is principally recovered from the skin of mammals and birds but seldom from the environment.[1,2] *Malassezia pachydermatis*, *Malassezia furfur*, *Malassezia globosa*, and *Malassezia symbodialis* are generally considered to be the main species associated with clinical diseases.[1] *Malassezia pachydermatis*, the only non–lipid-dependent species of the genus *Malassezia*, was first isolated from the scales of an Indian rhinoceros (*Rhinoceros unicornis*) with exfoliative dermatitis by F. D. Weidman in 1925 and named *Pityosporum pachydermatis*. With the synonymy of *Malassezia* (proposed by H. Baillon in 1889) and *Pityosporum* (proposed by R. Sabouraud in 1904) being increasingly recognized and accepted in 1984 with anteriority for the generic *Malassezia*, *P pachydermatis* was then adopted as *M pachydermatis*, a name first introduced by C. W. Dodge in 1935 and accepted by M. A. Gordon in 1976.[2] The importance of *M pachydermatis* has been recognized in both veterinary and human medicine.[2] Skin colonization by *M pachydermatis* is frequent in wild and domestic carnivores, including dogs, cats, bears, ferrets, and foxes; less frequent in rhinoceros, pigs, primates, pinnipeds, horses, and birds; and undetected in rodents and lagomorphs.[1,2] Human skin is commonly colonized by lipid-dependent *Malassezia* yeasts but rarely by *M pachydermatis*.[3] *Malassezia pachydermatis* has not yet been reported as an agent that causes skin infection, although it has been found to cause fungemia and other nosocomial infections in preterm newborns and immunocompromised adults.[3-6,7] We isolated a strain of *M pachydermatis* from an immunocompetent woman with facial granuloma in April 2004. To our knowledge, this is the first report of *M pachydermatis*–induced skin infection in humans.

REPORT OF A CASE

A 46-year-old woman presented with an asymptomatic papule on her face in January 2004. The lesion enlarged gradually and appeared erosive and exudative after self-treatment with topical applica-

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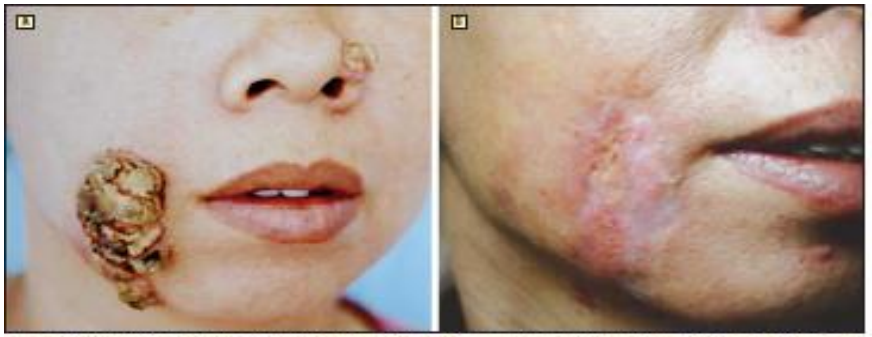
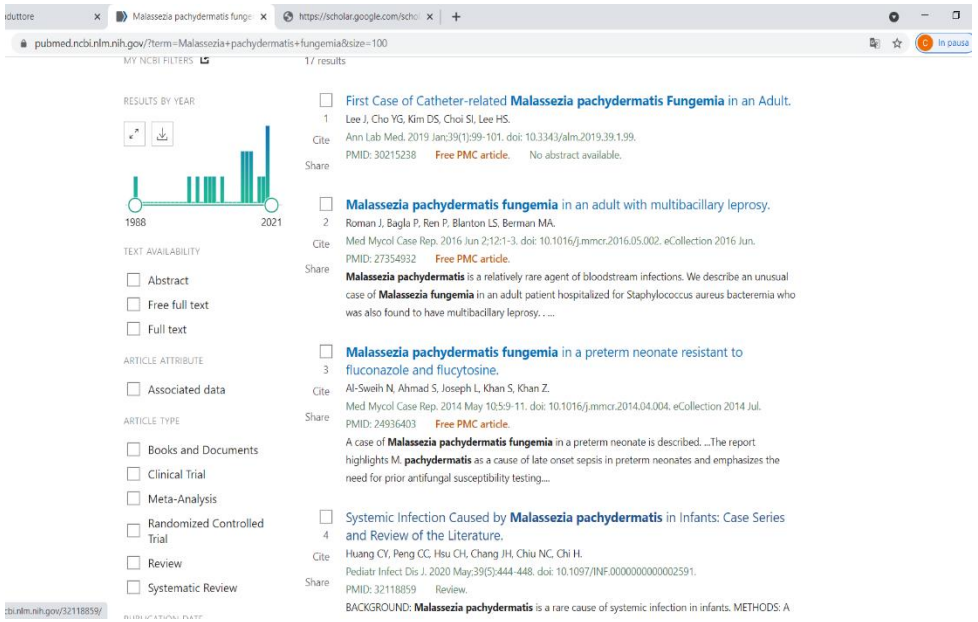


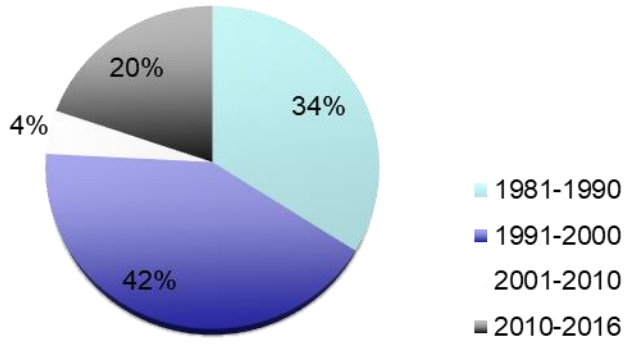
Figure 1. Patient before and after treatment. A, A verrucous plaque on the right side of the face and a hemispheroid nodule on the left ala nasi. B, After treatment, hypopigmented scar on the right side of the face.



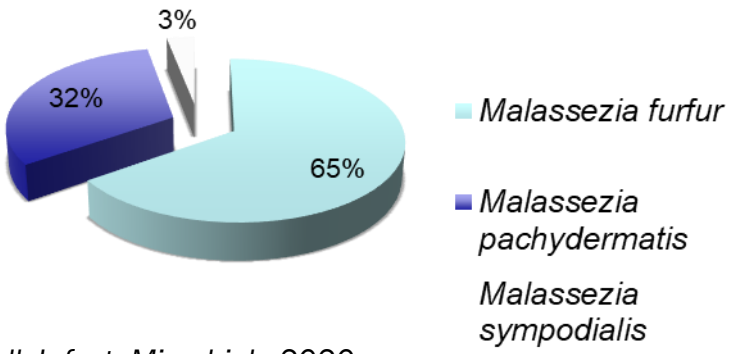
MALASSEZIA FUNGEMIA

- Il primo caso nel 1981 (Redline et al. 1981);
- Totale di case report = 118 Case report
- Focolai di infezioni invasive da Malassezia (1991-2000);
- Solo tre studi di sorveglianza;
- *M. furfur* seguito da ***M. pachydermatis*** e *M. sympodialis.*

Case reports *Malassezia* fungemia 1981-2020



Malassezia species in fungemia 1981-2020



Rhimi et al., Front. Cell. Infect. Microbiol., 2020

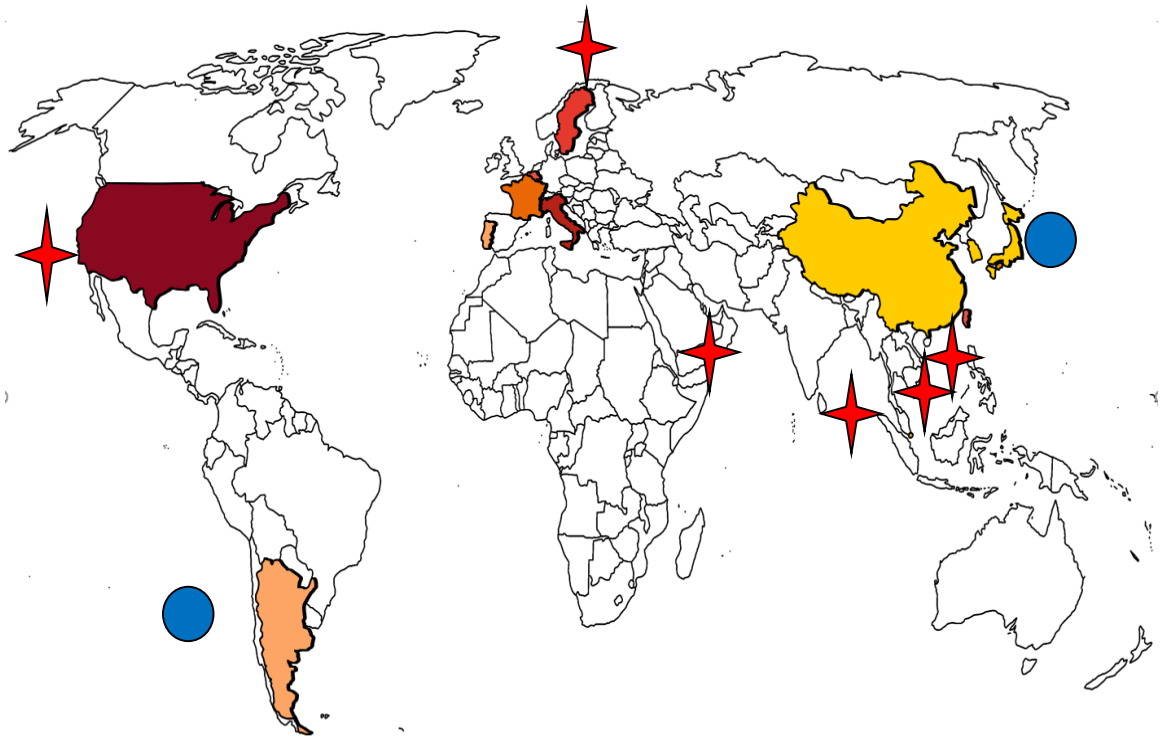
MALASSEZIA FUNGEMIA

Malassezia fungemia identificata da 17 paesi

La maggior parte dei casi sono stati segnalati in Italia e negli Stati Uniti nei neonati pretermine

Casi di M. pachydermatis nei paesi orientali.

M. sympodialis fungemia in anziani post-gastrectomia, post-appendicectomia e uso corticosteroidi



Country	USA	Italy	Sweden	Belgium	Taiwan	France	Portugal	Argentina	Japan	Singapore	China	South Korea
Fungemia cases	66	16	8	6	5	4	3	3	1	1	1	1

M. furfur

M. pachydermatis

M. sympodialis

Rhimi et al., Front. Cell. Infect. Microbiol., 2020

MALASSEZIA FUNGEMIA

July 2011- July 2012:

290 neonati and 17 pediatrici

- *Malassezia furfur:* 8/307 (2.6%)
- *Candida* spp.: 4/307 (1.3%)

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Bloodstream infections by *Malassezia* and *Candida* species in critical care patients

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Received 6 May 2013; Revised 20 September 2013; Accepted 29 October 2013

Malassezia BSIs è sottostimata!!!!!

MALASSEZIA FUNGEMIA

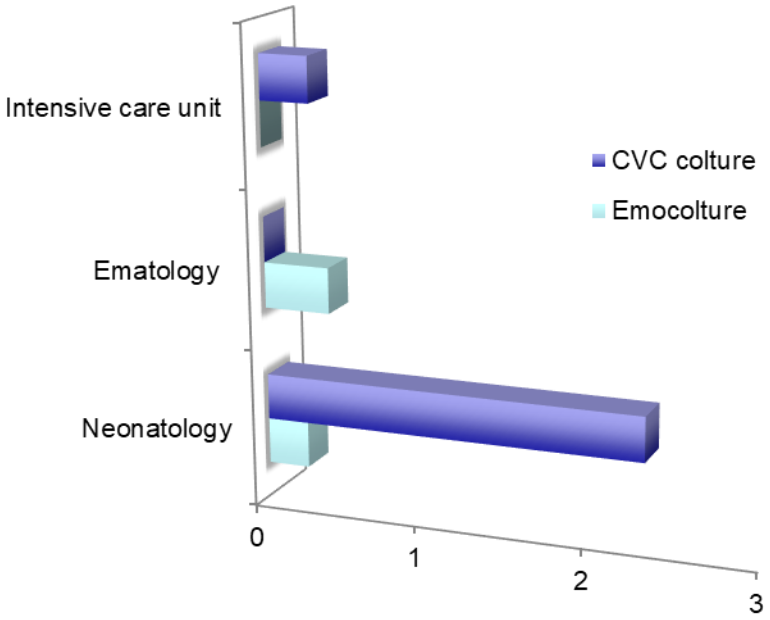
Studio di sorveglianza

Gennaio 2016-gennaio 2017

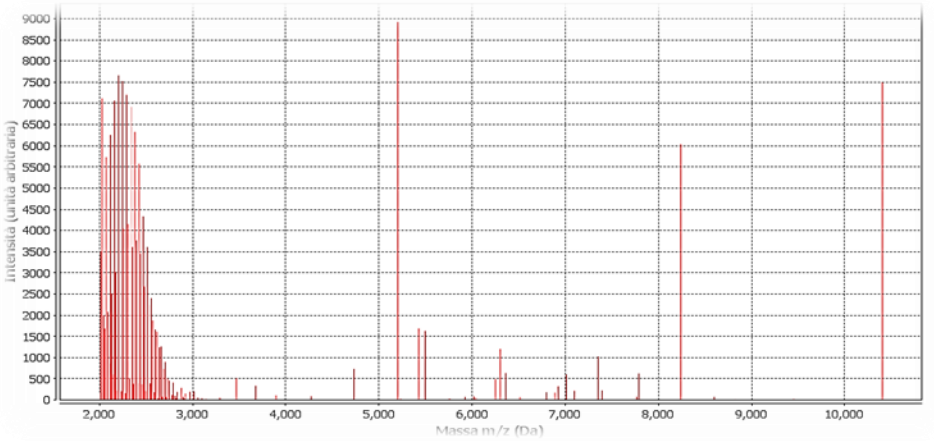
M. furfur: 12/964 (1,25%):

UTIN: 10/392 (2,5%);

Unità di terapia intensiva: 1/250 (0,4%);
Unità di ematologia: 1/322 (0,3%).



Rilevanza di questi lieviti nella fungemia mediata da cateteri



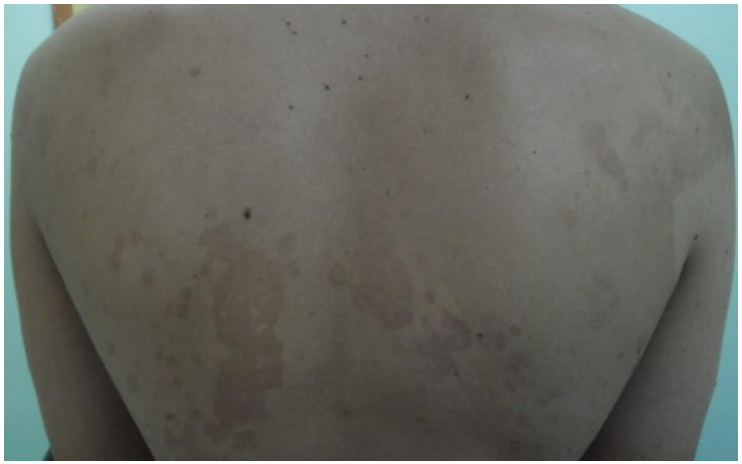
Cafarchia et al., Preliminary data, 2017

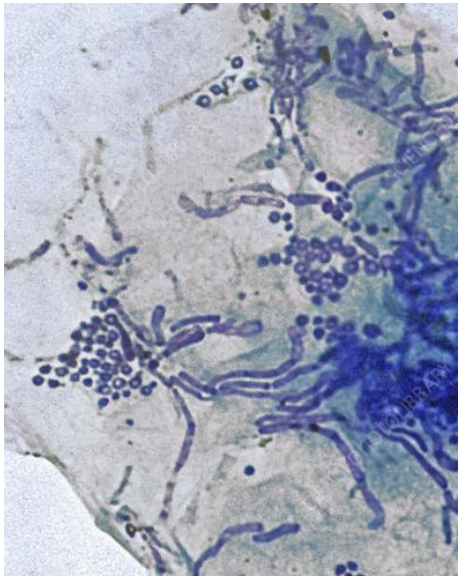
MALASSEZIA E DIAGNOSI

Isolamento e numerazione di Malassezia

La microscopia dei campioni di tampone è utile per diagnosticare dermatiti animali e umane

È necessaria una diagnosi eziologica più accurata nei pazienti ad alto rischio utilizzando terreni di coltura integrati con lipidi nell'attuale routine micologica.





MALASSEZIA FUNGEMIA : DIAGNOSI

Le caratteristiche cliniche, i marker di laboratorio, le strategie di gestione del paziente e gli esiti nella fungemia da Candida e Malassezia non differiscono;

La fungemia da *Malassezia* compare prima della candidemia;

La durata della fungemia da *Malassezia* è maggiore della candidemia;

Incubatrice, teli e cute dell ospite dell'operatore rappresentano le fonti di infezione da *Malassezia.*

Clinical features of patients with fungemia

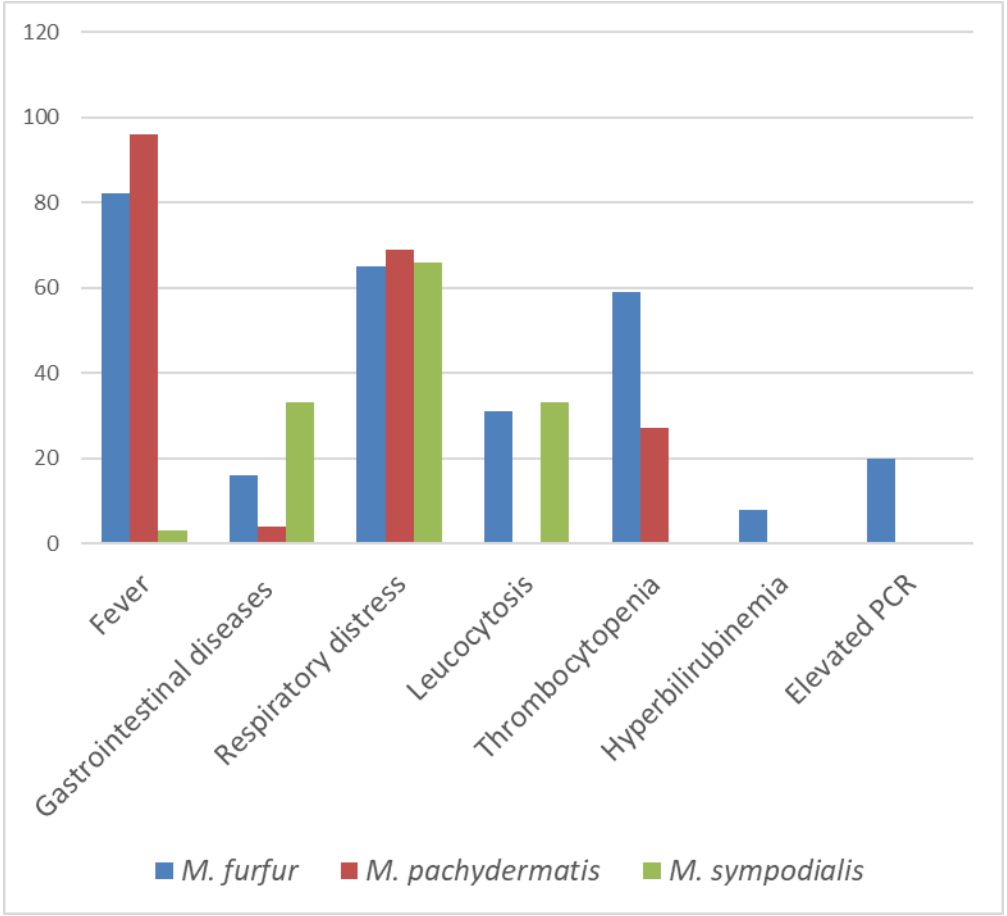
	M. furfur	*Candida* spp.
Ward	6 NICU; 2 pediatrics	4 NICU
Underlying disease	4 preterms, 1 birth asphyxia, 3 surgery	3 preterms, 1 surgery
CRP mean value ± sd	29 ± 3.0 mg/l	33 ± 5.1 mg/l
Antifungal prophylaxis	3 pts with fluconazole 3 mg/kg/72h	2 pts with fluconazole 3 mg/kg/72h
Fungemia onset (d ± sd)	26 ± 16.3	42 ± 53.3
CVC removal (d ± sd)	11 ± 8.2	3 ± 1.9
Treatment with l-AMB 5mg/kg/d	14 ± 6.0	13 ±1.9
Fungemia duration (d ± sd)	16 ± 16.3	6 ± 1.7
Enviromental and Human samples	incubator, sheets patients and mother skin	none

Rhimi et al., Front. Cell. Infect. Microbiol., 2020

MALASSEZIA FUNGEMIA: DIAGNOSI

Febbre, malattie respiratorie, trobocitopenia e PCR elevata per fungemia da *M. furfur* e *M. pachydermatis*

Malattie gastrointestinali e respiratorie per fungemia da *M. sympodialis*



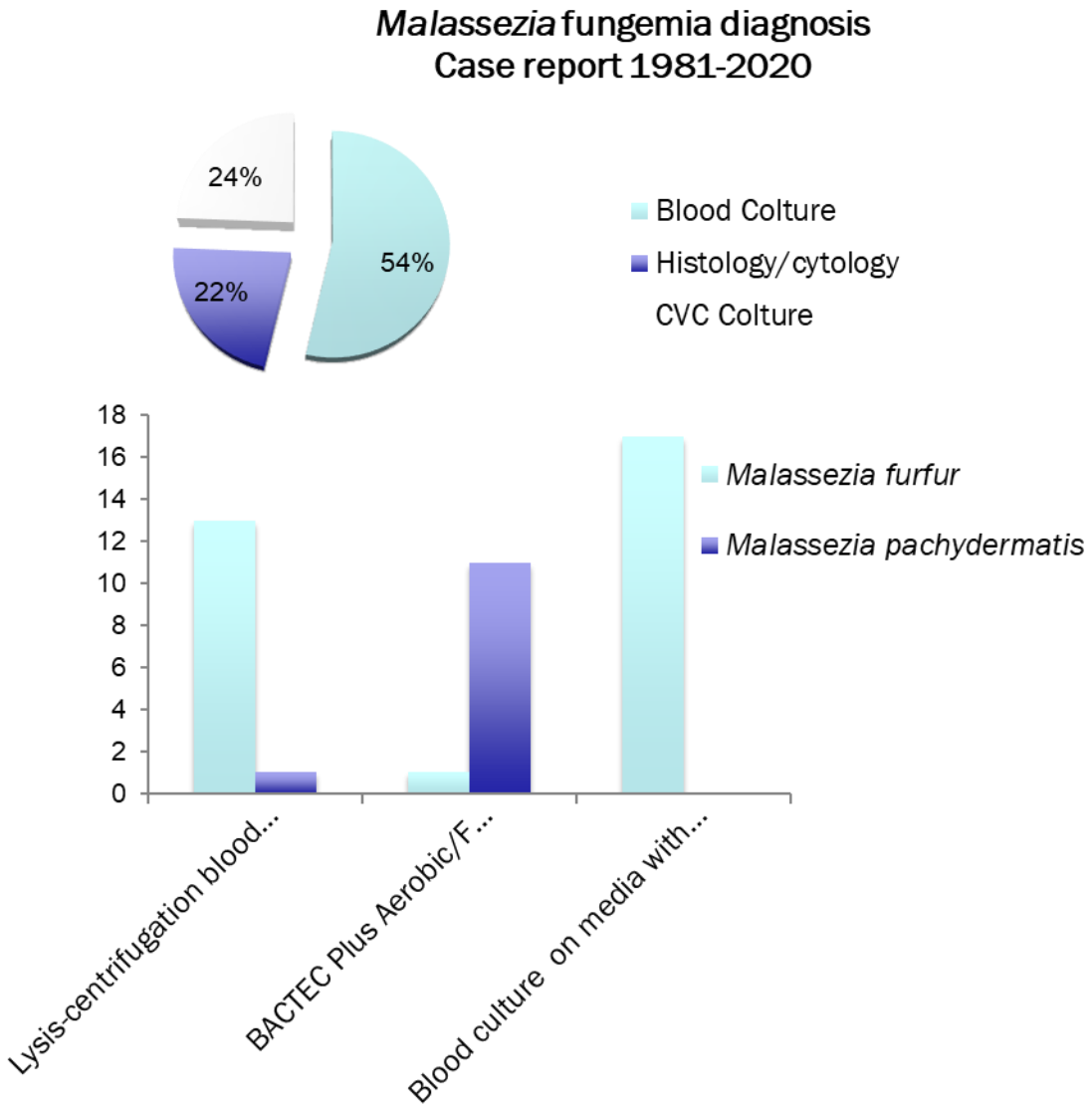
Rhimi et al., Front. Cell. Infect. Microbiol., 2020

MALASSEZIA FUNGEMIA E DIAGNOSI

I lieviti sono stati isolati mediante coltura da sangue o CVC direttamente su terreni arricchiti con lipidi

I sistemi di emocoltura automatizzati non sono utili per rilevare *M. furfur* ma solo *M. pachydermatis*

Su 12 casi di fungemia da Malassezia, solo 1 fungemia da *M. furfur* è stata rilevata mediante emocoltura automatizzata, ma il lievito non è stato identificato molecolarmente.

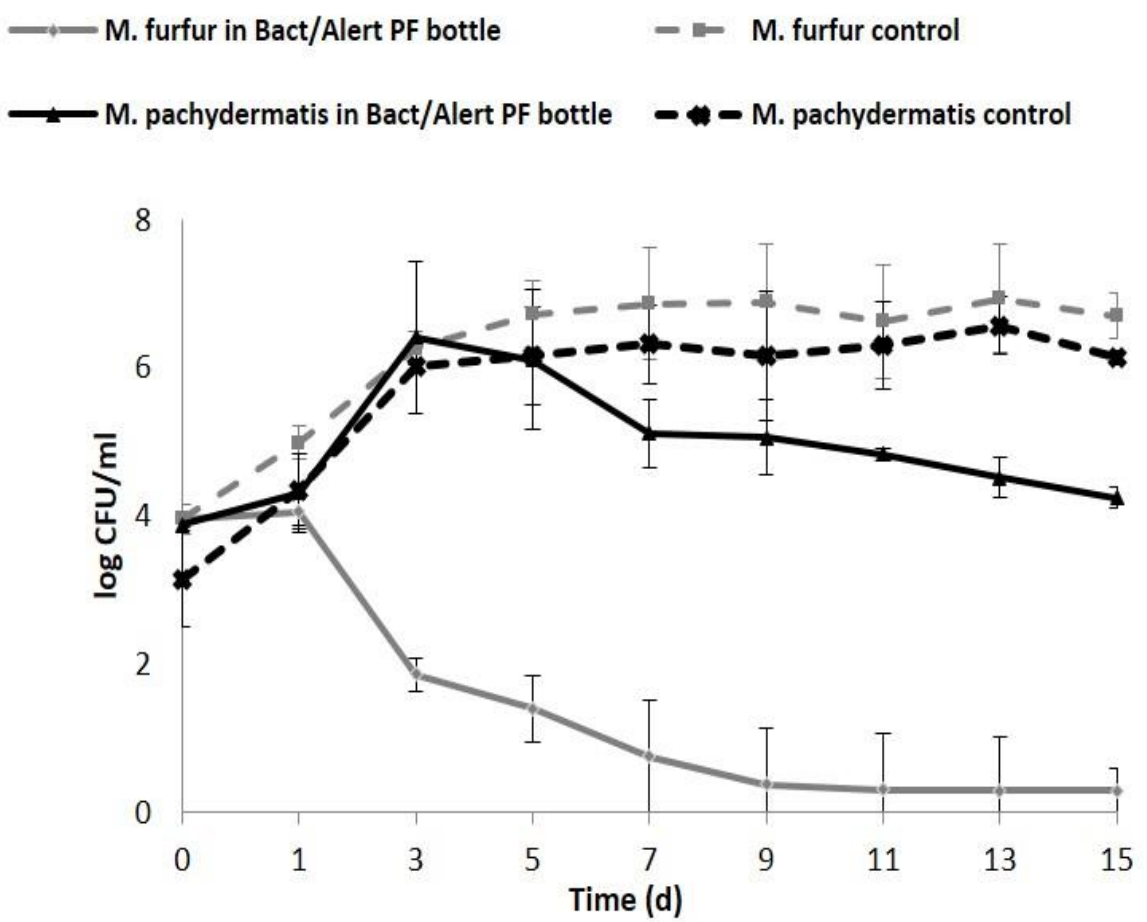


Rhimi et al., Front. Cell. Infect. Microbiol., 2020

MALASSEZIA FUNGEMIA E DIAGNOSI

Brodo Dixon: La carica di *M. furfur* e *M. pachydermatis* aumenta durante il periodo di incubazione raggiungendo la fase stazionaria dopo 3 giorni.

BacT/Alert PF bottles: La carica di *M. furfur* diminusce durante il periodo di incubazione mentre quella di *M. pachydermatis* aumenta.



Iatta et al., Medical Mycology 2017

MALASSEZIA FUNGEMIA E DIAGNOSI

Campioni di sangue e campioni CVC dello stesso paziente

Campioni di sangue raccolti da provette per centrifugazione di lisi (Gruppo I) e da flaconi BacT / Alert (Gruppo II)

Solo un campione di sangue del sistema automatizzato è risultato positivo.

Tutti i campioni CVC erano positivi

Le colture CVC su terreni arricchiti con lipidi possono essere proposte come procedura di routine per diagnosticare l'infezione.

Table 1. Number and percentage of infants from Group I (blood collected by lysis centrifugation tube) and Group II (blood collected by BacT/Alert pediatric - PF bottles) scored positive for *Malassezia* bloodstream infections by using blood and central venous catheter (CVC) cultures.

	Positive /Total (%)		
Diagnosis	Group I	Group II	Total
Blood in BacT/Alert system	—	0/202 (0)	0/202 (0)
Blood in Dixon agar at T_0	6/290 (2.1)	1/202 (0.5)	7/492 (1.6)
CVC in Dixon agar	6/290 (2.1)	9/202 (4.4)	15/492 (3.1)

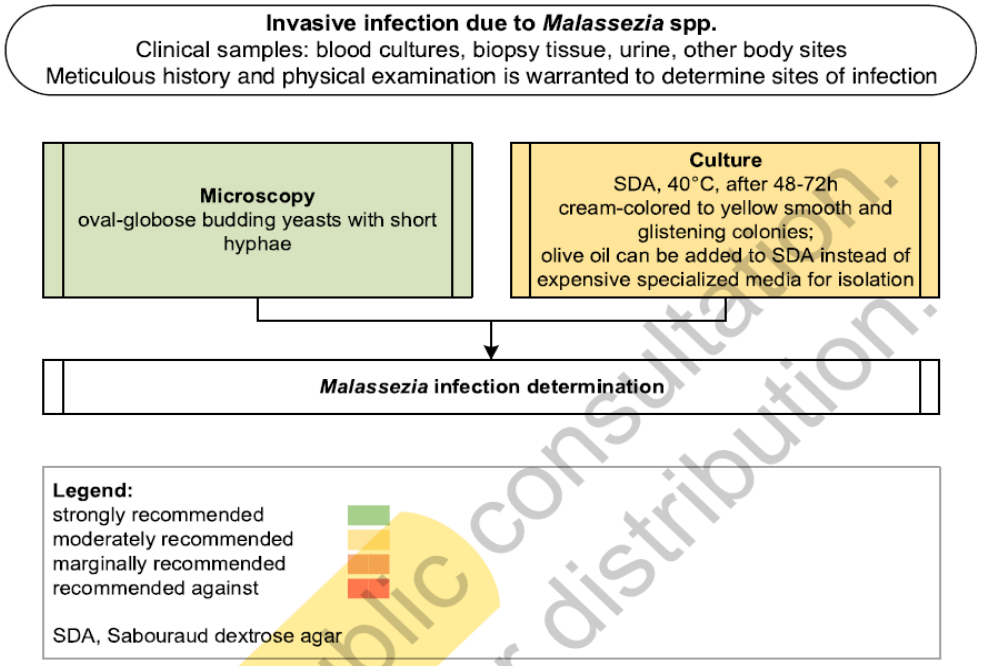
Iatta et al., Medical Mycology 2017

MALASSEZIA FUNGEMIA: DIAGNOSI

ESAME MICROSCOPICO sangue prelevato dalla CVC è spesso diagnostica ed è fortemente raccomandata

ESAME COLTURALE del sangue e delle punte CVC è consigliata a tutti i pazienti

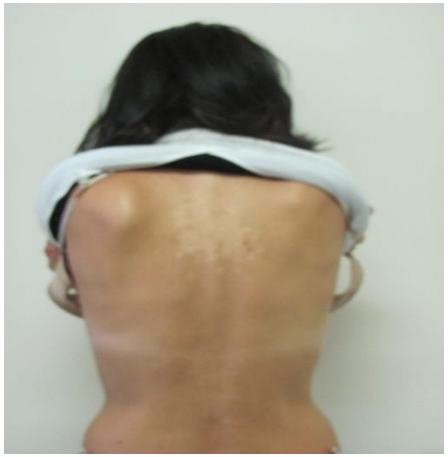
Figure 12. Diagnostic pathway for suspected cases of systemic *Malassezia* infections



Chen et al., 2020
https://www.clinicalsurveys.net/uc/Team_Fungiscope/2a73/images/Rare_Mold_Guideline_Draft_Public_Review.pdf.

MALASSEZIA SKIN: TERAPIA

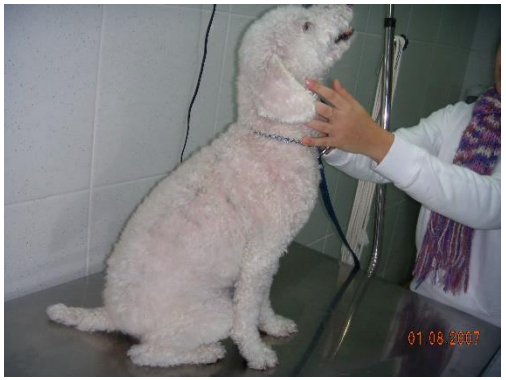
- ✓ KTZ Shampoo (due volte a settimana) o crema al miconazolo (ogni 2 giorni);
- ✓ Terapia sistemica con FLZ (300 mg/settimana per 2-3 settimane) o ITZ (200 mg/die per 3 settimane);
- ✓ FLZ è solitamente preferito per PV e MF e ITZ per SD;
- ✓ L'uso orale di TER sembra non efficace nel PV.



Hald et al., acta Derm Veneariol 2015; Gupta and Lyons, Expert Opin Pharmacother. 2014; Gupta et al., J Am Acad Dermatol. 2004

In vivo prospective studies on the treatment of *Malassezia dermatitis* reporting clinical and mycological outcome

Ref.	Agent Tested	Protocol	Length of Treatment	Animals	RCT	Blinded	Outcome: Improvement In Clinical Signs And Mycology (Complete >90%, Partial <50%)
Bond et al., 1995	2% Miconazole 2% chlorexidine Shampoo **VS** 0.25% selenium sulphide shampoo	10 mL/10Kg twice weekly	3 weeks	33 dogs	yes	yes	Complete with 2% Miconazole 2% chlorexidine shampoo
Marsella et al., 2000	Miconazole 1% or 2% **VS** control	Three times weekly for the first 2 weeks and twice weekly for an additional 2 weeks.	4 weeks	18 dogs	yes	yes	Partial in clinical signs and complete in mycology
Maynard, et al., 2011	3% chlorhexidine shampoo **VS** 2% miconazole-2% chlorhexidine shampoo	10 mL/10Kg; 3%CHX, thrice weekly for two weeks, twice weekly for two weeks, weekly for two weeks. 2% MIC/CHX was used twice weekly	up to 6 weeks	31 dogs	yes	no	Complete with both treatments
Carlotti and Laffort 1996	Ketoconazole with Enilconazole (case reports)	0.2% Eniconazole topically 2 days /weak, keto: 5mg/Kg SID	3 weeks	12 dogs	no	no	Partial in clinical signs and complete in mycology
Bensignor et al., 2001	Ketoconazole	10 mg kg^{-1} SID **VS** Ketoconazole 5 mg kg^{-1} SID	3 weeks	20 dogs	yes	no	Complete with both treatments
Rosales et al. 2005	Ketoconazole VS Terbinafine	Terbinafine 30 mg kg–1 **VS** Ketoconazole 5-10kg–1 ; SID	3 weeks	15 dogs	yes	no	Partial with both treatments
Bensignor et al., 2006	Ketoconazole **VS** Itraconazole	Itraconazolo 5 mg kg–1 for two consecutive days a week **VS** Ketoconazole 10 mg kg –1 SID	3 weeks	30 dogs	yes	yes	Partial in clinical signs and complete in mycology with both treatments
Sickafoose et al., 2010	Ketoconazole **VS** Fluconazole With Cephalexin	from 5 to 10mg/kg SID	3 weeks	13 dogs	yes	yes	Complete with both treatments
Pinchbeck et al. 2002	Itraconazole pulse **VS** continued administration	5 mg kg–1 SID for two consecutives days a week / xs SID	3 weeks	20 dogs	yes	no	Complete with pulse administration
Åhman et al., 2007	Itraconazole	5 mg kg–1 every second week **(itrafungol, Janssen)**	3 weeks	6 cats	no	no	Complete
Bensignor et al., 2010	Itraconazole (case reports)	Itraconazole 5 -10 mg kg–1 SID **(itrafungol, Janssen)**	4 weeks	15 cats	no	no	Complete
Berger et al., 2012	Terbinafine continued **VS** pulsed	Terbinafine 30 mg/kg once daily or Twice weekly.	3 weeks	20 dogs	Yes	no	Complete with twice-weekly terbinafine



MALASSEZIA FUNGEMIA: TERAPIA

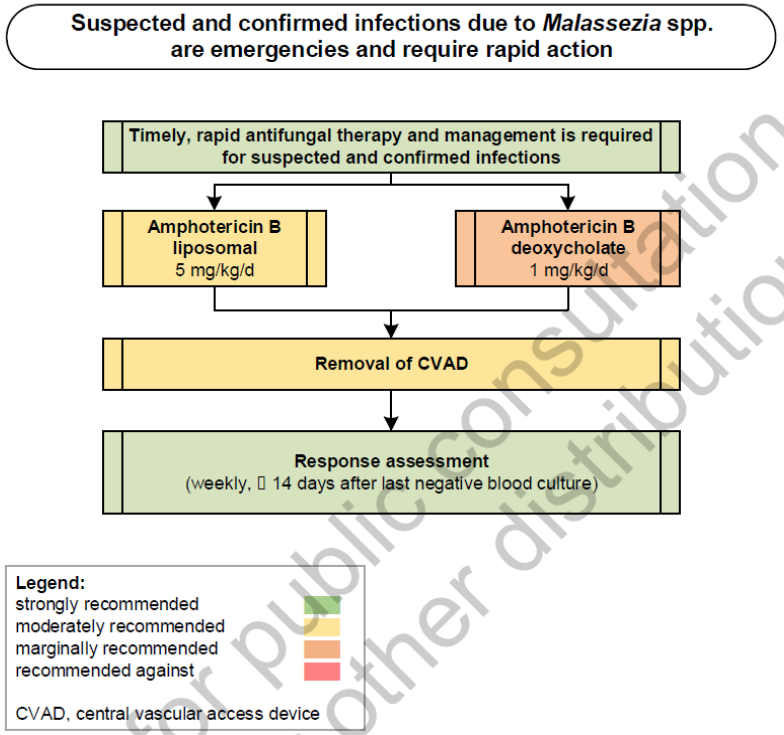
La rimozione dei CVCs è fortemente raccomandata.

La sospensione della alimentazione parenterali è moderatamente R.

Somministrazione amfotericina B per almeno 14 giorni dopo l'ultima emocoltura negativa

La prevenzione delle infezioni da Malassezia è fortemente supportata e deve essere effettuata mediante una attenta igiene delle mani (M. pachydermatis), e mediante un'adeguata pulizia ambientale delle unità neonatali comprese le incubatrici

Malassezia species.



Chen et al., 2020

MALASSEZIA FUNGEMIA: TERAPIA

AmB: UTILE

FLZ and POS: Fallimento nella prevenzione della fungemia

Table 1. I*n vivo* studies on the treatment of *Malassezia* spp. fungemia reporting clinical outcome.

References	Yeasts species	Agent Tested	Protocol	Length of Treatment	Hosts /Outcome
Chen et al., 2019	*M. furfur*	Amphotericin B	1 mg/kg/day/CVC removal	NR	1 Preterm infant/alive
Lee et al., 2019	*M. pachydermatis*	Amphotericin B	NR	2 days	1 adult 62-year-old/died
Pedrosa et al., 2018	*M. furfur*	Fluconazole and Liposomal Amphotericin B	10 mg/kg /day and/or (3 or 5 mg/kg /day) CVC removal	50 days	1 Preterm infant and 2 Adults with fluconazole prophylaxis/ Adults died and infant alive
Aguirre et al., 2015	*M. sympodialis*	Amphotericin B deoxycholate	1mg/kg/day (accumulate dosage 20 mg/kg)/ CVC removal	21 days	1 Preterm infant/ Alive
Roman, 2016	*M. pachydermatis* + mycobacteria	Liposomal Amphotericin B + nafcillin	5 mg/kg/day IV/CVC removal	7 days	1 Adult/Alive
Choudhury and Marte, 2014	*M. pachydermatis*	Liposomal Amphotericin B	1 mg/kg/day//CVC removal	NR	1 Adult with oral Posaconazole prophylaxis/Alive
Al-Sweih, 2014	*M. pachydermatis*	Liposomal Amphotericin B	NR	7 days	1 Preterm infant /Alive
Iatta et al., 2014	*M. furfur*	Liposomal Amphotericin B	From 2.5 to 5mg/kg/day/CVC removal	6-20 days	6 preterm infants 3 with fluconazole prophylaxis /Alive
Oliveri et al., 2011	*M. furfur*	Liposomal Amphotericin B	4 mg/kg/day/CVC removal	45 days	1 Preterm infants
Rosales et al., 2004	*M. furfur*	Amphotericin B	NR	26 days	1 preterm infant/Died

Rhimi et al., Front. Cell. Infect. Microbiol., 2020

FENOMENI DI RESISTENZA?

MALASSEZIA FUNGEMIA: TERAPIA

- MIC di FLZ e VOR diminuisce in presenza di concentrazioni sub-inibitorie di modulatori delle pompe di efflusso (aloperidolo-HAL, prometazina-PTZ);

- Effetto sinergico con ceppi -

FLZ MIC ≥128 µg/mL per *M. furfur*,- FLZ MIC≥64µg/mL per *M. pachydermatis*;

MIC VOR ≥4 µg / mL in entrambe le Malassezia spp.

Le pompe di efflusso dei farmaci sono coinvolte come meccanismi di difesa contro i farmaci azolici nel lievito *Malassezia*.

Il sinergismo potrebbe essere correlato ad una maggiore espressione dei geni della pompe di efflusso,

TABLE 1 Fluconazole (FLZ) minimal inhibitory concentration (MIC in µg/mL) values of *Malassezia furfur* and *Malassezia pachydermatis* alone or in combination with haloperidol (HAL), promethazine (PTZ) and cyclosporine A (CYS). FICI index is also reported in bracket

Malassezia spp.	Number of strains (culture collection number)	MIC FLZ alone	MIC with HAL (FICI index)*	MIC with PTZ (FICI index)*	MIC with CYS (FICI index)*
M. furfur	6 (1041; 1046; 1047; 10 471; 1048; 1050)	512	64 (<0.5)	128 or 256 (>0.5 and <4)	512 or 256 (>0.5 and <4)
	4 (1036; 1037; 1057; 1078)	256	32 (<0.5)	128 or 64 (>0.5 and <4)	256 (>0.5 and <4)
	2 (1086; 1086/15)	128	8 (<0.5)	32 (=0.5)	128 (>0.5 and <4)
	3 (1060; 1025; 1044)	64	16 (=0.5)	16 (=0.5)	32 or 64 (>0.5 and <4)
	2 (1006; 1017)	32	8 (=0.5)	8 (=0.5)	32 (>0.5 and <4)
	4 (1040; 1040a; 1054; 1055)	16	4 (=0.5)	4 (=0.5)	16 (>0.5 and <4)
M. pachydermatis	2 (789; 7891)	512	64 (<0.5)	256 (>0.5 and <4)	512 (>0.5 and <4)
	2 (9a; 91)	256	32 (<0.5)	128 (>0.5 and <4)	256 (>0.5 and <4)
	2 (88c; 8)	128	8 (<0.5)	128 (>0.5 and <4)	128 (>0.5 and <4)
	2 (810; 810/15)	64	8 (<0.5)	16 (=0.5)	16 (=0.5)
	3 (813; 81)	32	8 (=0.5)	16 (>0.5 and <4)	32 (>0.5 and <4)
	2 (828; 831)	16	4 (=0.5)	16 (>0.5 and <4)	4 (=0.5)
	1 (849; 8491)	8	2 (=0.5)	4 (>0.5 and <4)	4 (>0.5 and <4)

*FICI=FIC_A+FIC_B, where FIC_A=MIC of the combination/ MIC of drug A alone; FIC_B=MIC of the combination/ MIC of drug B alone; FICI<0.5=synergism; FICI≥4=antagonism; 0.5≤FICI>4=indifferent.

TABLE 2 Voriconazole (VOR) minimal inhibitory concentration (MIC in µg/mL) values of *Malassezia furfur* and *Malassezia pachydermatis* alone or in combination with haloperidol (HAL), promethazine (PTZ) and cyclosporine A (CYS). FICI index is also reported in bracket

Malassezia spp.	Number of strains (culture collection number)	MIC VOR alone	MIC with HAL (FICI index)*	MIC with PTZ (FICI index)*	MIC with CYS (FICI index)*
M. furfur	2 (1047; 10 471)	8	1 (<0.5)	1 (<0.5)	8 (>0.5 and <4)
	7 (1036; 1037; 1046; 1048; 1050; 1086; 1086/15)	4	0.5 or 0.25 (<0.5)	0.5 or 0.25 (<0.5)	2-4 (>0.5 and <4)
	3 (1041; 1057; 1078)	2	0.5 or 1 (>0.5 and <4)	0.5 or 1 (>0.5 and <4)	2 (>0.5 and <4)
	1 (1025)	1	0.25 (=0.5)	0.5 (>0.5 and <4)	1 (>0.5 and <4)
	5 (1017; 1040; 1040a; 1044; 1060)	0.5	0.25 or 0.125 (≥0.5 and <4)	0.25 or 0.125 (≥0.5 and <4)	0.25 (>0.5 and <4)
	2 (1006; 1054; 1055)	0.25	0.125 (>0.5 and <4)	0.06 (=0.5)	0.125 (>0.5 and <4)
M. pachydermatis	2 (789; 7891)	4	0.5 (<0.5)	0.5 (<0.5)	4 (>0.5 and <4)
	4 (9a; 91; 88c; 8)	2	0.5 (=0.5)	1 (>0.5 and <4)	2 (>0.5 and <4)
	4 (810; 810/15; 813; 81)	0.5	0.125 (=0.5)	0.5 or 0.125(≥0.5 and <4)	0.5 (>0.5 and <4)
	2 (828; 831)	0.25	0.064 (>0.5 and <4)	0.125 (>0.5 and <4)	0.25 (>0.5 and <4)
	2 (849; 849/15)	0.125	0.064 (>0.5 and <4)	0.064 (>0.5 and <4)	0.125 (>0.5 and <4)

*FICI=FIC_A+FIC_B, where FIC_A=MIC of the combination/ MIC of drug A alone; FIC_B=MIC of the combination/ MIC of drug B alone; FICI<0.5=synergism; FICI≥4=antagonism; 0.5≤FICI>4=indifferent.

CONCLUSIONI

- *Malassezia* spp. è un commensale della cute degli animali e dell'uomo
- Malassezia può avere un ruolo nelle patologie cutanee degli animali e dell'uomo oltre che nelle fungemie umane.
- NON esiste una stretta ospite specificità.
- I lieviti possono essere trasmessi da animali all'uomo per contatto diretto.
- Metodi molecolari sono necessari per l'identificazione e la genotipizzazione di isolati di *Malassezia* da uomo o animale.
- La composizione chimica e immunologica della cute dell'ospite ha un ruolo fondamentale nell'influenzare la patogenesi.
- La diagnosi di infezione cutanea è semplice mentre sono necessarie linee guida per una corretta diagnosi di fungemia nell'uomo.

CONCLUSIONI

- Anche se di recente line guida sono state pubblicate per il controllo delle infezioni da *Malassezia* sia nell'animale che per le infezioni sistemiche dell'uomo, le raccomandazioni non sono robuste poiché rappresentano **opinioni** di medici che sono state fatte utilizzando casi clinici pubblicati.

- Per gli animali le recidive possono essere evitate solo se si curano le infezioni scatenati

- Per la fungemia i medici devono essere consapevoli della popolazione a rischio di infezioni e devono comunicare al laboratorio la necessità di includere procedure speciali per isolare l'organismo;

- Infine, la sensibilità molto bassa di questi lieviti ai farmaci azolici (cioè fluconazolo e voriconazolo) e alle echinocandine deve essere considerata quando si prevede di utilizzare una terapia a lungo termine o profilattica.

Please do not hesitate to contact me if further information or clarification is required.

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