Infections fongiques. Traitement empirique, préemptif et probabiliste

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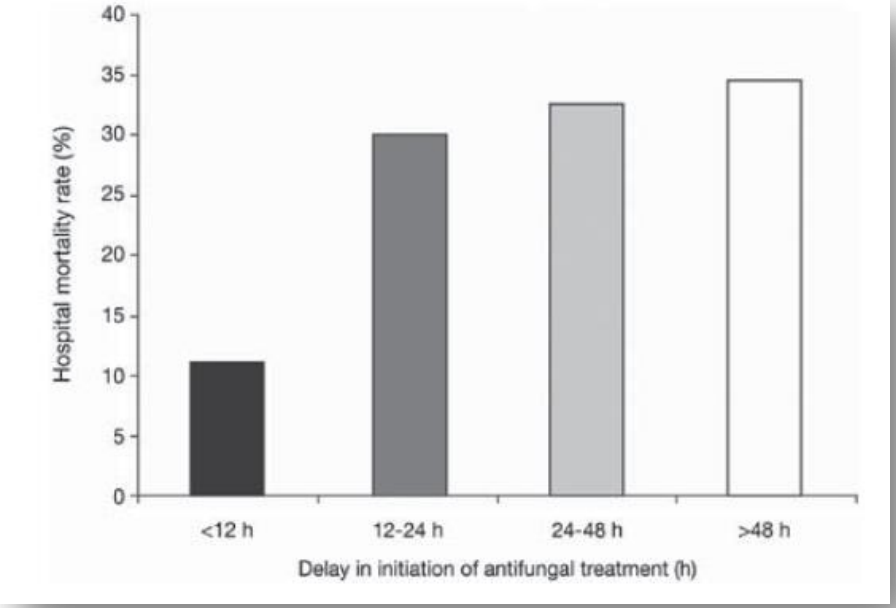
Candidémie chez les patients de réanimation: le délai d'introduction du traitement antifongique a un impact important sur la mortalité. **Un diagnostic précoce et une stratégie thérapeutique alternative sont nécessaires**

Prévalence : 7/1000. Mortalité : 42,6%

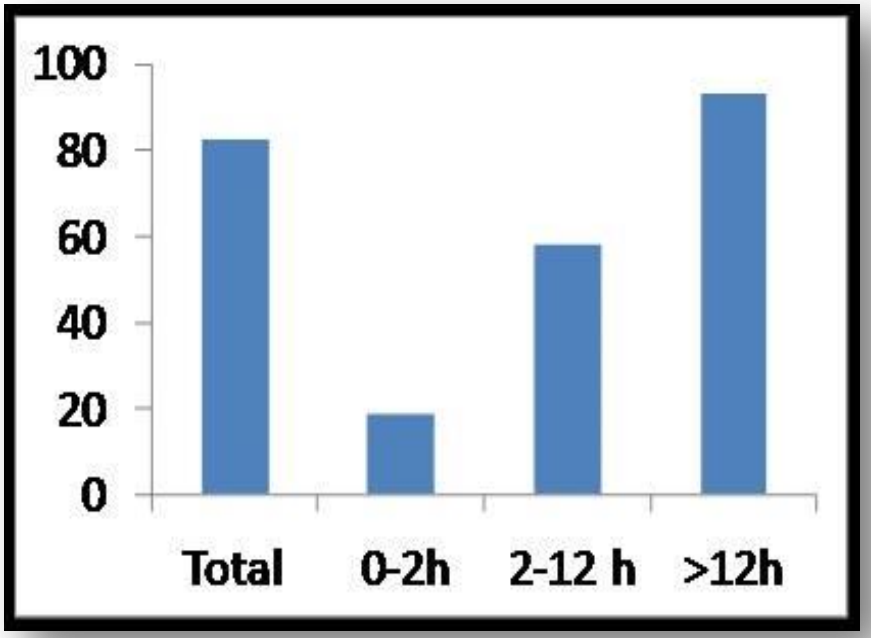
Kett DH et al. Crit Care Med. 2011

Tout patient confondu



Morrell M et al. AAC. 2005

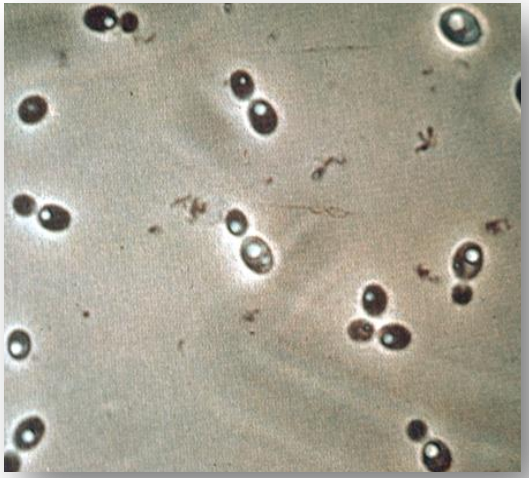
Patients en choc septique



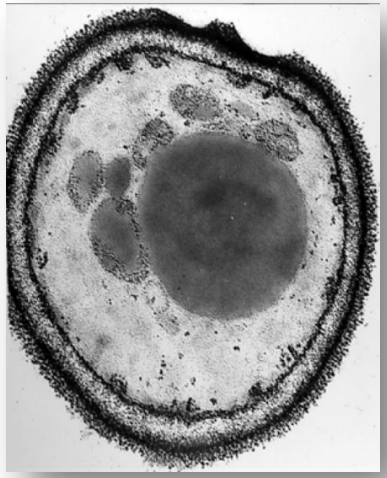
A partir de Kumar A et al. ICAAC 2007. K 2174

Qu'est donc Candida? **Levure**

Examen macroscopique
sur boite de Pétri

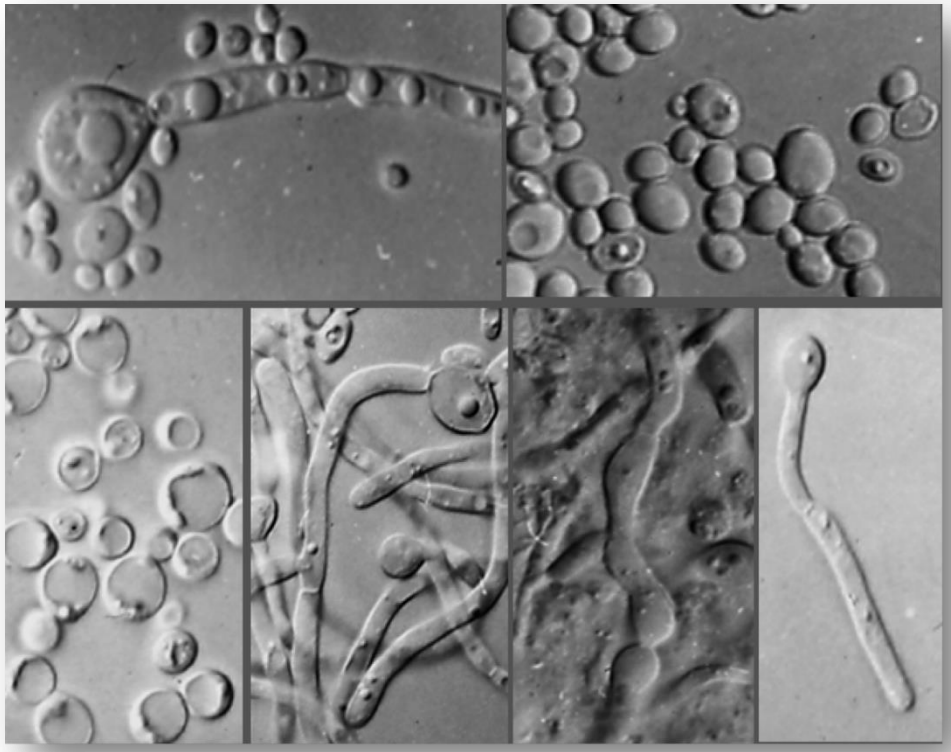


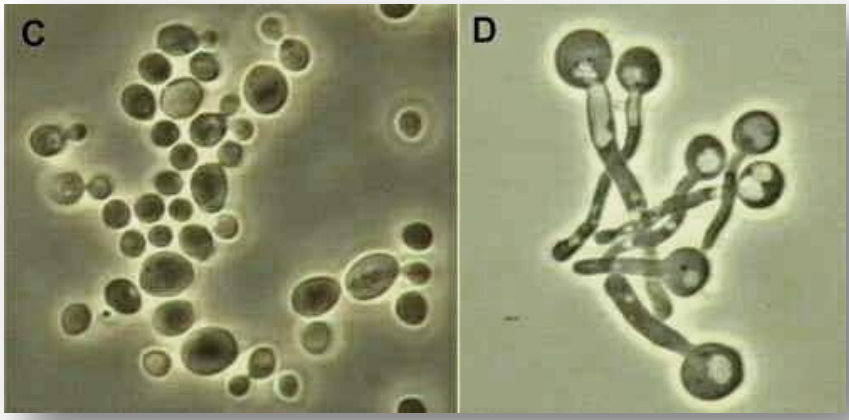
Microscopie
optique

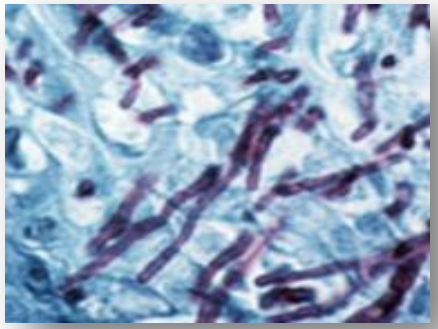


Microscopie
électronique

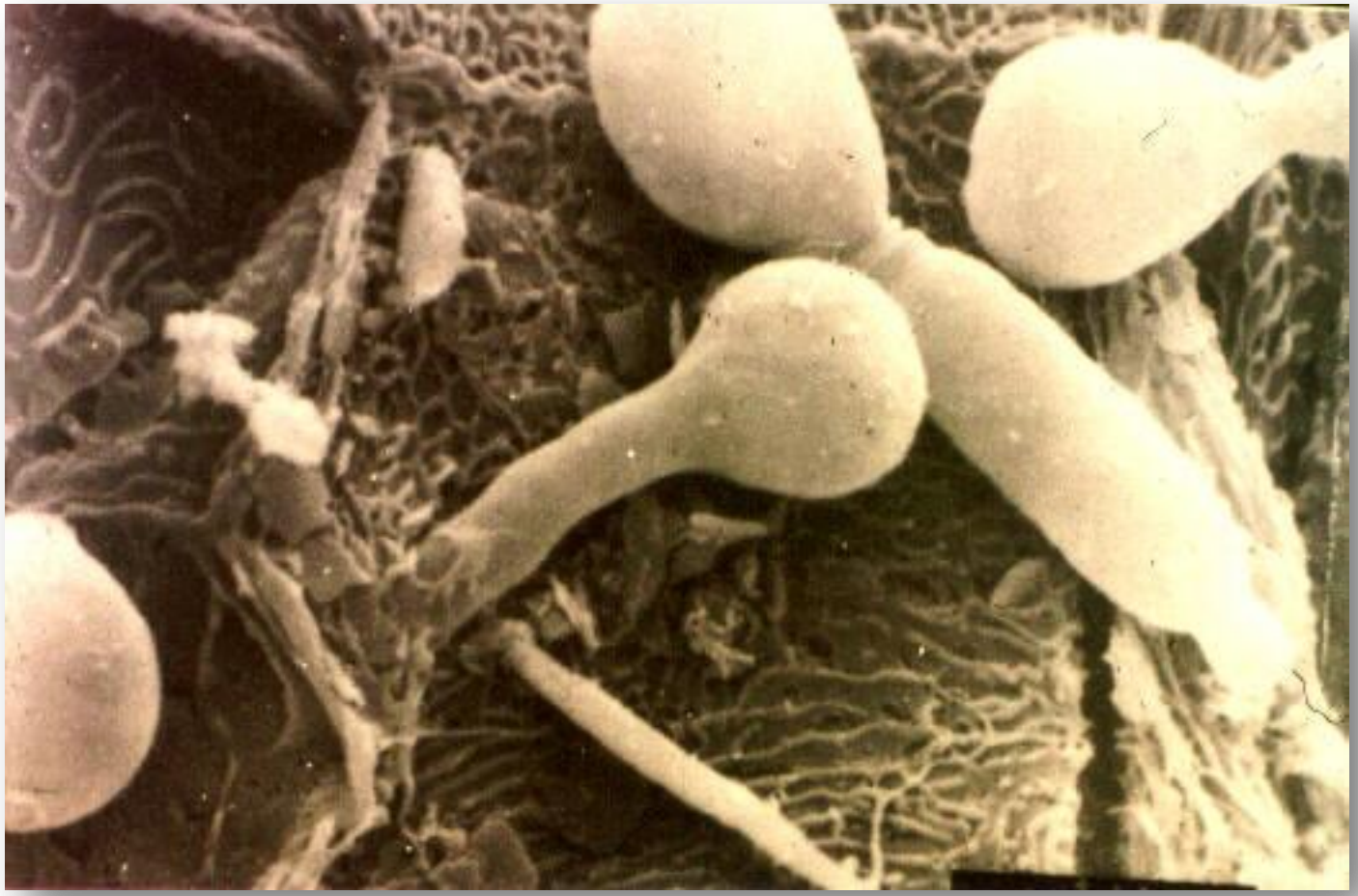
Capable de **filamenter** dans un **environnement favorable**



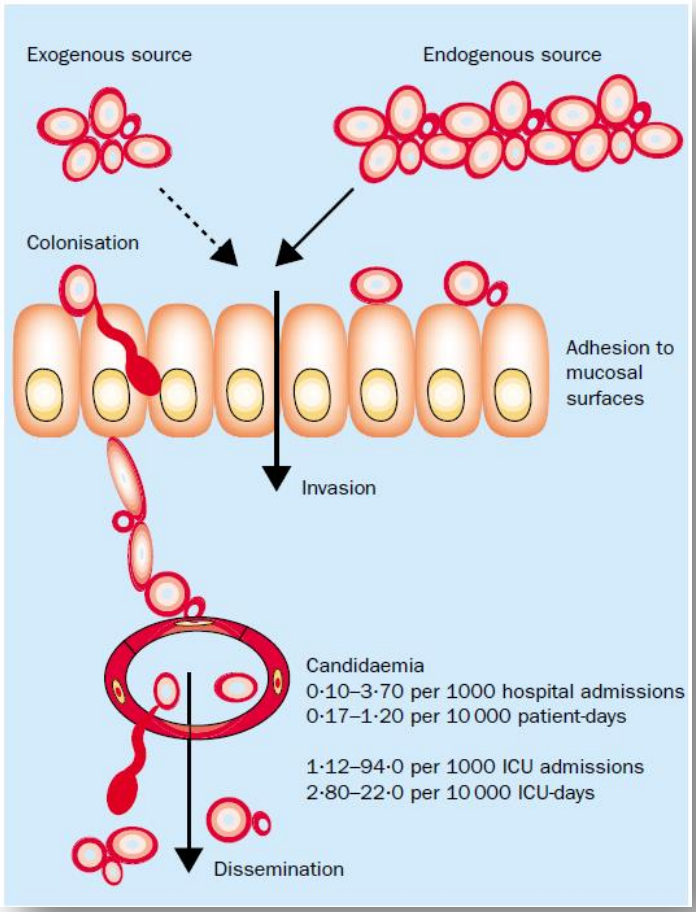




Le filament est la **forme d'invasion tissulaire**

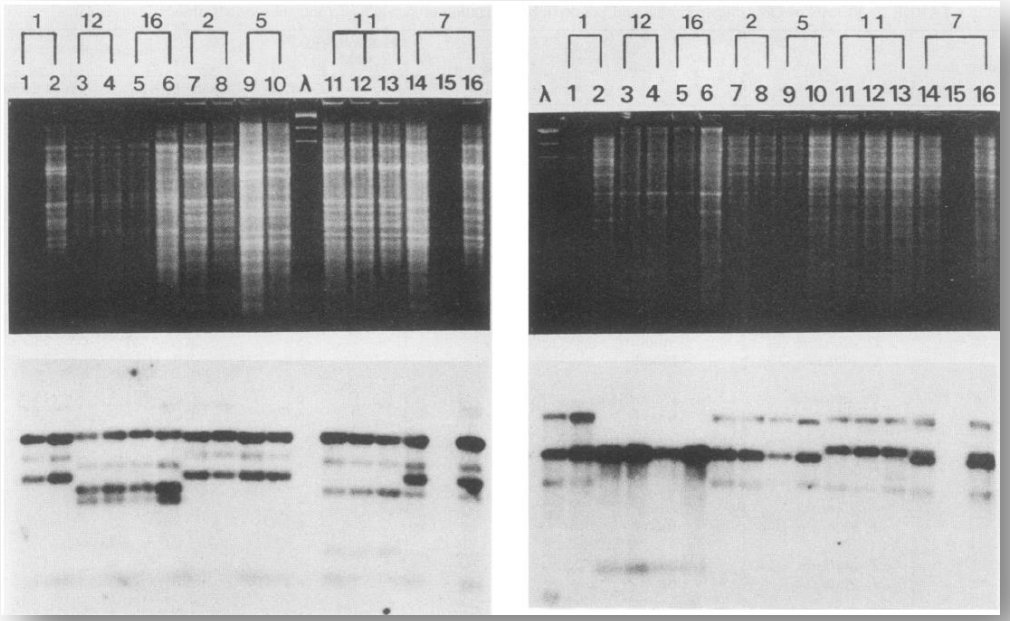


Physiopathologie: le rôle important de le **colonisation** et de **l'interface hôte-pathogène**



Eggimann P et al. Lancet Inf Dis. 2003

Origine endogène majoritaire



Reagan DR et al. JCM. 1990

Les moyens du **diagnostic plus précoce** et les outils pour une **stratégie thérapeutique alternative**

- Le flair: traitement empirique
  - Raisonnement sur facteurs de risque et tableau clinique
- Stratégie probabiliste
  - Mise en forme du raisonnement
  - Scores
- Stratégie préemptive
  - Arguments biologiques pour étayer la situation à risque
  - Colonisation
  - Biomarqueurs
- L'approche génétique
  - Polymorphisme et susceptibilité aux infections

Traitement empirique: recommandations IDSA

Empirique ou préemptif??

Pappas PG et al. CID. 2009

Candidose invasive sous toutes ses formes: **critères EORTC** *Ascioglu S et al. CID 2001*

TABLE 1. Unit clinical criteria for establishing a diagnosis of proven, possible, or probable invasive candidiasis

Type of candidiasis	Criteria
I. Proven invasive candidiasis	1. Candidemia with temporally related clinical signs and symptoms compatible with the relevant organism 2. *Candida* spp. from sterile site other than (i) urine or (ii) peritoneal fluid in a setting of gastrointestinal perforation
II. Probable invasive candidiasis	1. Candidemia without the clinical findings of criteria I.1 2. *Candida* spp. from ≥2 nonsterile sites in association with all of the following within the preceding or subsequent 3 days (day of positive cultures ± 3 days). If the nonsterile site cultures are obtained on different days, then the time window for the listed supporting factors extends from 3 days before the first positive culture for *Candida* spp. to 3 days after the last positive culture for *Candida* spp.: (a) Temperature ≥ 38.5°C (101.3°F) on at least on occasion (b) WBC[c] ≥ 12,000/mm^3 on at least one occasion (c) No bacterial pathogens at any possibly infected site, with the exception of coagulase-negative staphylococci in the blood or on a catheter tip 3. *Candida* spp. from urine at ≥100,000 CFU/ml plus other criteria as in II.2 4. *Candida* spp. from a central venous catheter tip at ≥15 CFU in association with all of the following within the preceding or subsequent 3 days (day of positive culture ± 3 days): (a) Temp ≥ 38.5°C (101.3°F) OR WBC ≥ 12,000/mm^3 (b) No bacterial pathogens at any possibly infected site, with the exception of coagulase-negative staphylococci in the blood or on a catheter tip 5. Empirical treatment with systemic antifungal agents initiated due to a persistent temp of ≥38.5°C (101.3°F) OR WBC ≥ 12,000/mm^3 despite ≥3 days of broad-spectrum antibiotics in association with one of the following clinical scenarios: Scenario A—the patient shows both of the following: (a) *Candida* spp. from at least one nonsterile site OR at least one central venous catheter tip at <15 CFU (b) No bacterial pathogens at any possibly infected site within the preceding or subsequent 3 days (day of initiation of therapy ± 3 days) with the exception of coagulase-negative staphylococci in the blood or on a catheter tip Scenario B[a]—the patient has *Candida* spp. at ≥2 of the following: (a) Any nonsterile site (b) A central venous catheter tip at <15 CFU
III. Possible invasive candidiasis	1. *Candida* from a central venous catheter tip at ≥15 CFU not satisfying criteria as in II.4[b] 2. Empirical treatment as in II.5, but without data satisfying either clinical scenario

Traitement empirique: basé sur l'analyse des **facteurs de risque**

Facteur de risque	Particularités
Colonisation	
ATB	C3G, carbapénèmes, vanco, durée prolongée
Accès vasculaire	Central, artériel, Swan, parapsilosis
Sondage urinaire	
Neutropénie	Durée, krusei, tropicalis
Diarrhée	
Nutrition parentérale	Durée, exclusive, lipides
Anti-H2	
Saignement digestif	
Chirurgie	Carcinologique, ORL, abdominale
Prophylaxie anti-fongique	Présence et krusei, glabrata; absence
Stéroïdes	tropicalis, krusei

Traitement empirique: basé sur l'analyse des **facteurs de risque**

Facteur de risque	Particularités
Chimiothérapie	
Transfusions multiples	
Insuffisance rénale	Épuration extra-rénale
Ventilation mécanique	Durée, antibiothérapie
Durée de séjour	
Sévérité maladie sous-jacente	Bactériémie préalable, score APACHE, leucémie non lymphoïde
Poids de naissance	
Age	>40 ans, <32 semaines

Traitement empirique par fluconazole des candidoses invasives suspectées en réanimation

- Critères d'inclusion
  - Plus de 18 ans
  - En réa depuis au moins 96 heures
  - APACHE II>16
  - 4 jours de fièvre
  - ATB à spectre large pendant au moins 4 jours des 6 jours précédents
  - KT central posé au moins dans les 24 heures précédent l'inclusion

Table 1. **Patient Characteristics at Baseline***

Characteristic	Fluconazole Recipients (n = 122)	Placebo Recipients (n = 127)
Mean age (SD), *y*	53 (19)	51 (19)
Women, *n (%)*	29 (24)	28 (22)
Median previous ICU stay (range), *d*	9.5 (4–171)	9 (4–57)
Median previous hospital stay (range), *d*	11 (5–173)	11 (4–58)
Median baseline APACHE II score (range)	22 (9–28)	20 (11–42)
Corticosteroids, *n (%)*	19 (16)	15 (12)
Total parenteral nutrition, *n (%)*	70 (57)	65 (51)
Renal insufficiency, *n (%)*†	70 (57)	65 (51)
Colonized with yeast in ≥1 site, *n (%)*	28 (23)	24 (19)
Diabetes mellitus, *n (%)*	23 (19)	26 (20)
Cancer, *n (%)*	12 (10)	8 (6)
Surgery within 7 d before study entry, *n (%)*	65 (53)	65 (51)

Schuster MG et al. Ann Intern Med. 2008

Traitement empirique par fluconazole des candidoses invasives suspectées en réanimation: **stratégie thérapeutique inefficace**

Table 3. Outcomes during the Primary Observation Period*

Outcomes	Fluconazole Recipients (n = 122), n (%)	Placebo Recipients (n = 127), n (%)	Relative Risk (95% CI)	P Value
Primary analysis†‡				
Success	44 (36)	48 (38)	0.95 (0.69–1.32)	0.78
Failure	78 (64)	79 (62)	–	–

Table 4. Reasons for Failure at the End of the Primary Observation Period*

Outcome	Fluconazole Recipients (n = 122), n (%)	Placebo Recipients (n = 127), n (%)
Total failures	67 (55)	73 (57)
No resolution of fever	62 (51)	68 (54)
Documented invasive fungal infection	6 (5)†	11 (9)‡
Need for alternative antifungal agent	12 (10)	20 (16)

Schuster MG et al. Ann Intern Med. 2008

Analyse coût-efficacité d'un traitement empirique anti-candida en réanimation.

Golan Y. Ann Int Med, 2005

- Modélisation mathématique d'un traitement empirique chez:
  - Patients hospitalisés en réanimation
  - Fièvre
  - Ou hypothermie
  - Ou hypotension inexpliquée
  - Malgré 3 jours d'antibiothérapie bien conduite

- 9 stratégies
  - Pas de traitement anti fongique
  - Traitement basé sur la culture
  - Traitement empirique
  - Molécules testées: amphoB, amphoB-L, caspofungine, fluconazole

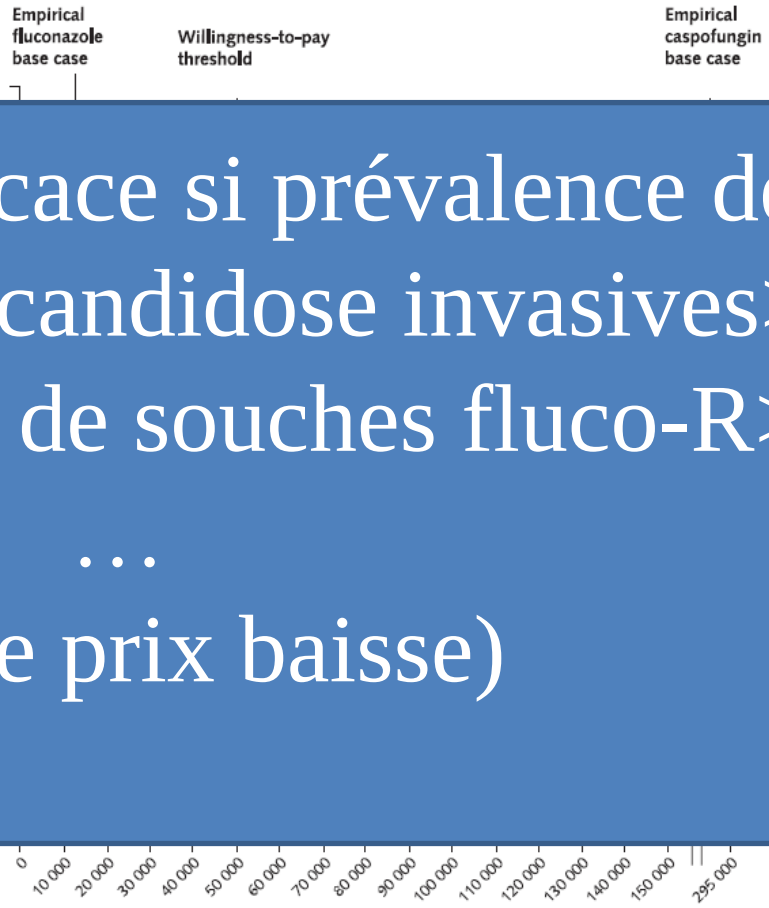
Analyse coût-efficacité d'un traitement empirique anti-candida en réanimation: **fluconazole coût efficace**

Molécule	Mortalité attendue (%)*		Mortalité sous traitement (%)*		Patients à traiter pour une vie sauvée	Coût par année de vie sauvée ($)
	Candidose invasive	Cohorte entière	Candidose invasive	Cohorte entière		
Fluco	44,0	22,4	30,0	21,0	71	12 600
Caspo	30,0	21,0	29,0	20,9	250	295 100

* Vs stratégie sur culture

Golan Y. Ann Int Med. 2005

Analyse coût-efficacité d'un traitement empirique anti-candida en réanimation



Caspo coût-efficace si prévalence des candidémies et des candidose invasives>60%
et si le pourcentage de souches fluco-R>30%
…
(et si le prix baisse)

Golan Y. Ann Int Med. 2005

Elaboration par analyse rétrospective d'une **règle de prédiction clinique** sur population de réanimation médicale et chirurgicale *Ostrosky-Zeichner L et al. Eur J Clin Microbiol Inf Dis, 2007*

Table 2 Post-hoc performance of selected predictive rules on the complete population analyzed

Rule[a] (n=2,890)	Rule description	No. of patients selected by rule (% of total)	No. of cases selected by rule (% of total)	Infection rate among IC patients		Relative risk[b]	p-value[c]	Sensitivity	Specificity	PPV	NPV
				Not selected by rule (%)	Selected by rule (%)						
1 (n=2,889)	Any antibiotic use (day 1–3) AND CVC (day 1–3)	1,801 (62.3)	78 (88.6)	0.9	4.3	4.71 (2.45, 9.06)	<0.001	0.89	0.38	0.04	0.99
2 (n=2,879)	Any antibiotic use (day 1–3) AND CVC (day 1–3) AND at least one of the following additional risk factors: any surgery (day −7–0); immunosuppressive use (day −7–0); pancreatitis (day −7–0); TPN (day 1–3); any dialysis (day 1–3); steroid use (day −7–3)	916 (31.8)	58 (65.9)	1.5	6.3	4.14 (2.69, 6.39)	<0.001	0.66	0.69	0.06	0.98
3 (n=2,859)	Any antibiotic use (day 1–3) OR CVC (day 1–3) AND at least two of the following additional risk factors: any surgery (day −7–0); immunosuppressive use (day −7–0); pancreatitis (day −7–0); TPN (day 1–3); any dialysis (day 1–3); steroid use (day −7–3)	303 (10.6)	30 (34.1)	2.3	9.9	4.36 (2.85, 6.67)	<0.001	0.34	0.90	0.09	0.97

Elaboration par analyse rétrospective d'une règle de prédiction clinique sur population de réanimation médicale et chirurgicale

Ostrosky-Zeichner L et al. Eur J Clin Microbiol Inf Dis, 2007

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Elaboration rétrospective et validation prospective d'une règle de prédiction clinique d'isolement de Candida dans le liquide péritonéal *Dupont H et al. Crit Care Med, 2003*

Table 4. Independent predictive factors of yeast isolation in peritonitis

Parameters	β Coefficient	Odds Ratio	95% CI	*p* Value
Cardiovascular failure	0.8981	2.45	[1.31–4.61]	.005
Upper gastrointestinal tract origin	0.8681	2.38	[1.27–4.48]	.007
Female	0.8652	2.37	[1.28–4.4]	.006
Ongoing antimicrobial therapy	0.8131	2.25	[1.19–4.27]	.01
Constant	−2.2858	—	—	<.0001

Table 5. Operational values of the predictive score of yeast isolation according to grade of the score

Grade of Score	Se	Sp	PPV	NPV	OA
Grade A	3	100	40	100	40
Grade B	33	87	46	79	54
Grade C	84	50	67	72	71
Grade D	100	13	100	64	65

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; OA, overall accuracy; grade A, zero or one risk factor; grade B, at least two risk factors; grade C, at least three risk factors; grade D, four risk factors.

Elaboration rétrospective et validation prospective d'une règle de prédiction clinique d'isolement de Candida dans le liquide péritonéal *Dupont H et al. Crit Care Med, 2003*

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Score clinique chez les patients **non neutropéniques** de **réanimation colonisés**: « **Candida score** ». Evaluation des facteurs de risque cohorte EPCAN

Table 3. Results of multivariate analysis: Risk factors for proven candidal infection in 1,669 adult patients

Variable	Proven Candidal Infection %	*p* Value	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)
Surgery on ICU admission				
No	6.9			
Yes	16.5	<.001	2.69 (1.76–4.10)	2.71 (1.45–5.06)
Total parenteral nutrition				
No	2.8			
Yes	15.5	<.001	6.46 (3.48–11.98)	2.48 (1.16–5.31)
Severe sepsis				
No	4.5			
Yes	28.8	<.001	8.63 (5.49–13.56)	7.68 (4.14–14.22)
Candida species colonization				
No	4.2			
Yes	12.3	<.001	3.20 (1.85–5.53)	3.04 (1.45–6.39)

Léon C et al. Crit Care Med. 2006

« **Candida score** ». Construction du modèle logistique multivarié

Table 4. Calculation of the Candida score: Variables selected in the logistic regression model

Variable	Coefficient (β)	Standard Error	Wald χ^2	*p* Value
Multifocal *Candida* species colonization	1.112	.379	8.625	.003
Surgery on ICU admission	.997	.319	9.761	.002
Severe sepsis	2.038	.314	42.014	.000
Total parenteral nutrition	.908	.389	5.451	.020
Constant	−4.916	.485	102.732	.000

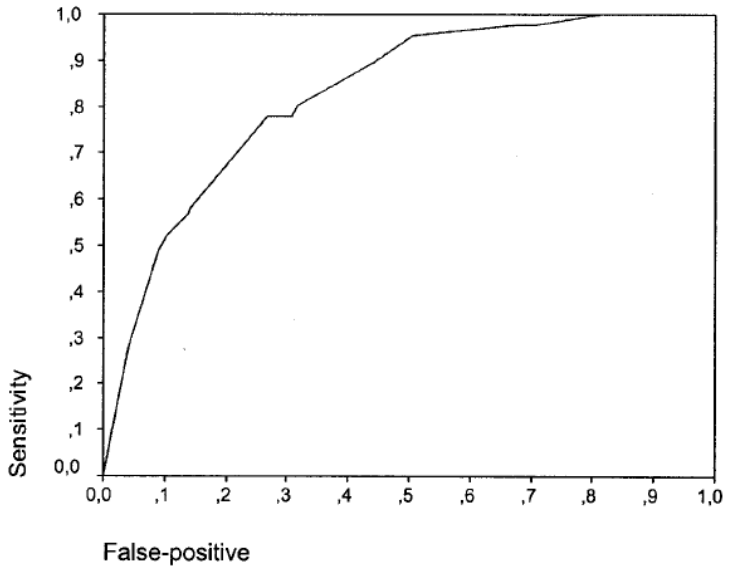
ICU, intensive care unit.

Candida score = .908 × (total parenteral nutrition) + .997 × (surgery) + 1.112 (multifocal *Candida* species colonization) + 2.038 (severe sepsis). Candida score (rounded) = 1 × (total parenteral nutrition) + 1 × (surgery) + 1 (multifocal *Candida* species colonization) + 2 × (severe sepsis). All variables coded as follows: absent, 0; present, 1.

Léon C et al. Crit Care Med. 2006

Performances du modèle. Pour CS>2,5, Se=81% et Sp=74%

A



B

Cutoff value	Sensitivity	False positive
1.055	.983	.653
1.509	.949	.495
1.963	.898	.426
2.069	.831	.312
2.074	.814	.301
2.528	.814	.259
2.982	.780	.231
3.026	.610	.132
3.093	.593	.130
3.547	.525	.092
4.001	.492	.077

Léon C et al. Crit Care Med. 2006

« **Candida score** ». Validation prospective: un modèle avec une **excellente VPN.**

Table 4. Rates of invasive candidiasis according to the *Candida* score

Cutoff Value	Incidence Rate (%) (95% CI)	Relative Risk (95% CI)
<3	2.3 (1.1–3.5)	1
3	8.5 (4.2–12.7)	3.7 (1.8–7.7)
4	16.8 (9.7–23.9)	7.3 (3.7–14.5)
5	23.6 (12.4–34.9)	10.3 (5.0–21.0)

Table 5. *Candida* score vs. colonization index discriminatory power

	Candida Score ≥3 (95% CI)	Colonization Index ≥0.5 (95% CI)
Area under ROC curve	0.774 (0.715–0.832)	0.633 (0.557–0.709)
Sensitivity	77.6 (66.9–88.3)	72.4 (60.9–83.9)
Specificity	66.2 (63.0–69.4)	47.4 (44.0–50.8)
Predictive positive value	13.8 (10.0–17.5)	8.7 (6.2–11.3)
Predictive negative value	97.7 (96.4–98.9)	96.1 (94.2–98.0)
Relative risk for invasive candidiasis	5.98 (3.28–10.92)	2.24 (1.28–3.93)

Léon C et al. Crit Care Med. 2009

Et en pratique, que font les réanimateurs?

Azoulay E et al. Crit Care Med, 2012.

Table 1. Patient characteristics

Median (25–75) or Number (%)	Missing Values	Patients Without Systemic Antifungal Treatment (n = 1893)	Patients With Systemic Antifungal Treatment (n = 154)		p^b
			No Documented Invasive Fungal Infection (n = 100)	Documented Invasive Fungal Infection (n = 54)	
Age, yrs	1	61 [45–74]	62 [48.5–73]	59 [50–70]	.9889
Male gender	0	1174 (62)	61 (61)	33 (61.1)	.8098
Severity at ICU admission[a]	0				<.0001
1, not severe		490 (25.9)	6 (6)	10 (18.5)	
2, intermediately severe		586 (31)	27 (27)	16 (29.6)	
3, severe		420 (22.2)	35 (35)	12 (22.2)	
4, very severe		397 (21)	32 (32)	16 (29.6)	
Time (days) from ICU admission to the study day	5	7 [4–16]	11 [6–21]	14.5 [8–29]	<.0001
Admission category	4				<.0001
Medical		1211 (64.1)	56 (56)	28 (51.9)	
Scheduled surgery		215 (11.4)	4 (4)	5 (9.3)	
Emergency surgery		463 (24.5)	40 (40)	21 (38.9)	
Comorbidities	0				
Solid tumor		115 (6.1)	3 (3)	1 (1.9)	.0761
Hematologic malignancies		48 (2.5)	19 (19)	5 (9.3)	<.0001
Immunosuppressive agents		206 (10.9)	29 (29)	11 (20.4)	<.0001
High-dose or long term steroids		223 (11.8)	24 (24)	23 (42.6)	<.0001
Need for life-sustaining therapies since ICU admission					
Mechanical ventilation	0	1471 (77.7)	89 (89)	46 (85.2)	.0039
Central venous line	0	1431 (75.6)	95 (95)	53 (98.1)	<.0001
Parenteral nutrition	0	784 (41.4)	62 (62)	37 (68.5)	<.0001
Renal replacement therapy	0	269 (14.2)	32 (32)	19 (35.2)	<.0001
Vasopressors	0	972 (51.3)	78 (78)	36 (66.7)	<.0001
Candida colonization at any site	0	159 (8.4)	57 (57)	41 (75.9)	<.0001
Severe sepsis or septic shock	0	733 (38.7)	83 (83)	45 (83.3)	<.0001
Candida score[c]	0				<.0001
0/1		1012 (53.5)	7 (7)	3 (5.6)	
2		317 (16.7)	18 (18)	6 (11.1)	
>2		564 (29.8)	75 (75)	45 (83.3)	

Et en pratique, que fait-on? *Azoulay E et al. Crit Care Med, 2012.*

Table 1. Patient characteristics

Median (25–75) or Number (%)	Missing Values	Patients Without Systemic Antifungal Treatment (n = 1893)	Patients With Systemic Antifungal Treatment (n = 154)		p^b
			No Documented Invasive Fungal Infection (n = 100)	Documented Invasive Fungal Infection (n = 54)	
Age, yrs	1	61 [45–74]	62 [48.5–73]	59 [50–70]	.9889
Male gender	0	1174 (62)	61 (61)	33 (61.1)	.8098
Severity at ICU admission[a]	0				<.0001
1, not severe		490 (25.9)	6 (6)	10 (18.5)	
2, intermediately severe		586 (31)	27 (27)	16 (29.6)	
3, severe		420 (22.2)	35 (35)	12 (22.2)	
4, very severe		397 (21)	32 (32)	16 (29.6)	
Time (days) from ICU admission to the study day	5	7 [4–16]	11 [6–21]	14.5 [8–29]	<.0001
Admission category	4				<.0001
Medical		1211 (64.1)	56 (56)	28 (51.9)	
Scheduled surgery		215 (11.4)	4 (4)	5 (9.3)	
Emergency surgery		463 (24.5)	40 (40)	21 (38.9)	
Comorbidities	0				
Solid tumor		115 (6.1)	3 (3)	1 (1.9)	.0761
Hematologic malignancies		48 (2.5)	19 (19)	5 (9.3)	<.0001
Immunosuppressive agents		206 (10.9)	29 (29)	11 (20.4)	<.0001
High-dose or long term steroids		223 (11.8)	24 (24)	23 (42.6)	<.0001
Need for life-sustaining therapies since ICU admission					
Mechanical ventilation	0	1471 (77.7)	89 (89)	46 (85.2)	.0039
Central venous line	0	1431 (75.6)	95 (95)	53 (98.1)	<.0001
Parenteral nutrition	0	784 (41.4)	62 (62)	37 (68.5)	<.0001
Renal replacement therapy	0	269 (14.2)	32 (32)	19 (35.2)	<.0001
Vasopressors	0	972 (51.3)	78 (78)	36 (66.7)	<.0001
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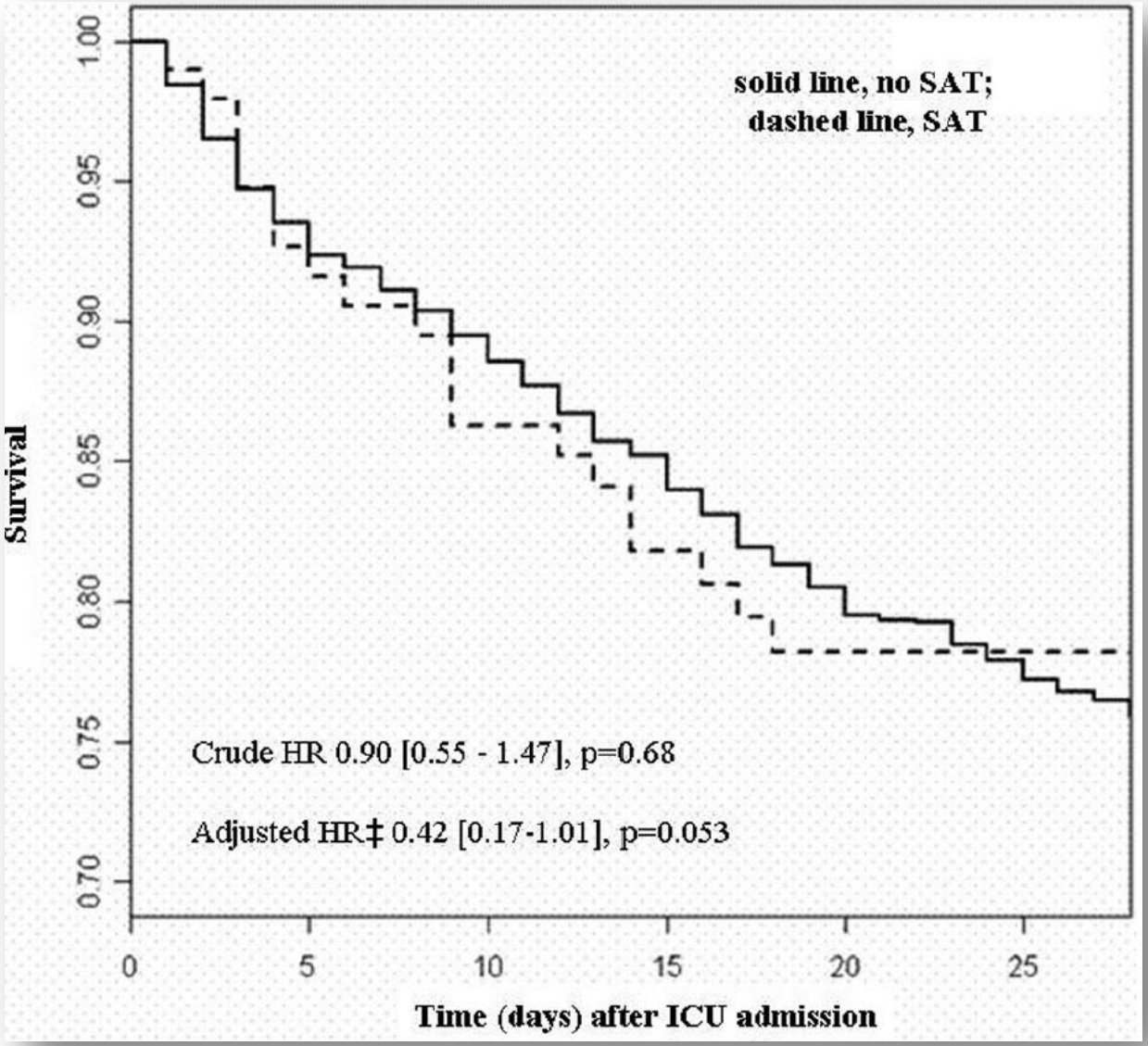
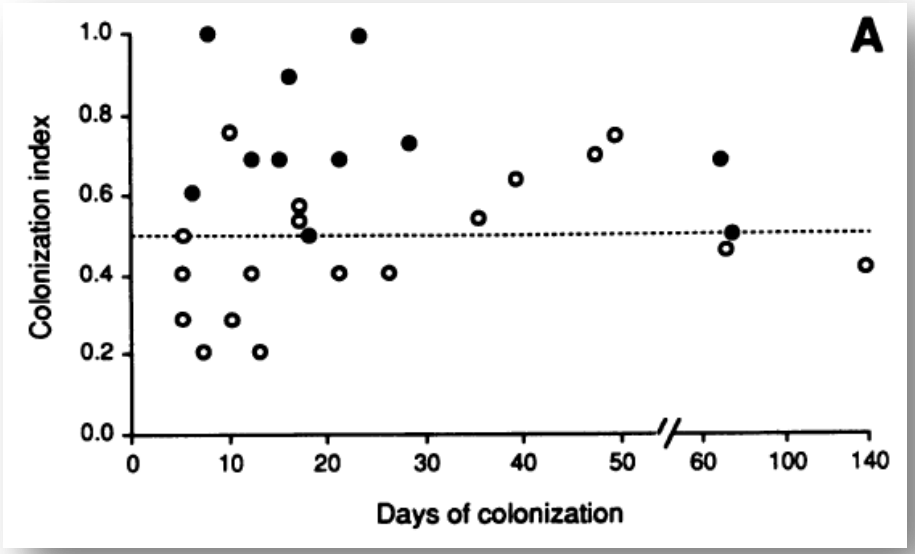
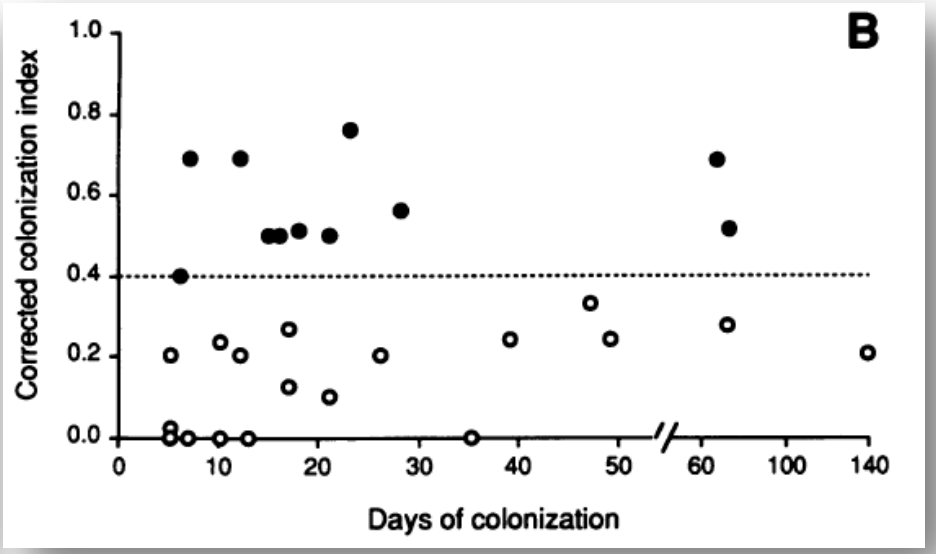
2		317 (16.7)	18 (18)	6 (11.1)	
>2		564 (29.8)	75 (75)	45 (83.3)	

Avec quel impact? *Azoulay E et al. Crit Care Med, 2012.*



Traitement préemptif et colonisation: évaluation **IC et ICC** en **réanimation chirurgicale**





Index de colonisation: n de sites colonisés à Candida/ n total sites testés
Index de colonisation corrigé: IC x (n sites fortement colonisés/n sites colonisés)

Pittet D et al. Ann Surg. 1994

IC et ICC : performances en réanimation chirurgicale

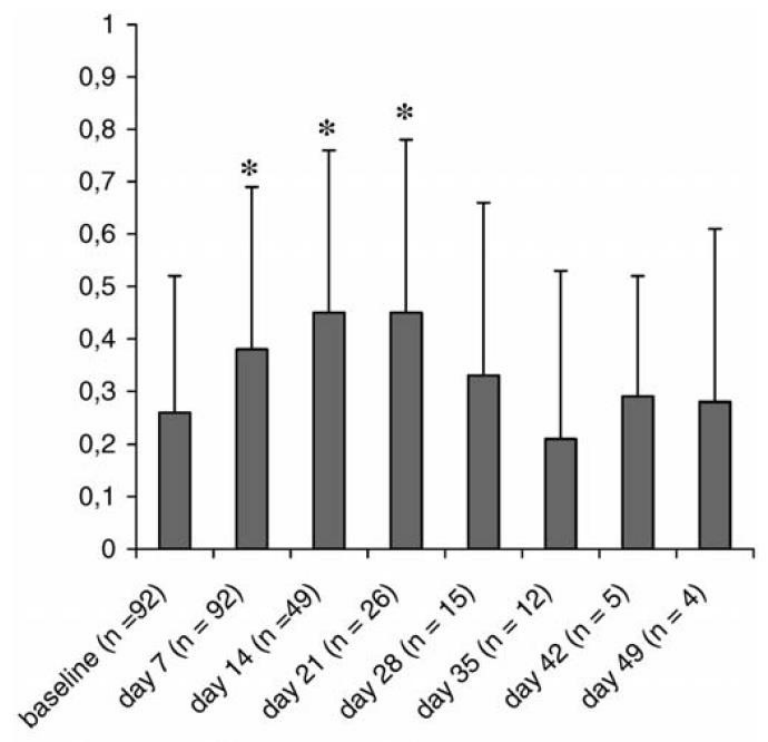
Table 2. CLINICAL VALUE OF *CANDIDA SPP* COLONIZATION PARAMETERS*

Colonization Parameters	Sensitivity	Specificity	Positive Predictive Value†	Negative Predictive Value
No. of distinct body sites colonized with *Candida spp*				
Two sites or more	100	22	44	100
More than two sites	73	56	50	77
Three sites or more	45	72	50	68
Candida colonization index	100	69	66	100
Candida corrected colonization index	100	100	100	100

Pittet D et al. Ann Surg. 1994

Colonisation en **réanimation médicale**: beaucoup de malades concernés mais **augmentation** au cours du séjour. *Charles PE et al. Int Care Med, 2005*

	ICU admission	ICU discharge or death
CI value	0.26±0.26	0.35±0.33*
Patients without colonization (0.2≥ CI)	32 (34.8%)	33 (35.9%)
Patients with mild colonization (0.5> CI >0.2)	39 (42.4%)	22 (23.9%)
Patients with heavy colonization (CI ≥0.5)	21 (22.8%)	37 (40.2%)*



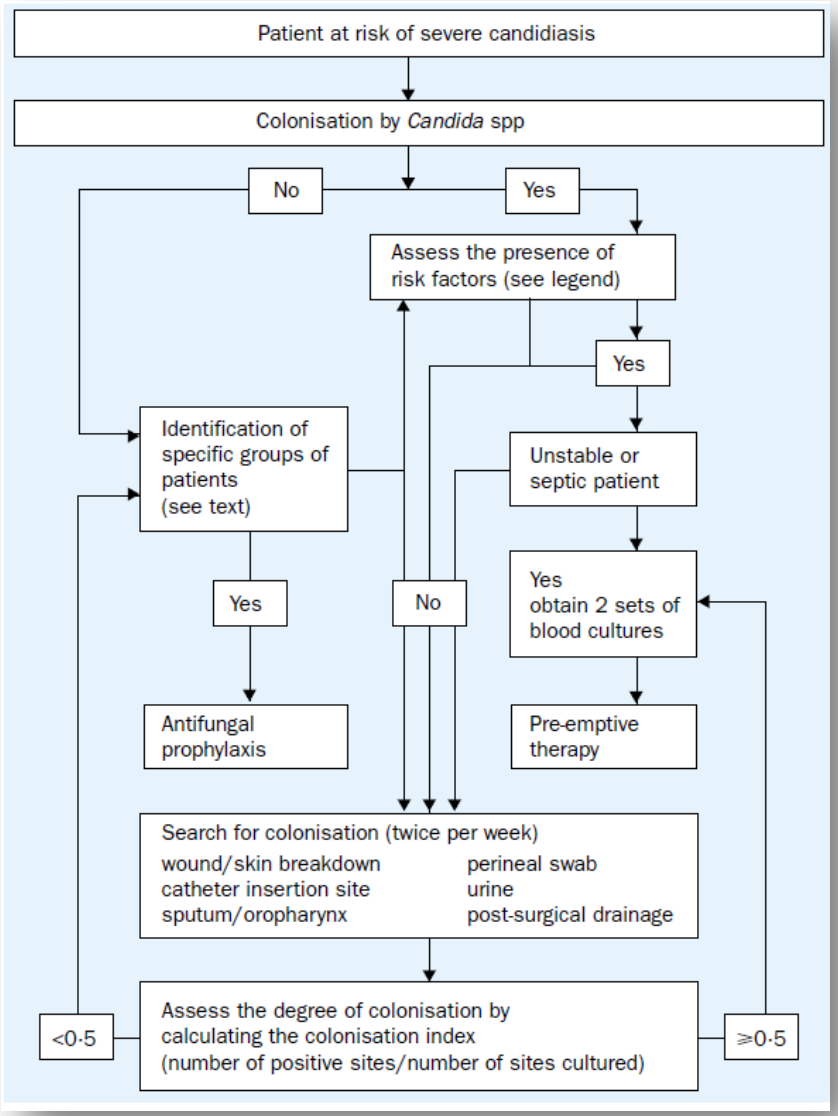
Facteurs liés à cette évolution de colonisation

Table 4 Multivariate analysis of predictive factors of growing colonization index in the ICU (β regression coefficient, *Conf. int.* confidence interval)

	β	95% Conf. int.	p
Broad-spectrum antibiotic therapy (no. of days)	0.01	0.01 to 0.02	$\leq$0.05
Systemic antifungal therapy (no. of days)	–0.02	–0.03 to 0.01	$\leq$0.05
Hematological malignancy	0.41	0.09 to 0.73	$\leq$0.05
Candiduria	0.20	0.09 to 0.31	$\leq$0.05

Charles PE et al. Int Care Med. 2005

Comment utiliser la colonisation dans une stratégie préemptive en pratique? *Eggimann P et al. Lancet Inf Dis. 2003*



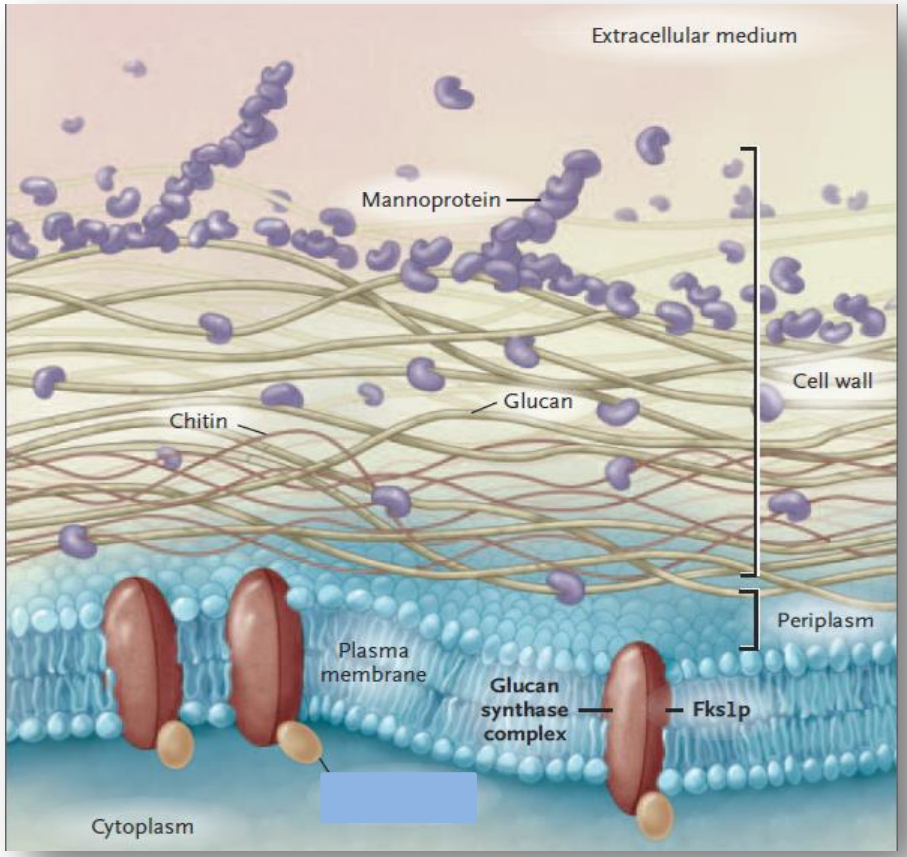
Mais les attitudes ne sont pas consensuelles

Table 5 Management options for clinical suspicion of ventilator-associated pneumonia

	Infectious disease specialists (*n*=39)		Critical care specialists (*n*=47)		Total (*n*=86)	
	n	%	*n*	%	*n*	%
Colonizing organism, no treatment	37	94.9	22*	46.8	59	68.6
Colonizing organism, I start prophylaxis	0	–	1	2.1	1	1.2
Pathogen, I start antifungals[a]	2	5.1	23**	48.9	25	29.1
I don't know, I would seek advice	0	–	1	2.1	1	1.2

Eggimann P et al. Int Care Med. 2005

Stratégie préemptive et **biomarqueurs**: molécules de la **paroi fongique** circulant dans le sérum des patients



Représentation schématique de la paroi de *Candida* (*Bennett JE. NEJM. 2006)*

Test immunologique: détection des manannes circulant par Platelia® ELISA.

Immunocapture par un anticorps m

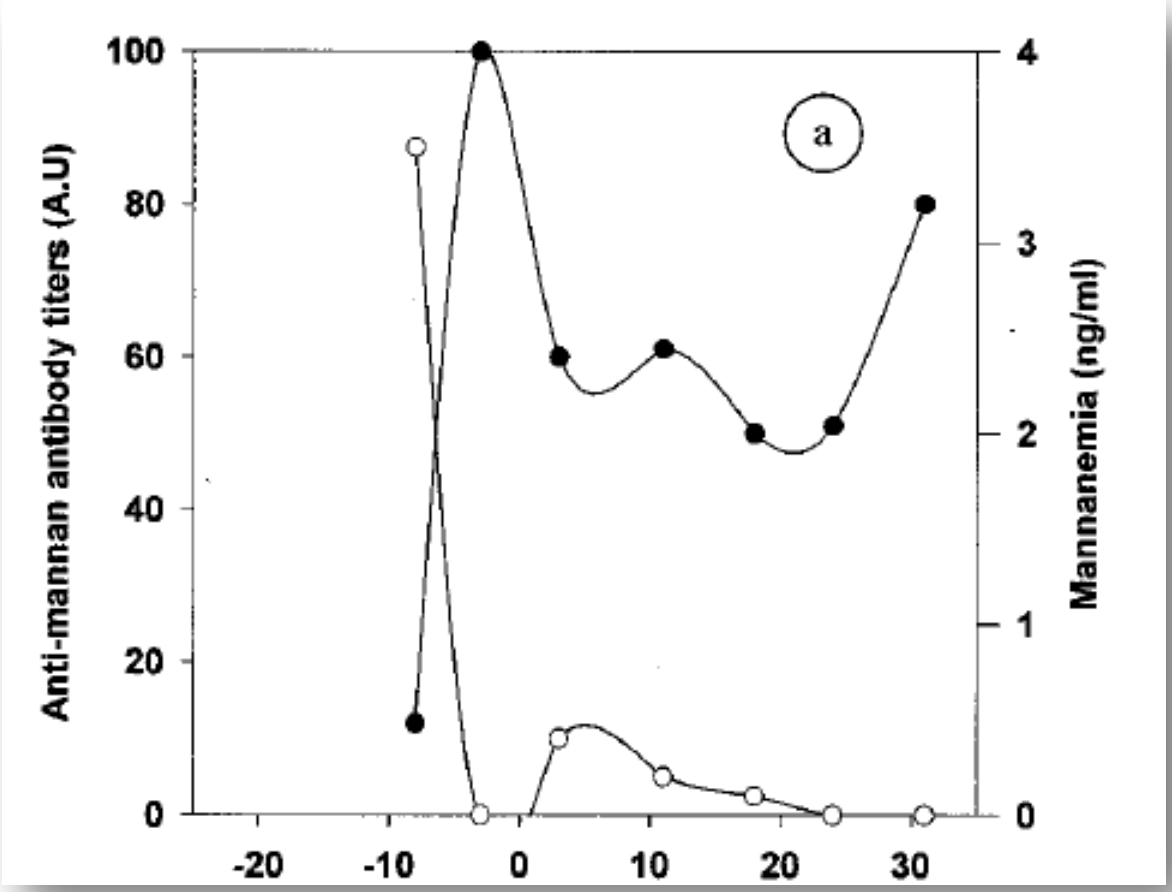
D

g

Repose l'activation de la cascade enzymatique du limulus test, rendue spécifique pour les glucanes.

Récemment introduit en France.

Une **cinétique** complémentaire de la mannanémie et de la réponse Ac anti-mannanes



Sendid B et al. JCM. 1999

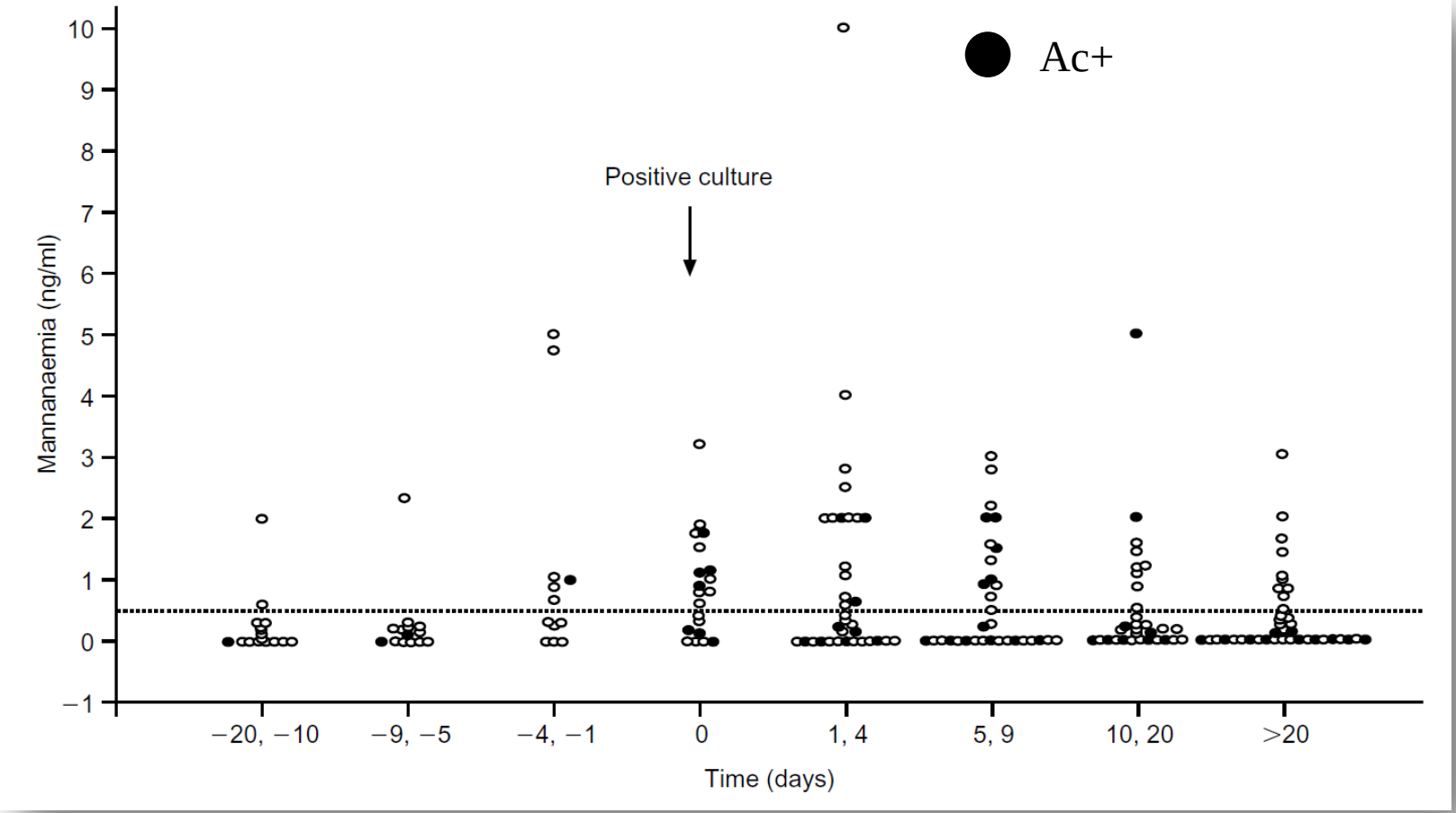
Mannanes circulant : un biomarqueur **spécifique**

TABLE 5. Sensitivity, specificity and predictive values for the detection of α- and β-mannanemia detection tests[a]

Parameter	Value (%) for test		
	Platelia *Candida* Ag	EIA 5B2 homologous system	Combination of both tests
Sensitivity	69	69	85
Specificity	98	95	95
Positive predictive value	86	75	79
Negative predictive value	94	94	97

Sendid B et al. JCM. 2004

Mais **peu précoce**



Sendid B et al. J Med Microbiol. 2002

Détection combinée Ag/Ac sensible, mais **peu précoce**

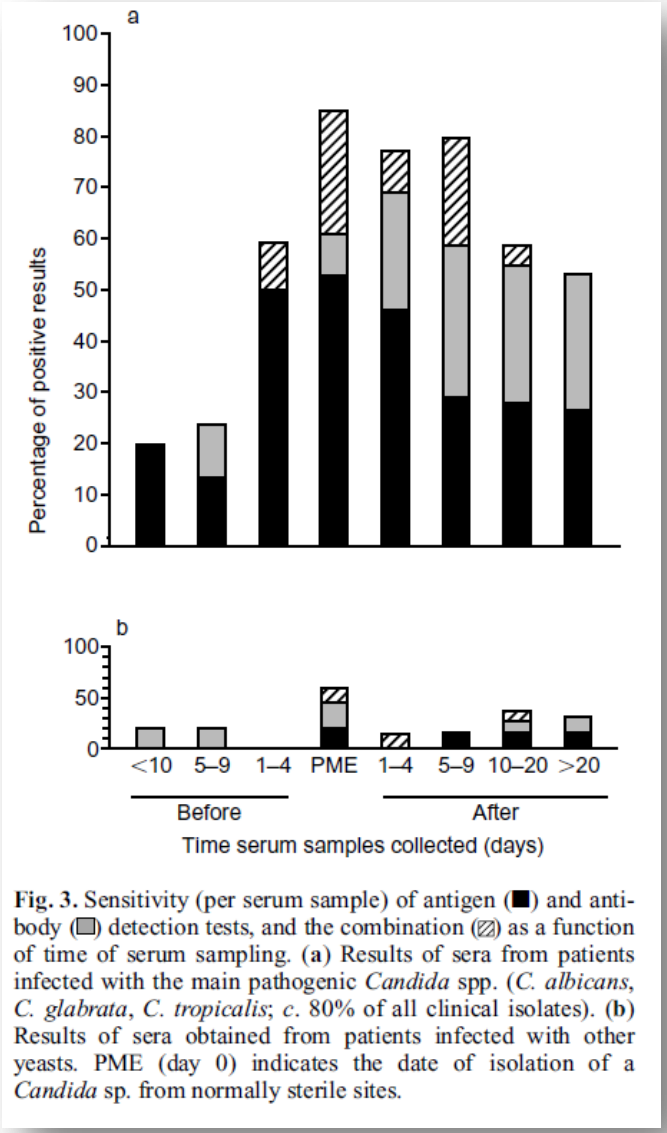


Fig. 3. Sensitivity (per serum sample) of antigen (■) and antibody (▩) detection tests, and the combination (▨) as a function of time of serum sampling. (**a**) Results of sera from patients infected with the main pathogenic *Candida* spp. (*C. albicans*, *C. glabrata*, *C. tropicalis*; *c.* 80% of all clinical isolates). (**b**) Results of sera obtained from patients infected with other yeasts. PME (day 0) indicates the date of isolation of a *Candida* sp. from normally sterile sites.

- Sensibilité<50% pour parapsilosis, krusei et kefyr
- Meilleures performances en hématologie vs réanimation

Sendid B et al. J Med Microbiol. 2002

Glucanémie en réanimation, des performances contrastées

Table 3 (1,3)-β-D-Glucan serum levels and presumed efficiency parameters of (1,3)-β-D-glucan serum concentrations ≥40 pg/ml in long-term ICU patients with proven fungal infections (group A, *N* = 24) and in long-term ICU patients without fungal infections (group B, *N* = 58)

	Day 7 Group A/group B	Day 10 Group A/group B	Day 14 Group A/group B	Day 17 Group A/group B
(1,3)-β-D-Glucan (pg/ml), median (range)	44 (10–>44)/22 (0–>44)	44 (10–>44)/20 (0–>44)	34.1 (8–<44)/19.8 (0–52)	33.3 (0–>44)/19.3 (0–>44)
No. of patients with (1,3)-β-D-glucan ≥40 pg/ml	12/14	11/8	8/8	6/5
Sensitivity (95% CI)	52.2 (31.1–73.6)	55 (32.1–76.2)	44.4 (22.4–68.7)	33.3 (14.4–58.9)
Specificity (95% CI)	75.9 (62.5–85.7)	82 (67.4–91.5)	80 (63.9–90.4)	85.3 (68.2–94.5)
PPV (95% CI)	46.2 (27.1–66.3)	57.9 (34–78.9)	50 (25.5–74.5)	54.6 (24.6–81.9)
NPV (95% CI)	80 (66.6–89.1)	80 (65.6–90.1)	76.2 (60.2–87.4)	70.7 (54.3–83.4)
LR+ (95% CI)	2.16 (1.19–3.94)	3.09 (1.47–6.5)	2.22 (0.99–4.98)	2.67 (0.8–6.41)
LR– (95% CI)	0.63 (0.4–1.0)	0.55 (0.33–0.91	0.69 (0.44–1.08)	0.78 (0.55–1.12)
AUC ROC[a] (95% CI)	0.7 (0.58–0.82)	0.72 (0.58–0.86)	0.71 (0.57–0.84)	0.65 (0.49–0.82)

ICU, intensive care unit; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positivity; LR–, likelihood ratio negativity; AUC ROC, area under the receiver operating characteristics curve.

[a] AUC of ROC curve for assessing the discriminatory power of the concentration of (1,3)-β-D-glucan in serum.

Presterl E et al. Int J Inf Dis. 2009

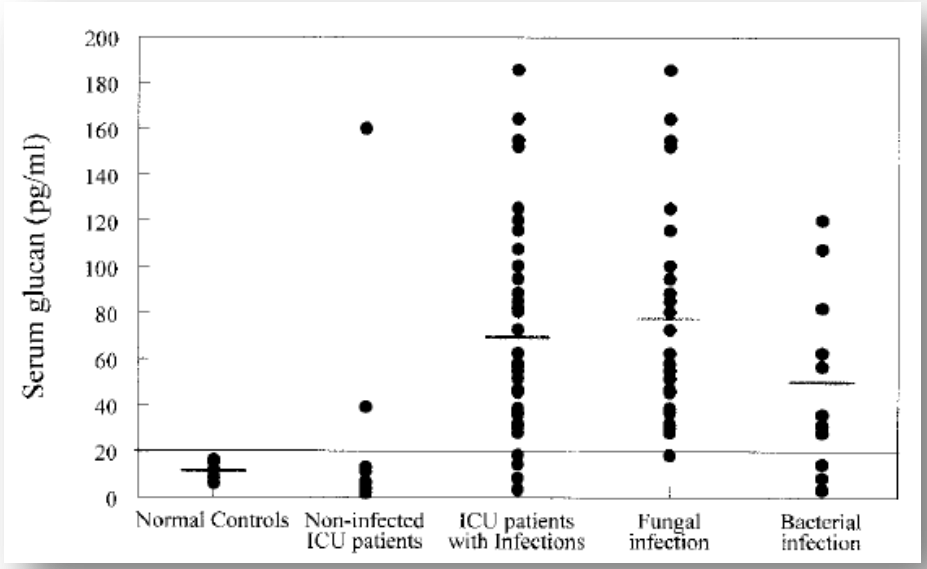
Réanimation chirurgicale: glucanémie sensible, spécificité faible améliorée par la répétition des prélèvements. Faux positifs précoces

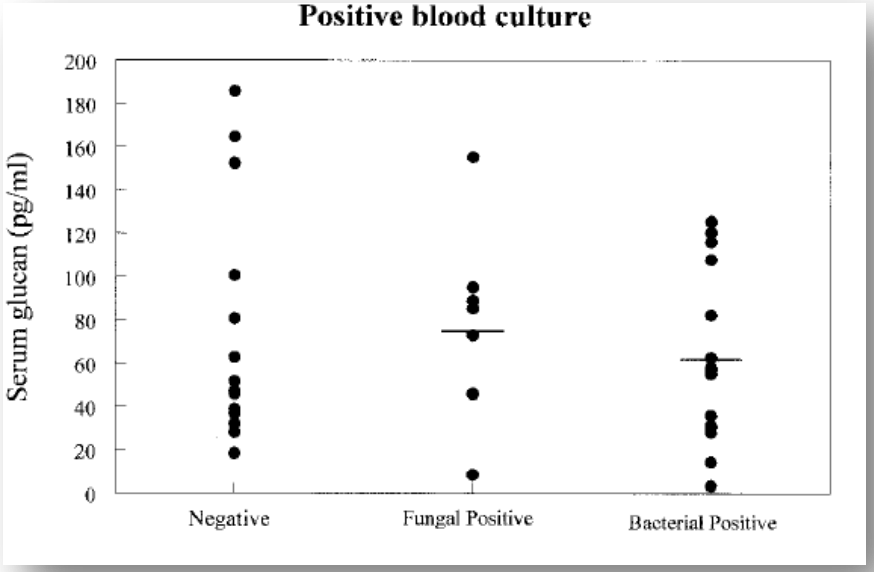
TABLE 3. Sensitivity and specificity of positive (1→3)-β-D-glucan assay for invasive candidiasis in surgical ICU patients based on all samples obtained

No. of positive BG samples	Sensitivity and specificity (%)					
	Proven (n = 3)		Proven plus probable (n = 9)		Proven plus probable plus possible (n = 15)	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
1	100	50	91	57	93	61
2	100	59	66	73	73	80
≥3	100	67	63	73	71	80

Mohr JF et al. JCM. 2011

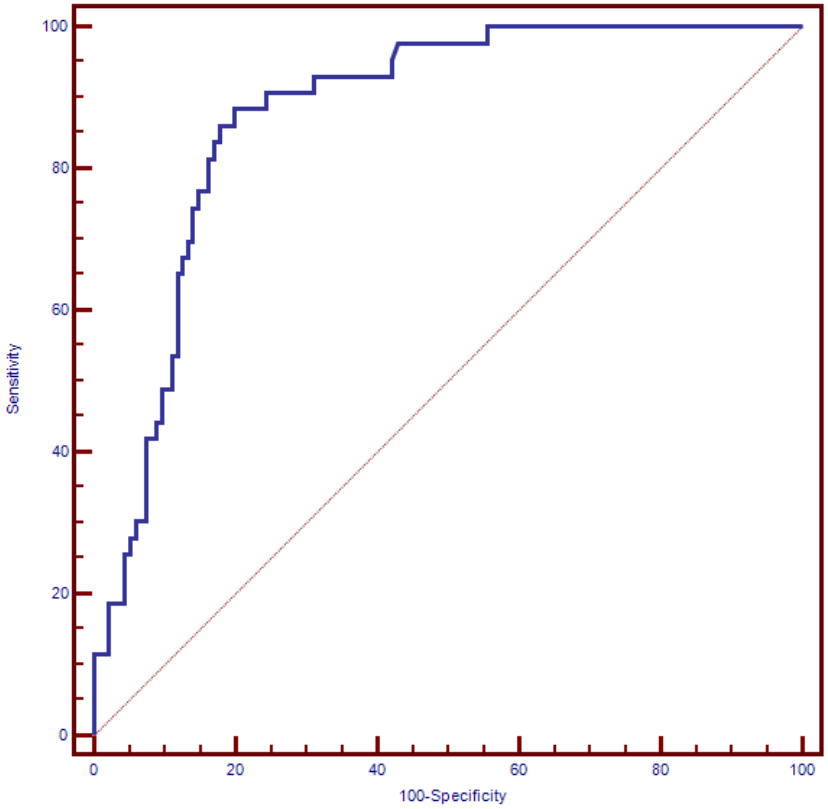
Manque de spécificité régulièrement décrit



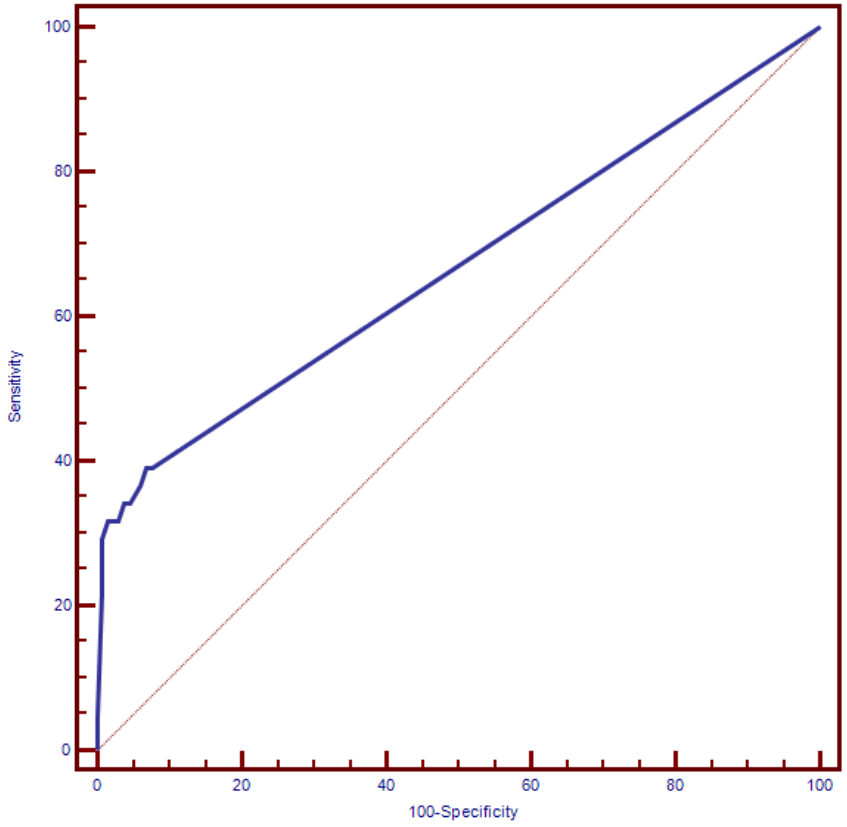


Digby J et al. Clin Diagn Lab Immunol.2003

Evaluation « locale » en réa patients vs candidémiques vs non candidémiques



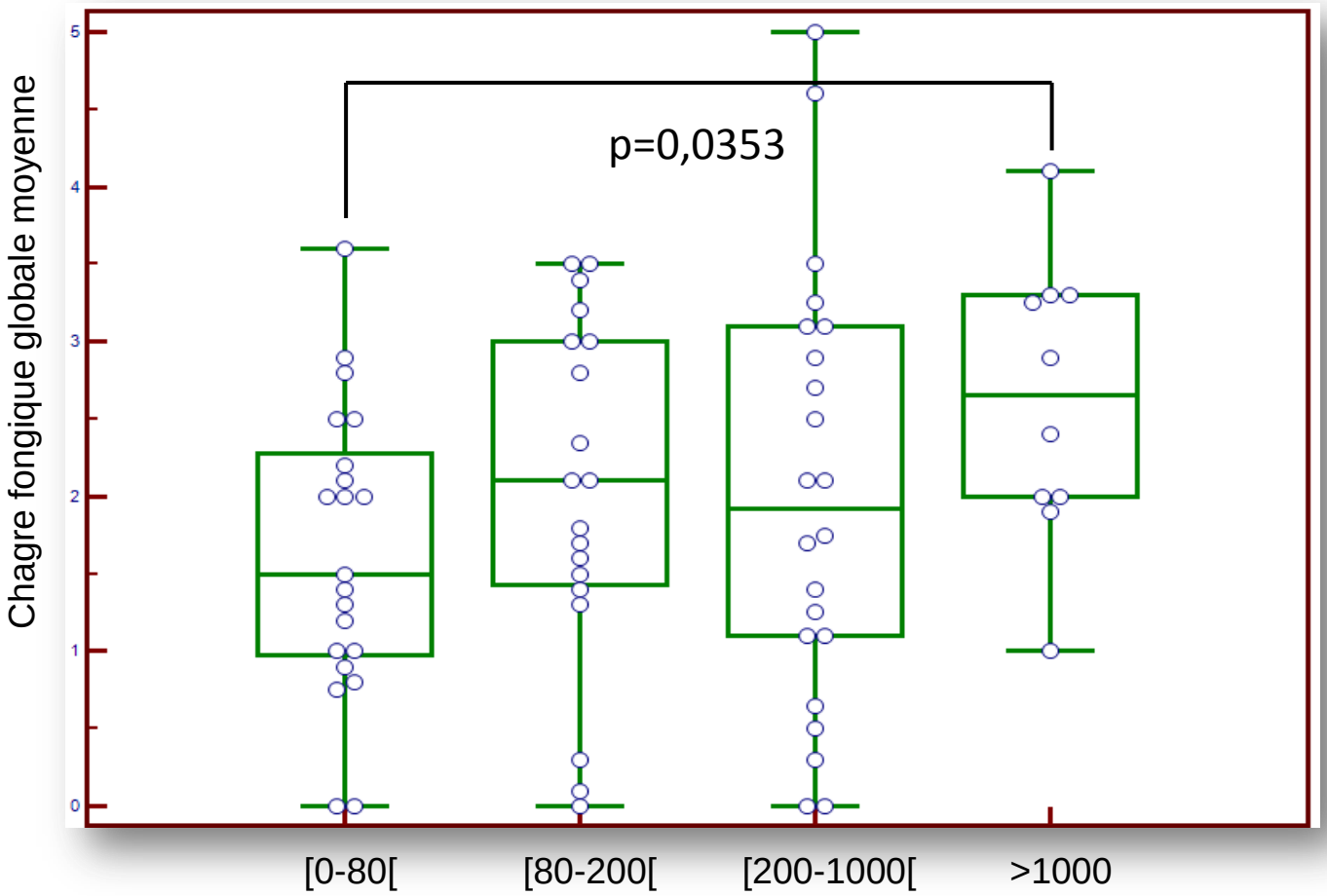
Courbe ROC glucanes



Courbe ROC mannanes

Poissy J et al.

Relation colonisation-glucanémie



Poissy J et al.

Faut il les utiliser en pratique: **recommandations Surviving Sepsis Campaign**

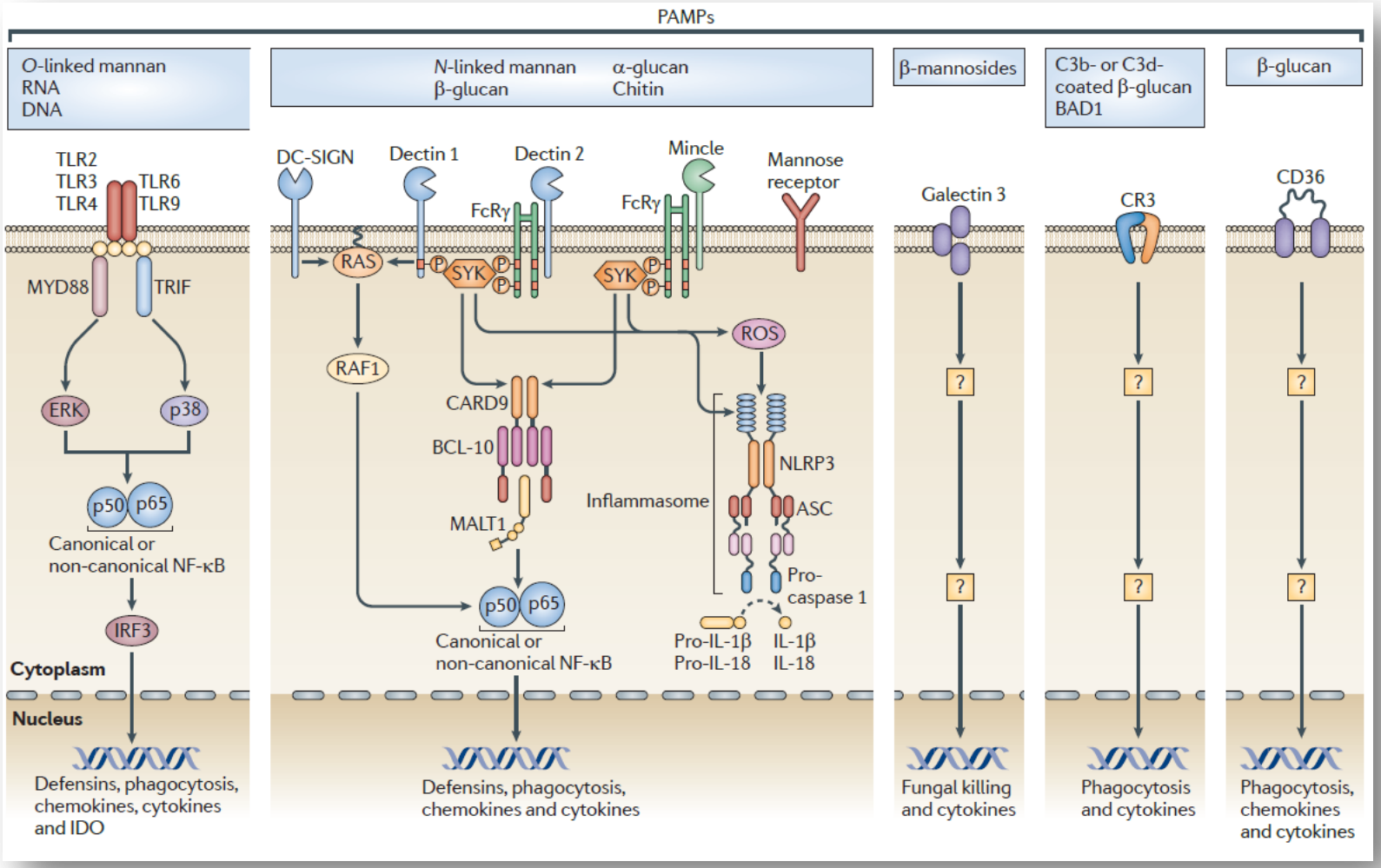
Table 5 Recommendations: initial resuscitation and infection issues

C. Diagnosis

2. Use of the 1,3 β-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available and invasive candidiasis is in differential diagnosis of cause of infection.

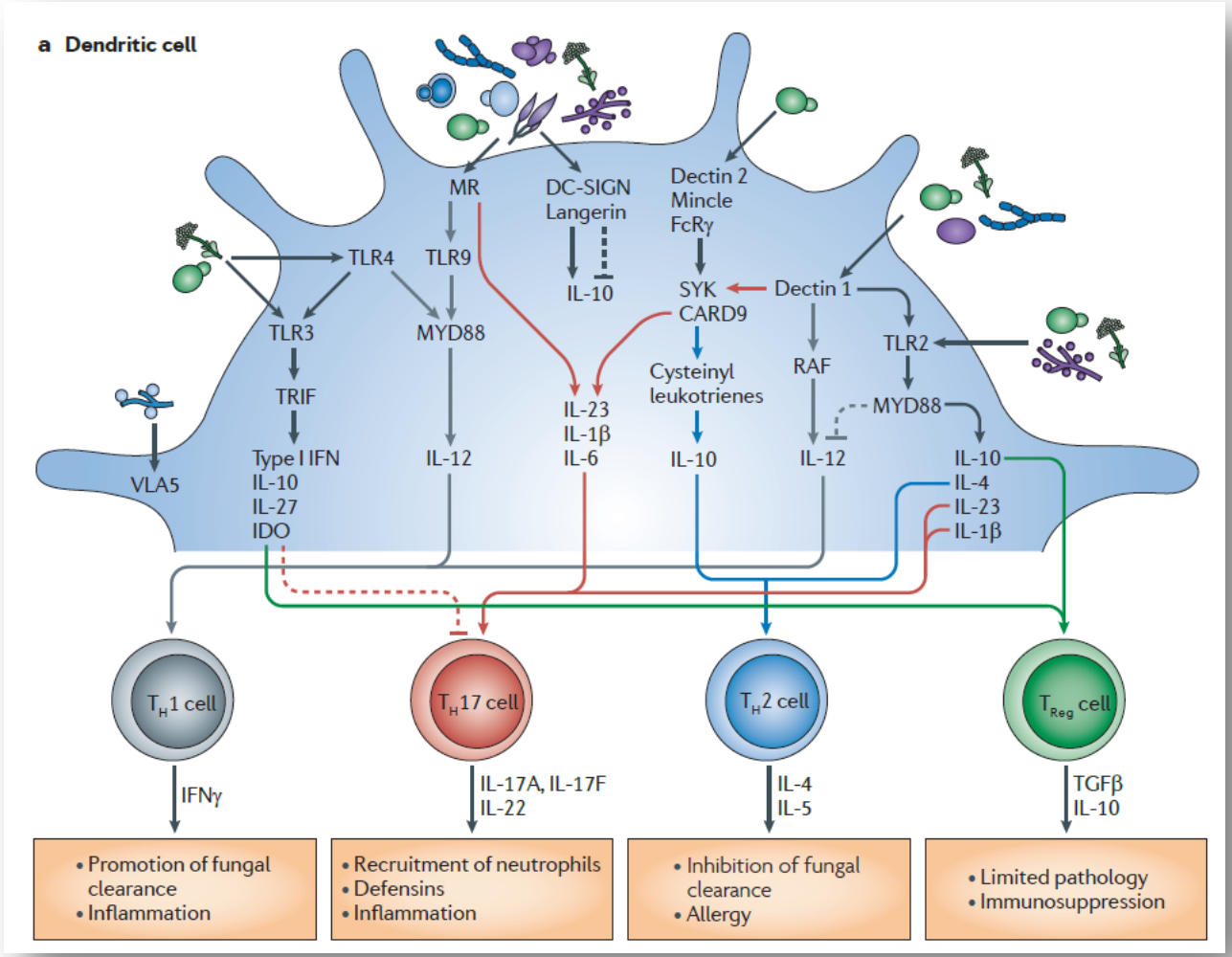
Dellinger RP et al. Int Care Med. 2013

Approche génétique: de nombreux récepteurs impliqués dans la **reconnaissance immune non spécifique** *Romani L. Nat Rev Immunol. 2011*

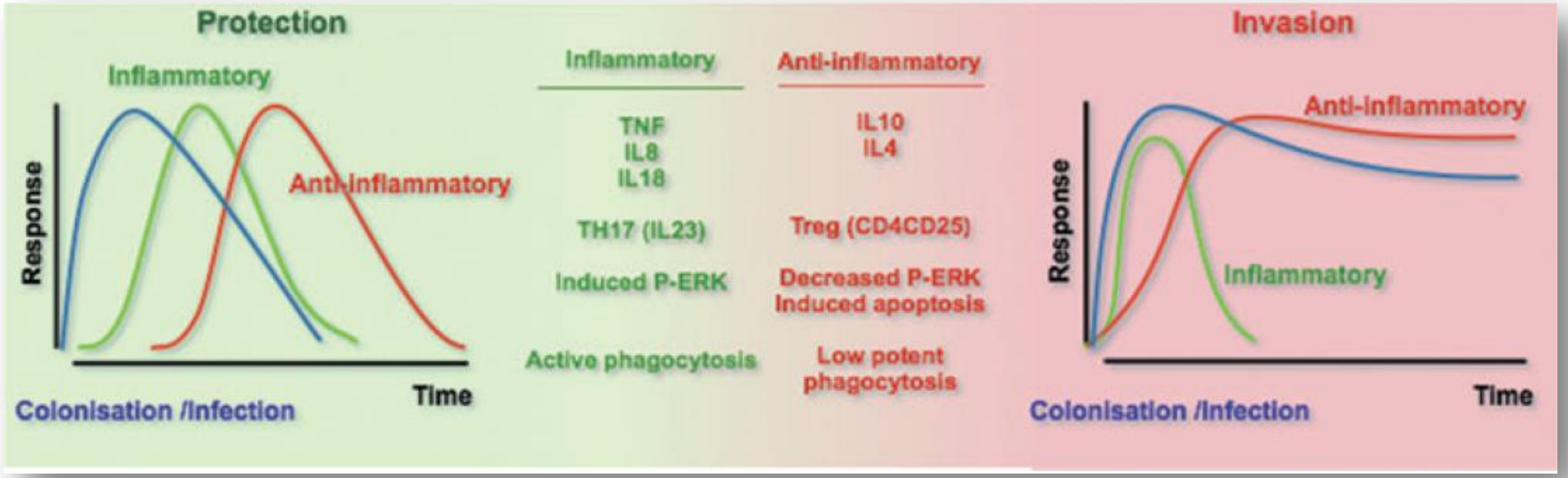


Aboutissant à une **réponse variable**

Romani L. Nat Rev Immunol. 2011

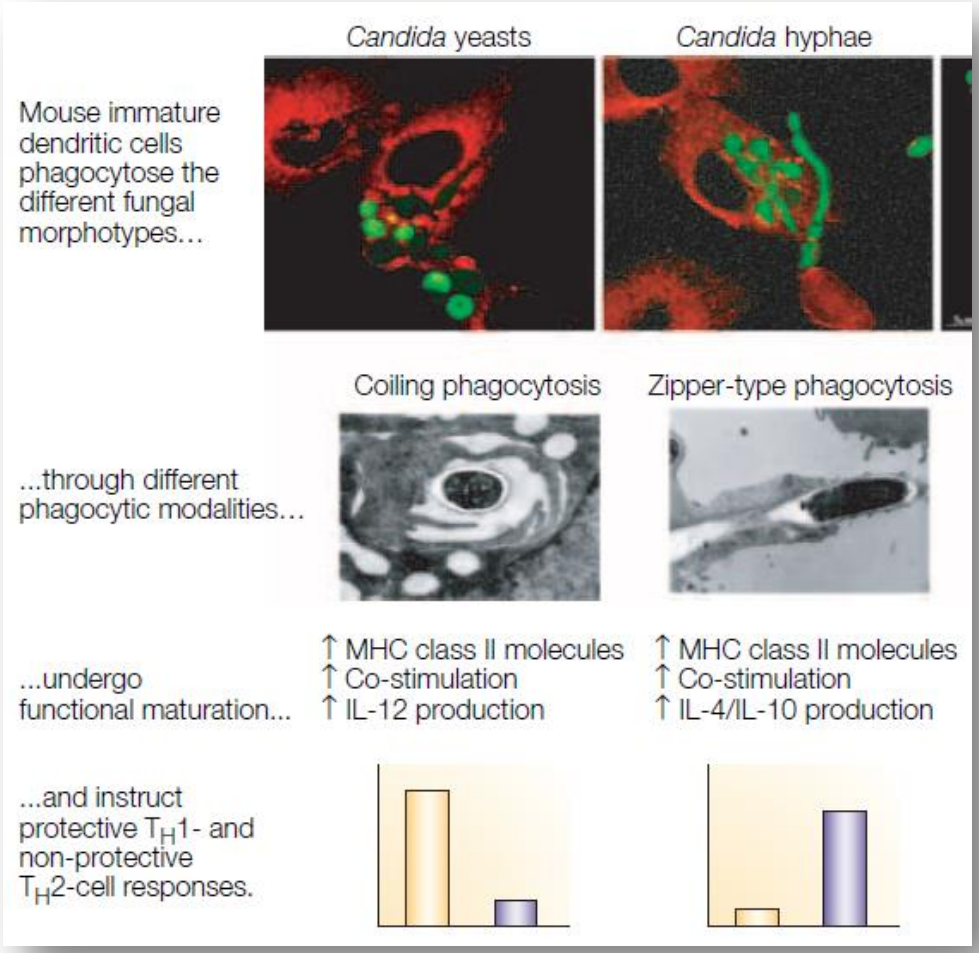


Dont résulte un **équilibre pro/anti inflammatoire** variable



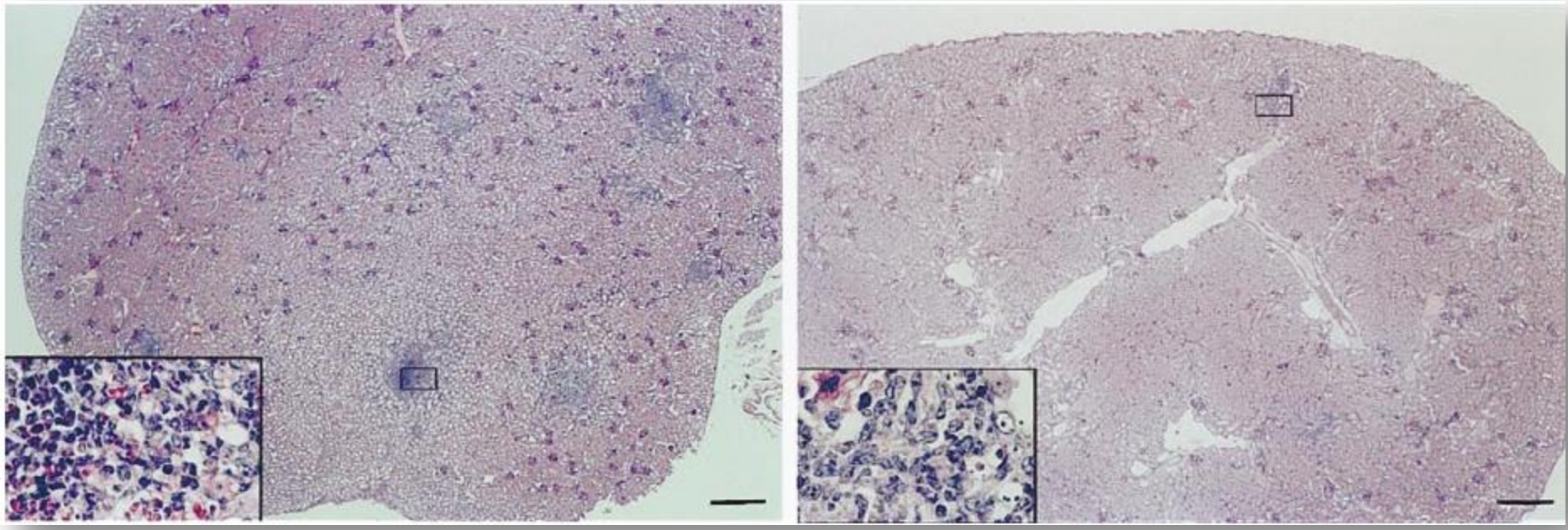
Jouault T et al. Cellular microbiology. 2009

Candida étant par ailleurs capable d'orienter la réponse inflammatoire à son avantage, en fonction de son stade de développement



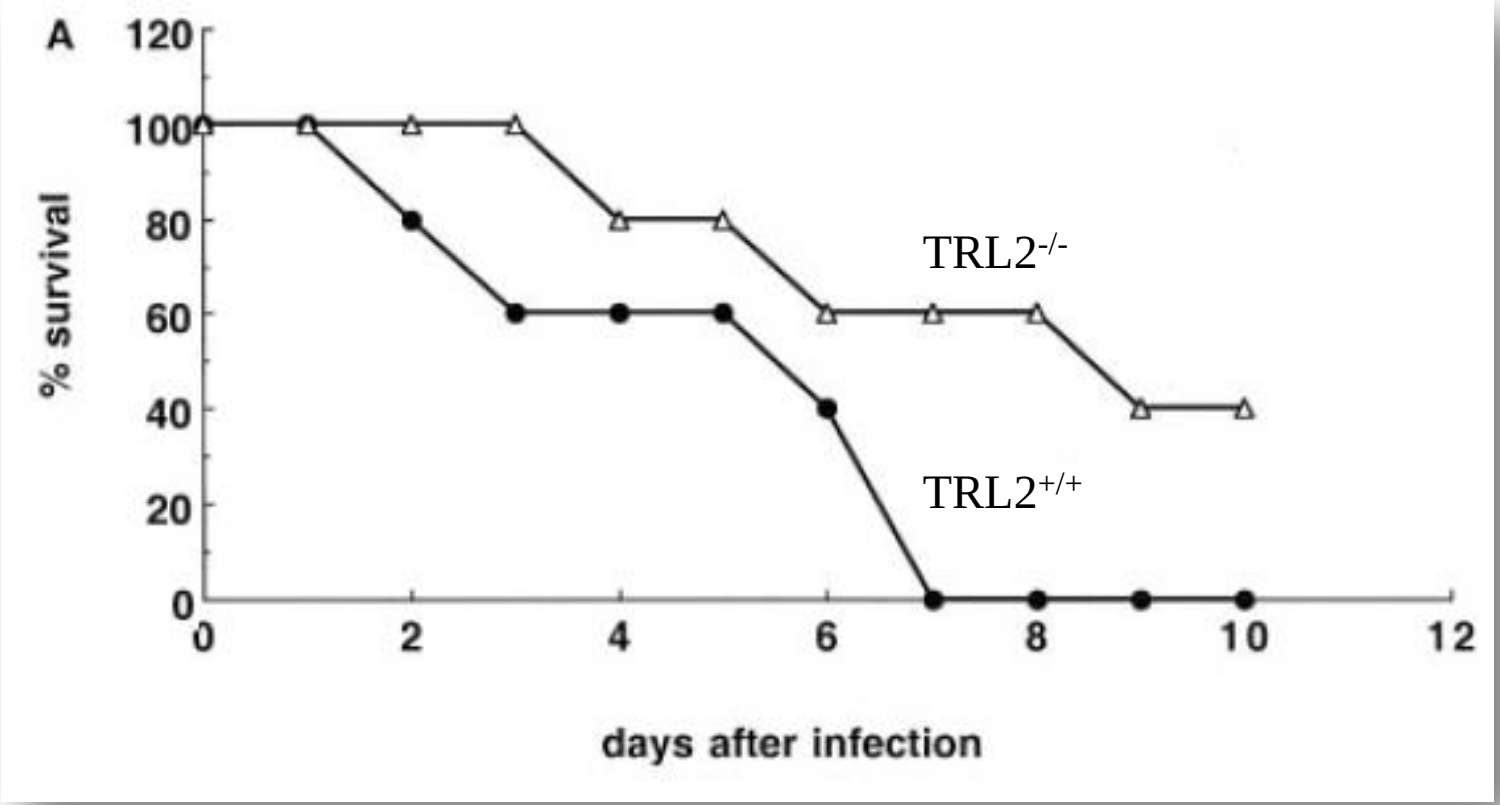
Romani L. Nature Reviews Immunology. 2004

L'effet délétère de l'IL10 dans les infections à Candida



Del Sero G et al. Microbes and infection. 1999

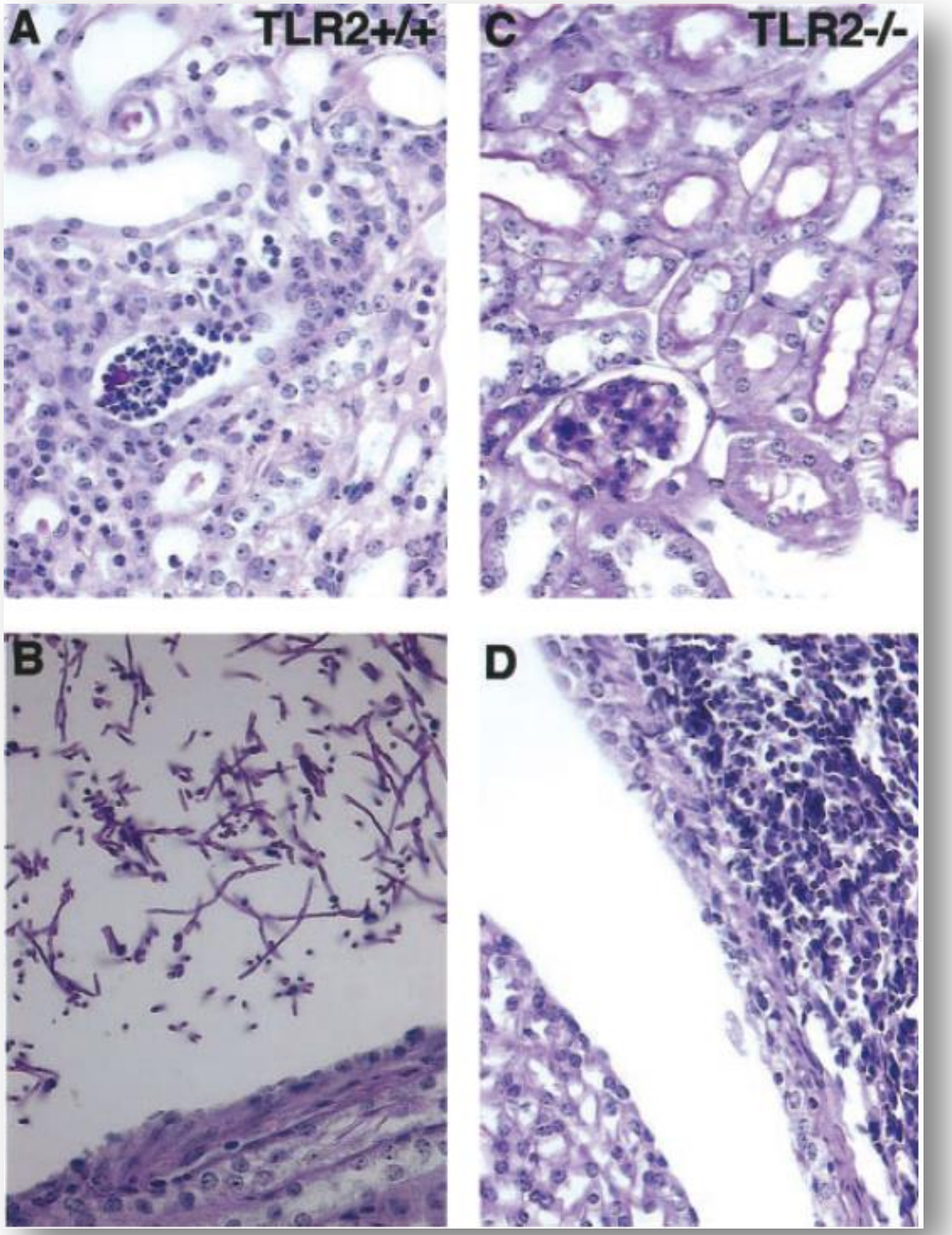
L'impact du **polymorphisme des TLR :** meilleure survie des souris TLR2 KO



Netea MG et al. J Immunol. 2004

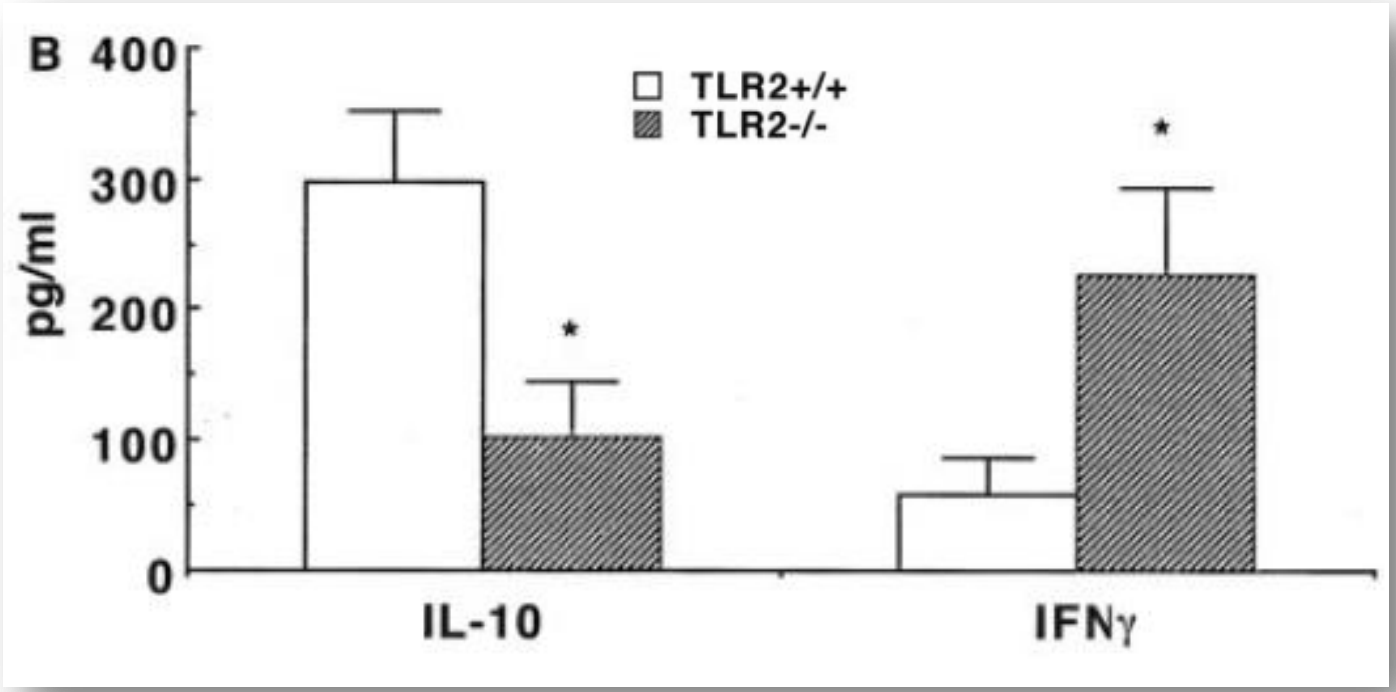
Parenchyme rénal

Cavités pyéliques



Netea MG et al. J Immunol. 2004

Relation entre cytokines et TLR



Netea MG et al. J Immunol. 2004

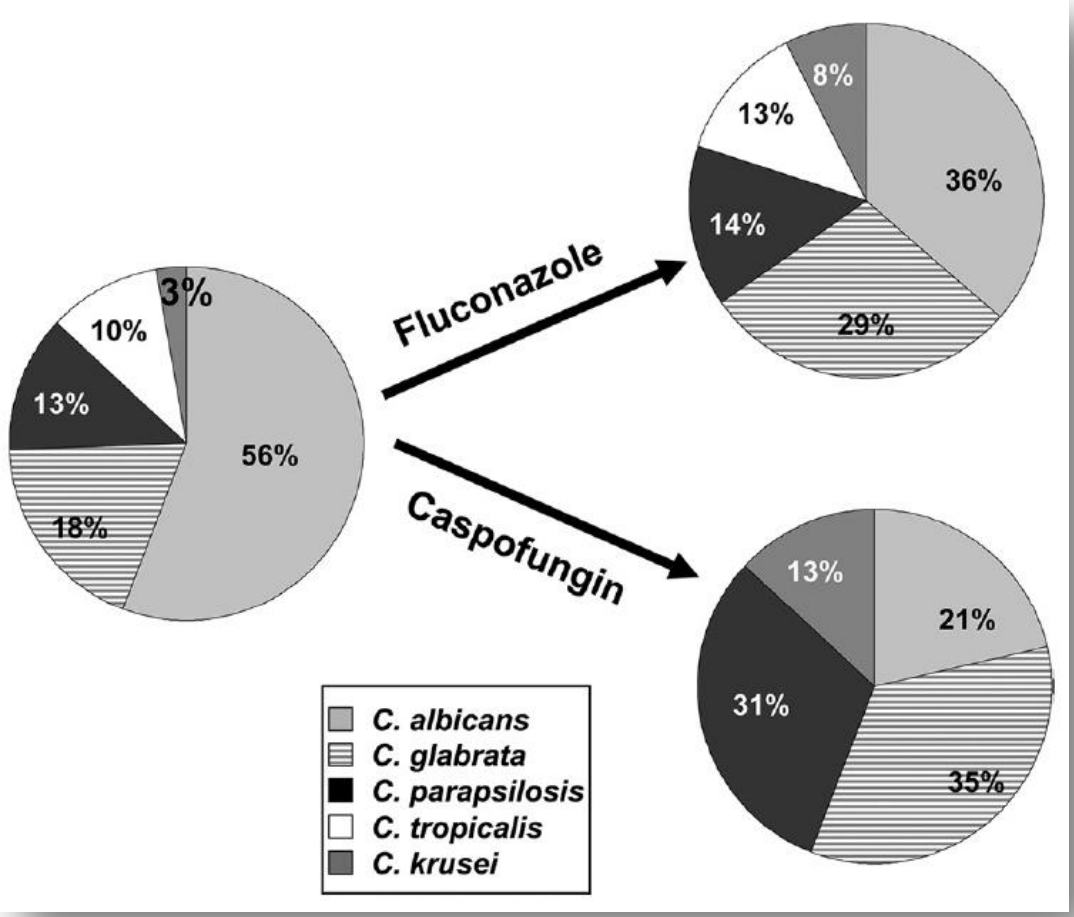
Impact des **polymorphismes** sur **colonisation et candidoses invasives**: exemple de *DECTIN-1* en hématologie

Table 3. Observed *Candida* Species Colonization and Invasive Fungal Disease among Hematopoietic Stem Cell Transplant Recipients

Clinical outcome	Percentage (ratio) of recipients		*P*	OR
	Homozygous wild-type for *DECTIN-1*	Heterozygous for *DECTIN-1* Y238X		
Candida species colonization at hospital admission	31.5 (35/111)	84.6 (11/13)	<.001	11.9
Candida species colonization on day of HSCT (day 0)	45.1 (50/111)	92.3 (12/13)	.001	14.6
Surveillance-culture guided fluconazole therapy	37.8 (42/111)	69.2 (9/13)	.03	3.7
Early candidemia (day 21 or earlier)	8.0 (9/112)	18.2 (2/11)	.26	2.5
Invasive mold disease (day 100 or earlier)	3.0 (3/100)	5.0 (1/20)	.52	1.7

Plantinga TS et al. CID. 2009

N'y a-t-il que des bénéfices à attendre de ces stratégies thérapeutiques dites précoces?



Lortholary O et al. AAC 2011

Pour conclure

- Stratégie empirique à l'efficacité discutable
- Scores cliniques pour une approche probabiliste insuffisamment performants en termes de Se
- Biomarqueurs disponibles
  - Compromis à trouver entre sensibilité et spécificité
  - Les coupler?
  - Les utiliser dans une stratégie de dépistage de patients à « sur-risque »?
  - Les utiliser pour éliminer des patients non à risque et ainsi éviter des traitements inutiles?
- L'avenir?
  - L'approche génétique
- Attention à l'impact écologique potentiel