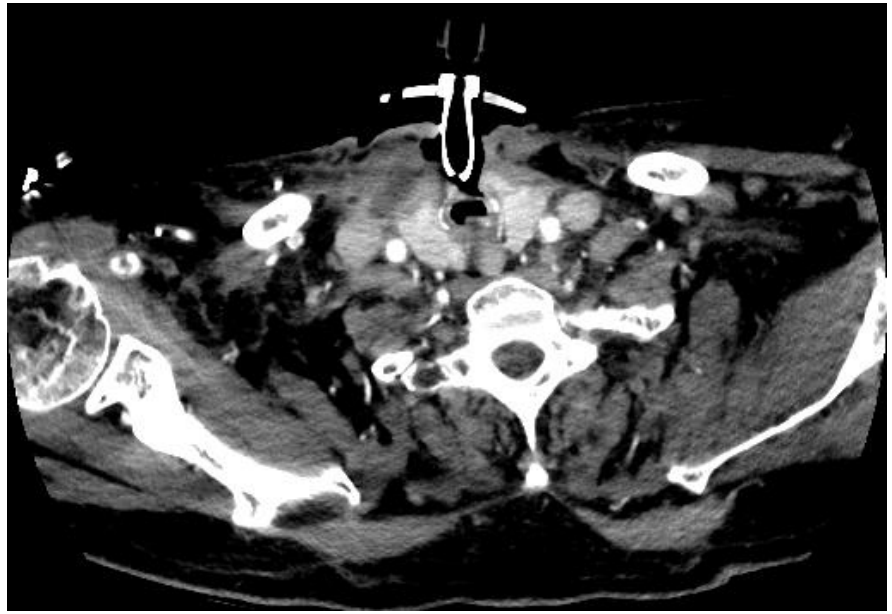
Candidémie

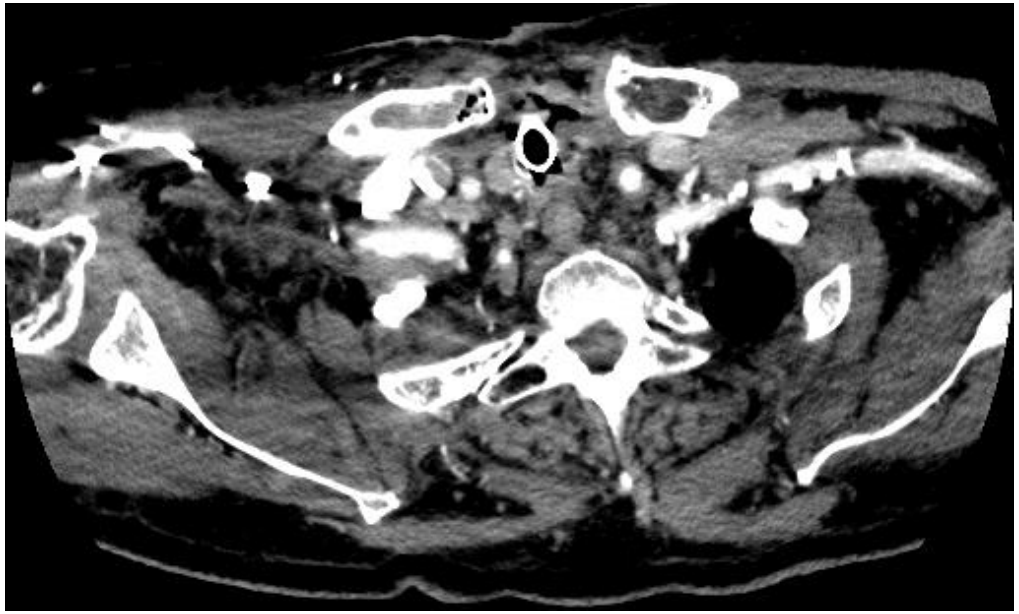
Pr Julien Poissy
Médecine intensive/Réanimation CHRU Lille

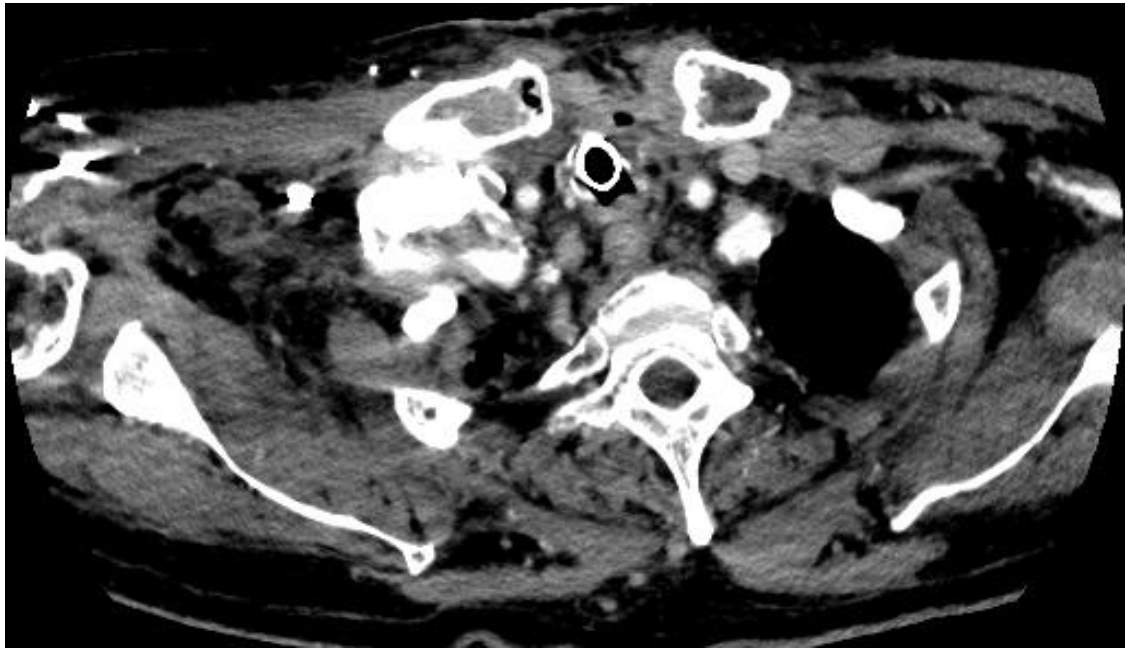
DUCAI
15/02/2024

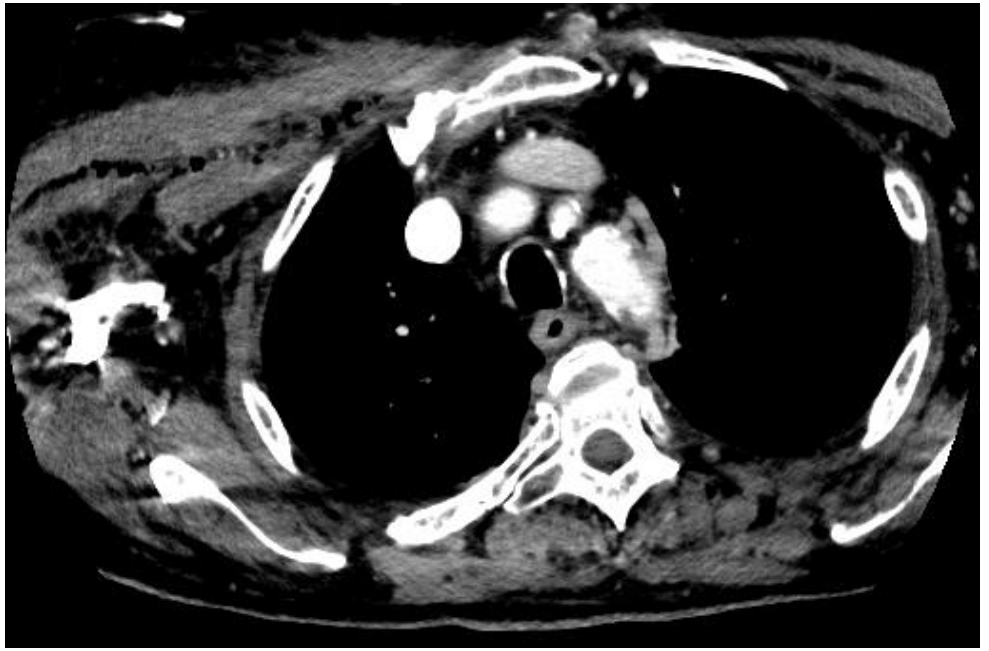
Petite histoire clinique

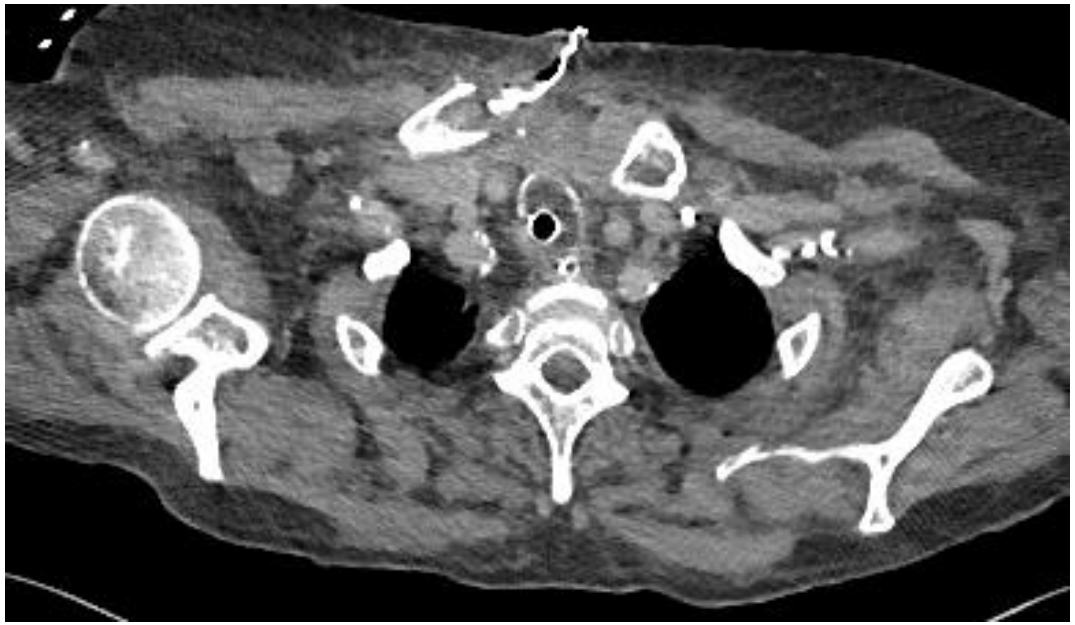
- **Homme de 67 ans**
- **Polyvasculaire : cardiopathie ischémique stentée et hypertensive, AVC sylvien, sténose carotidienne**
- **BPCO post-tabagique (120 PA)**
- **Laryngectomie sus-glottique pour adénocarcinome ORL avec curage ganglionnaire et radiothérapie en mars 2022**
- **03/09/2022 : dyspnée et douleur thoracique. Contexte de douleur d'épaule depuis 3 semaines, traitée par amoxicilline par MT**
- **Urgences : masse pectorale, CRP=480 mg/L, PCT=2,8 ng/mL. Ins rénale aiguë modérée**
- **Apparition d'un état de choc nécessitant noradré. Introduction ATB pipéracilline/tazobactam + linézolide**

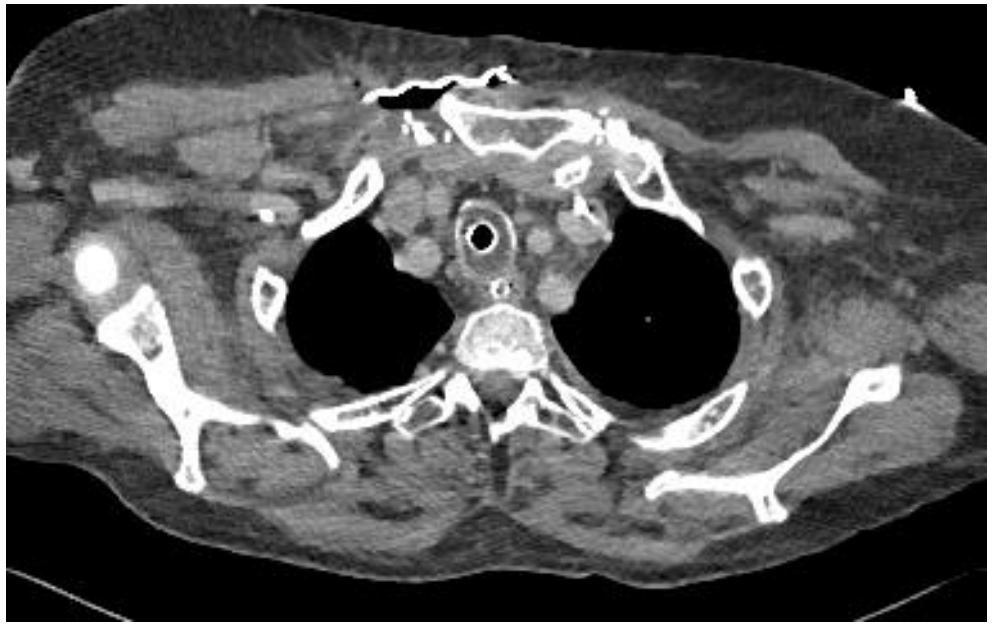


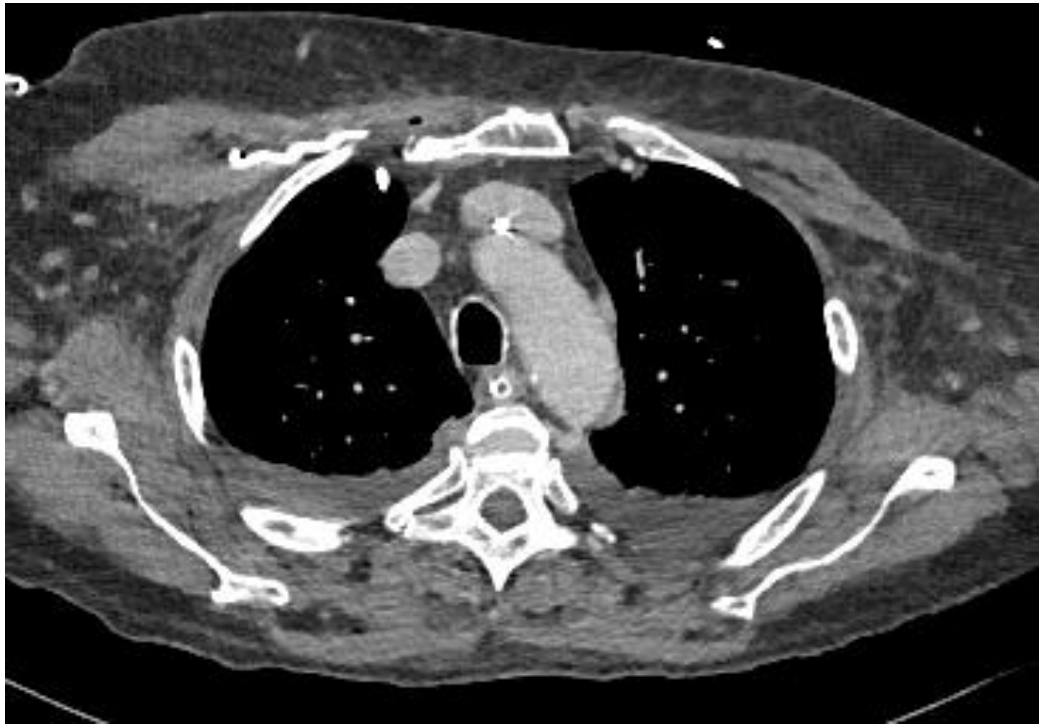


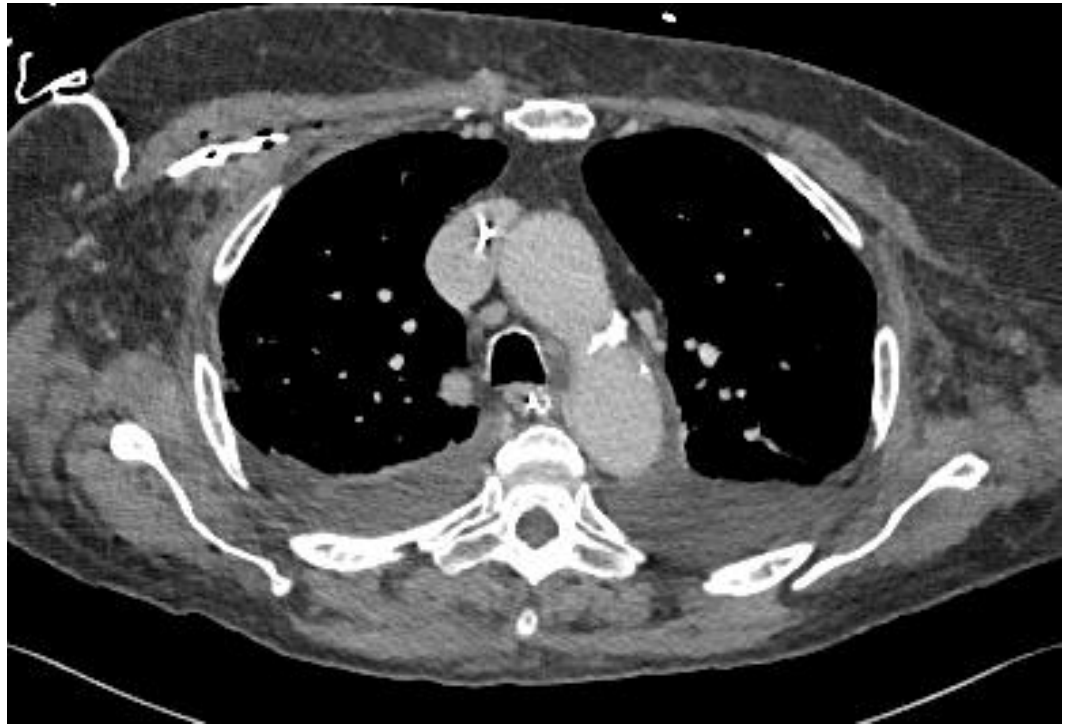


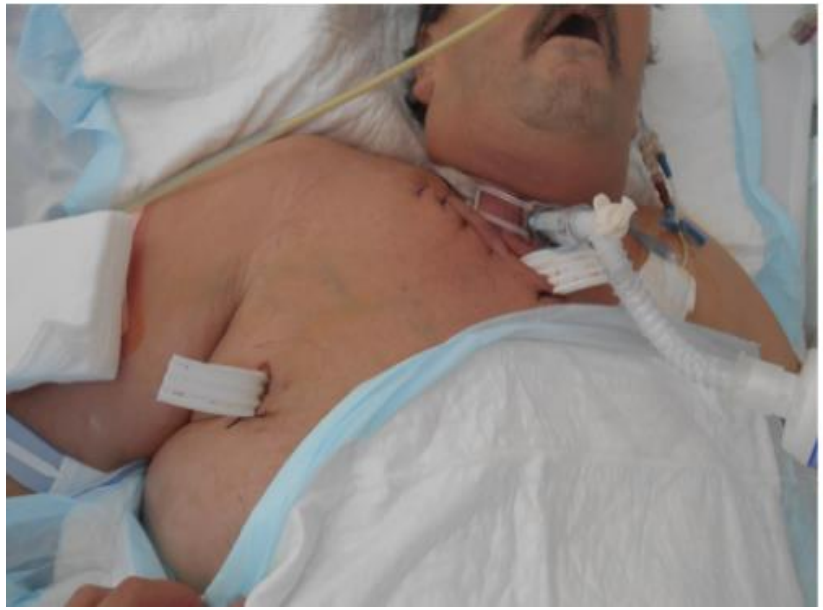
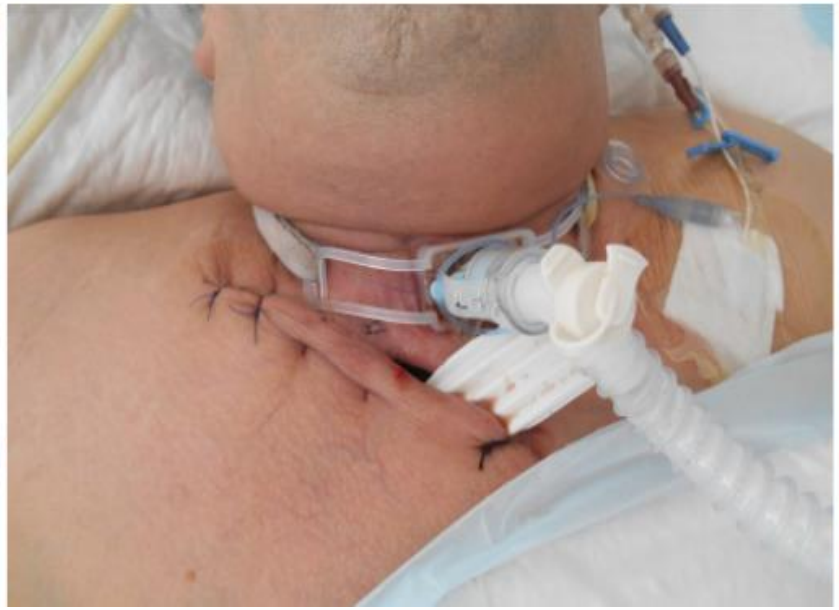
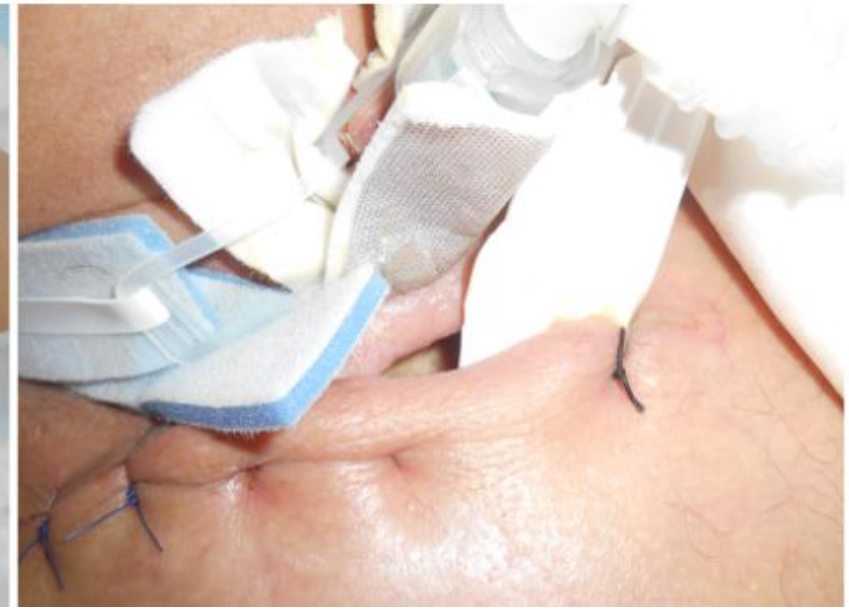




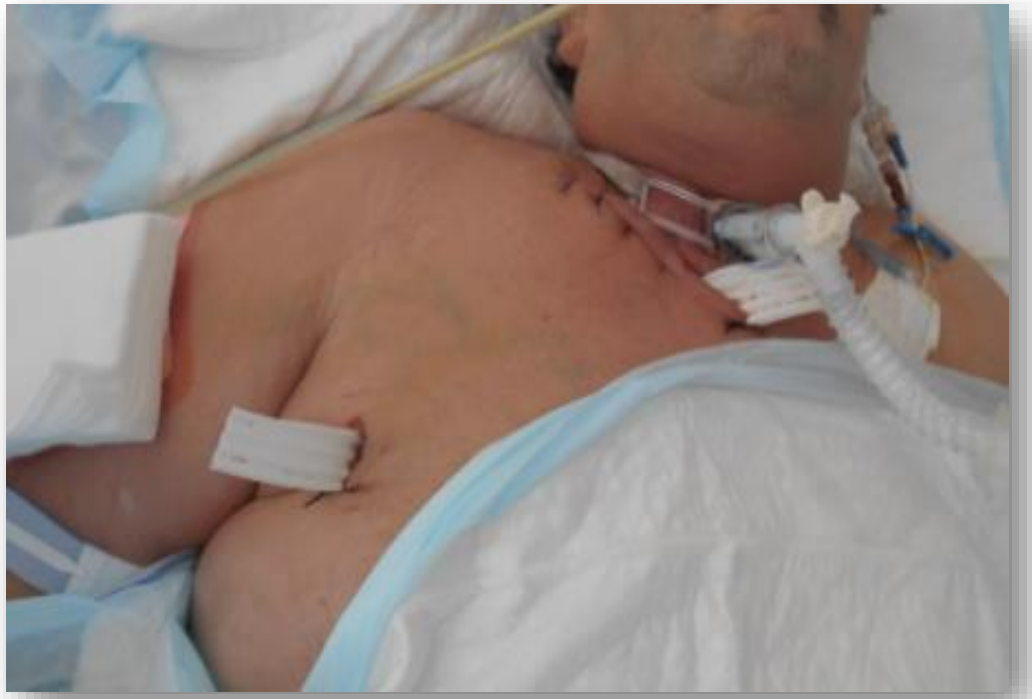






T2MR :
albicans/tropicalis
Prélevé le 06/09 17h30
Rendu le 07/09 13h



Per-op
tropicalis/krusei (07/09)
S/fluco-R (09/09)

Mannane : 220 pg/mL
BDG : 92 pg/mL
(rendu le 06/09)

Colonisation (culture) :
tropicalis posa R : gastrique/urines
krusei fluco R : gastrique/nasal

Hémoc mycosis
neg

Mannane : 43 pg/mL
BDG : 65 pg/mL
(rendu le 06/09)

05/09
ATB/chir

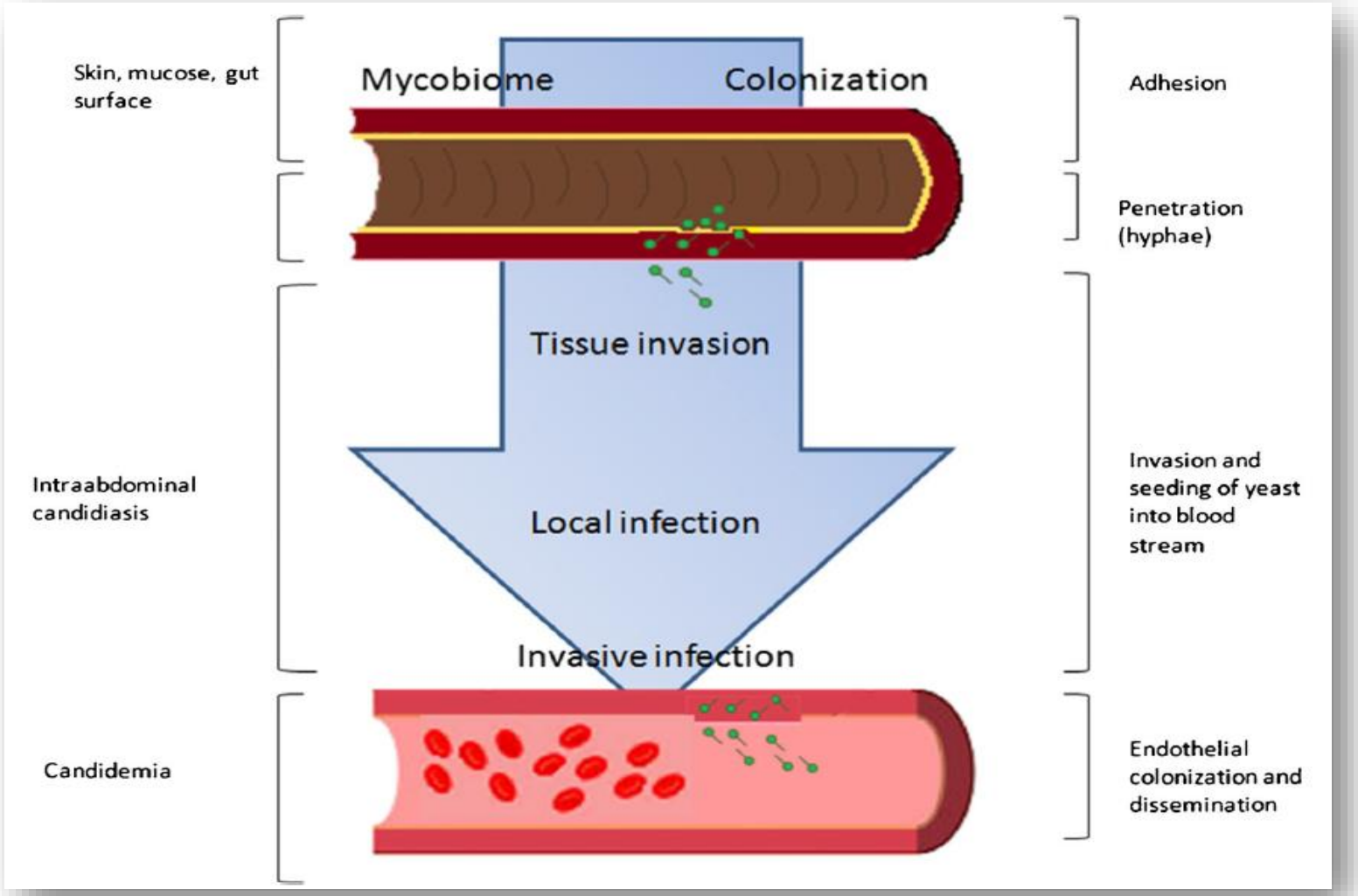
06/09
ATF

07/09

08/09

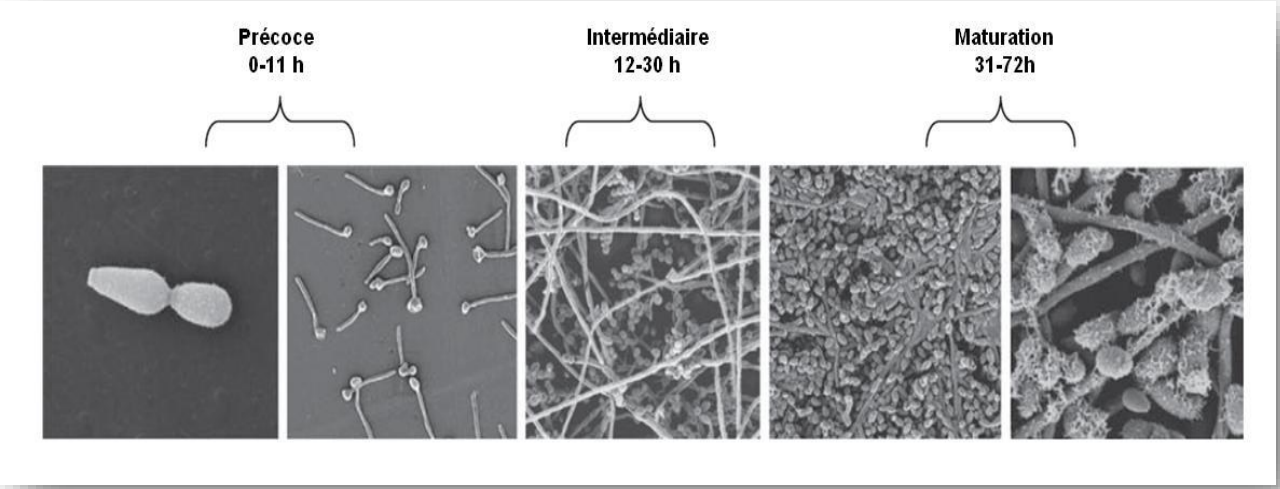
25/09
PAVM

Candidose invasive (CI): un **modèle de relation hôte-pathogène** dans la **transition colonisation/infection**

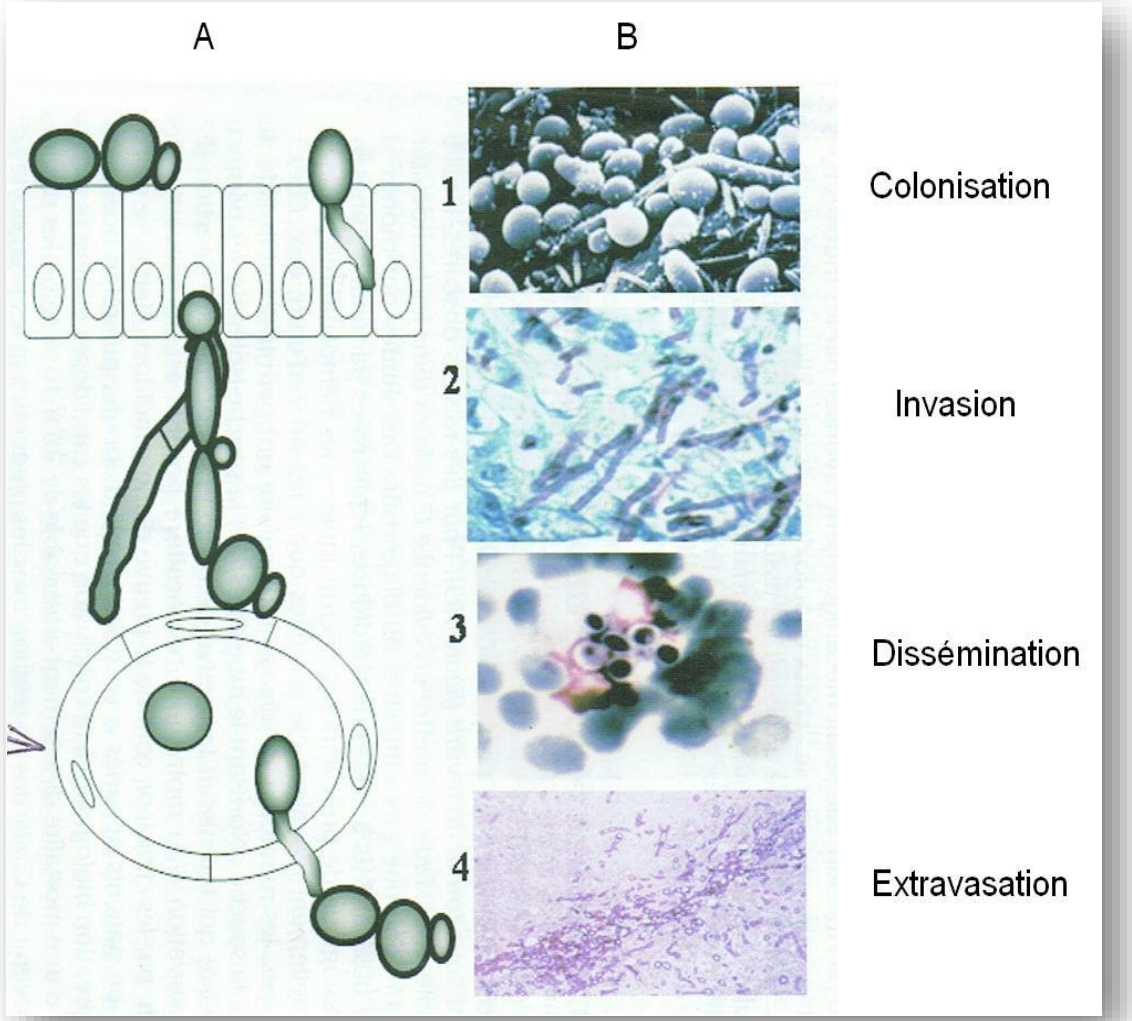


Lagunes L, Relo J. Eur J Clin Microbiol Infect Dis. 2016

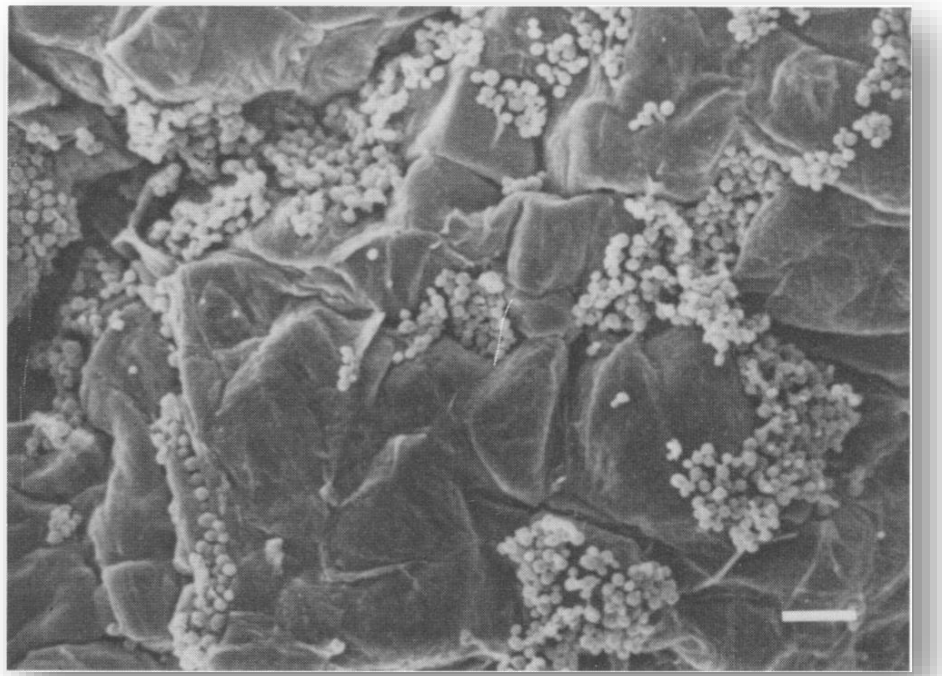
Transition colonisation/infection : **-1) expression d'un programme intégré de virulence** -2) déséquilibre dans la réponse de l'hôte

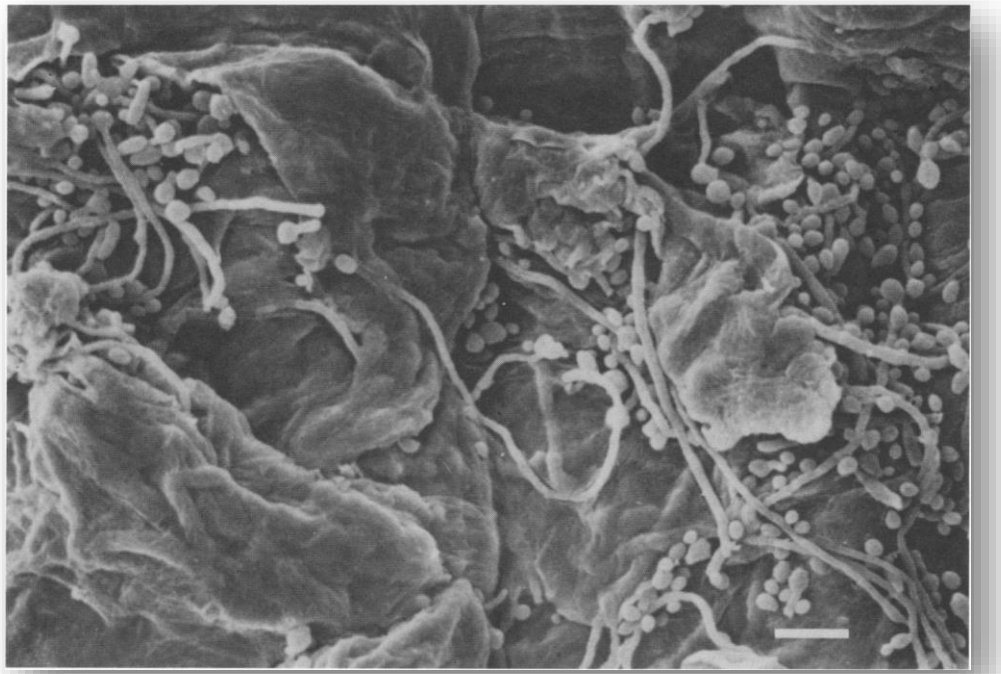


Ramage G et al. Crit Rev Microbiol. 2009



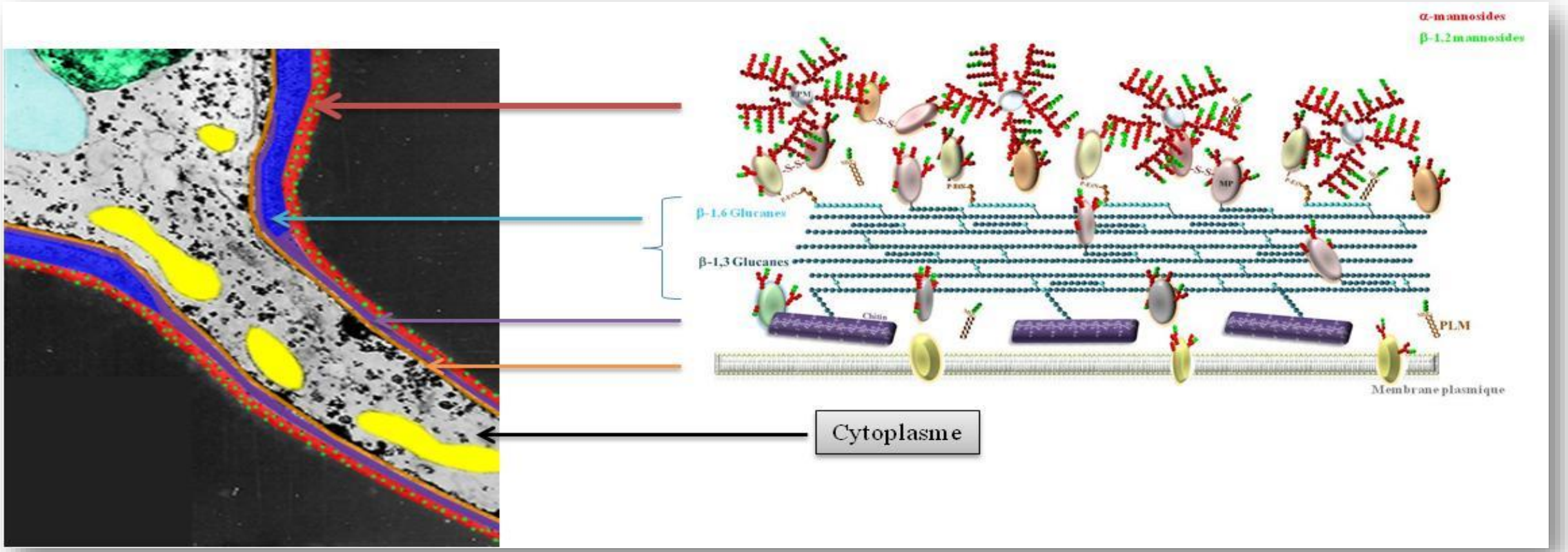
Poulain D. In « Les mycoses ». Ed Elsevier. 2003.



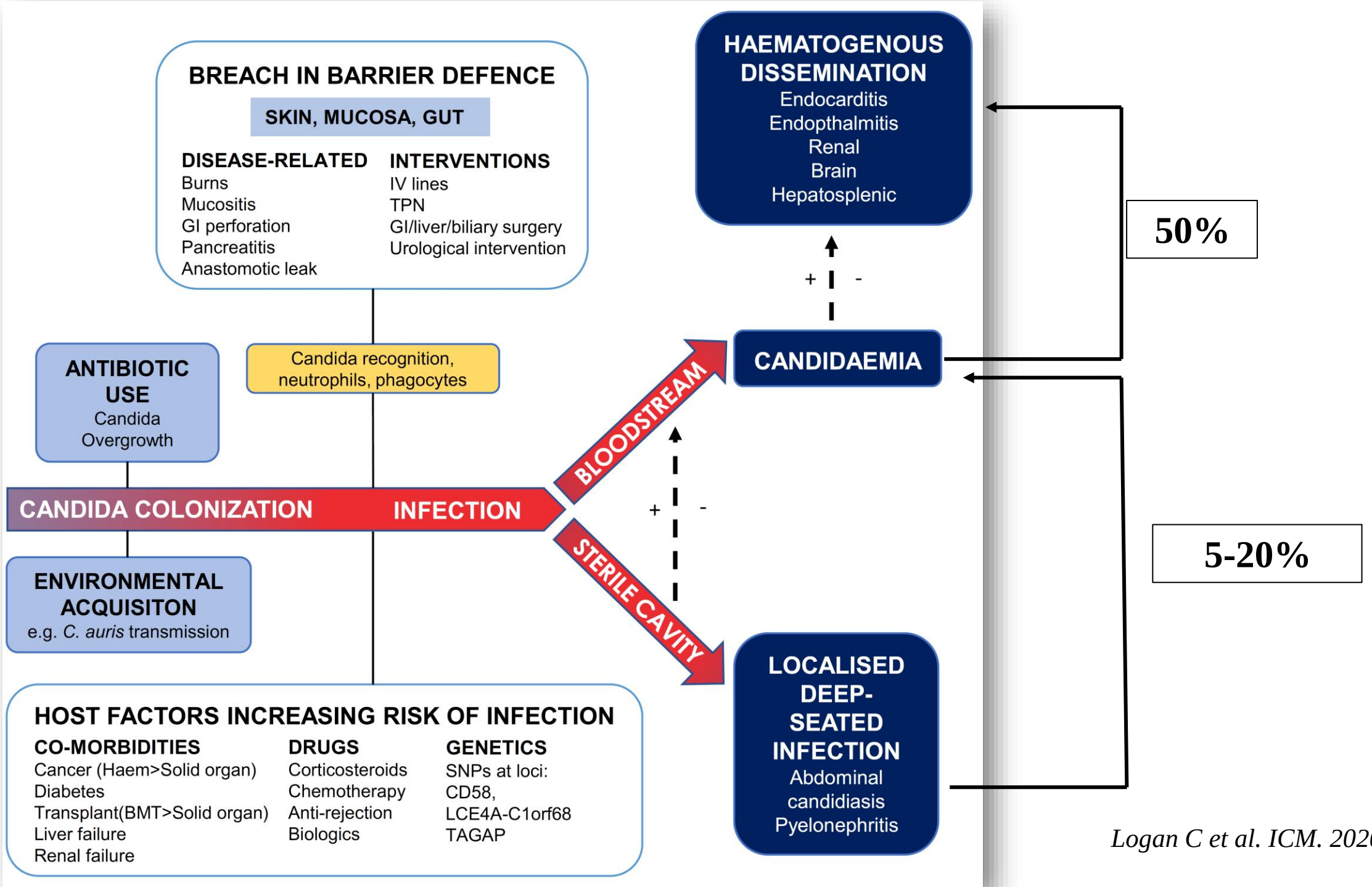


Ray TL. Infect and Imm. 1998

L’adhésion aux cellules épithéliales implique des **composants de la paroi**

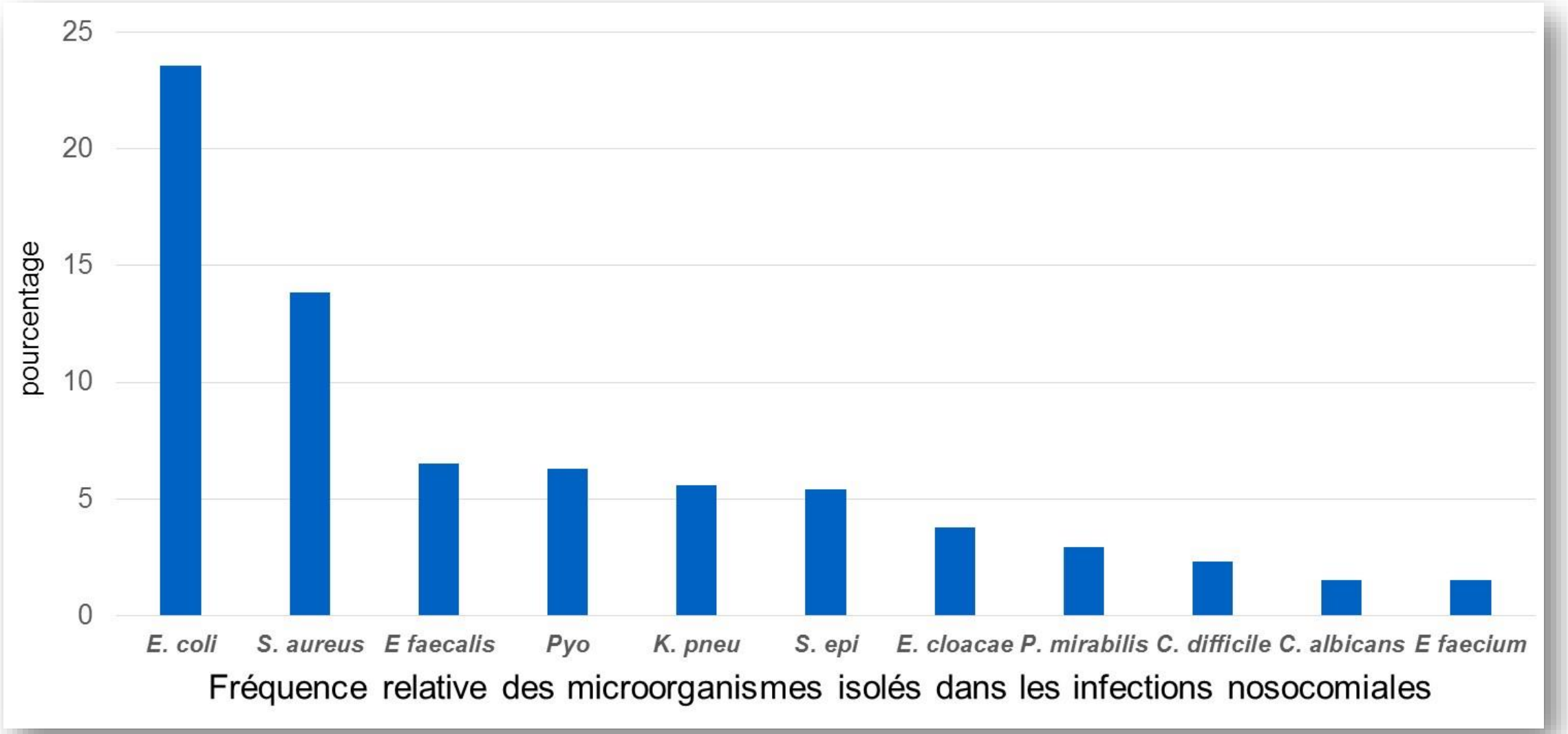


Picture EM: D Poulain; schedule: C Fradin



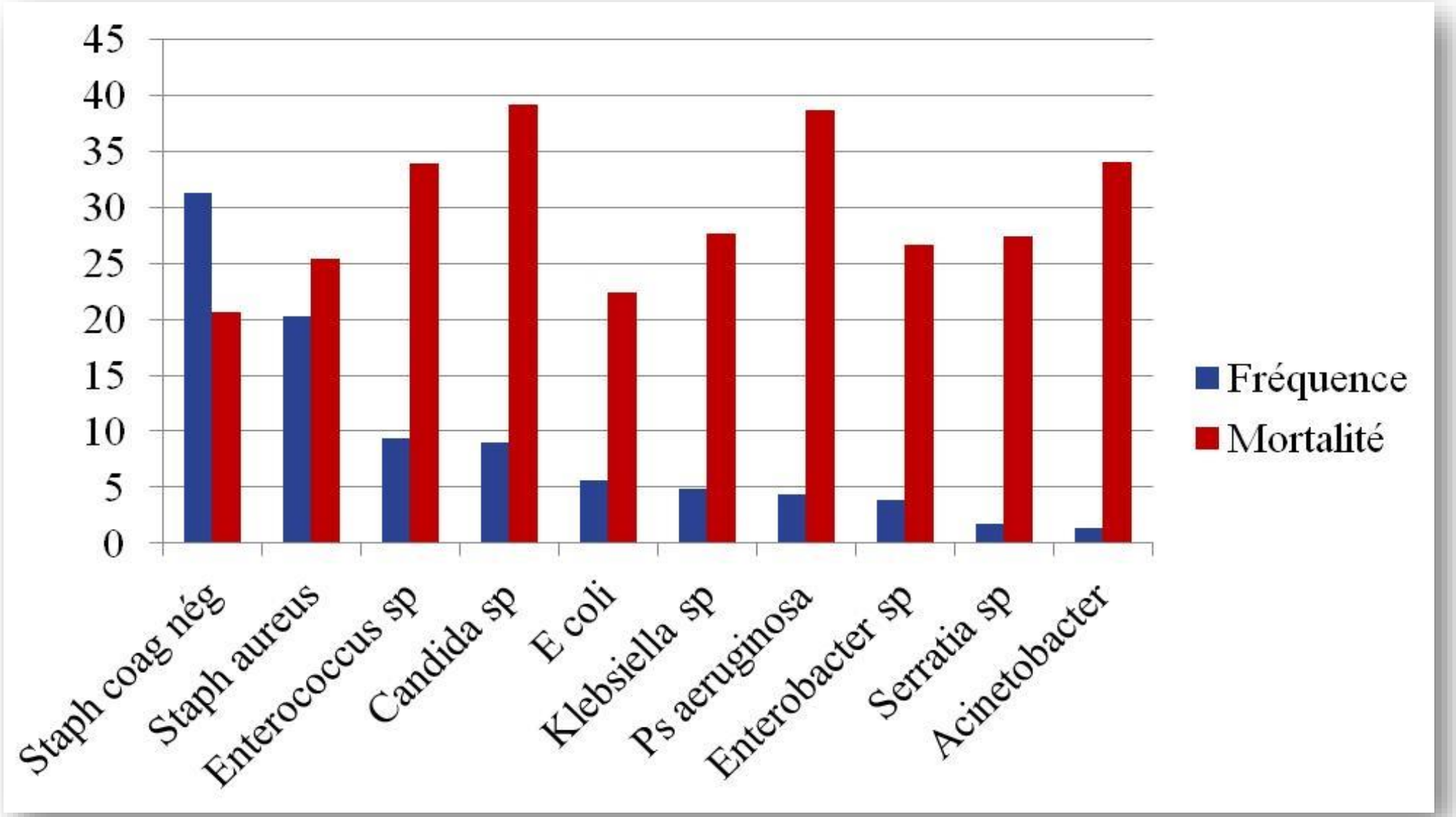
Logan C et al. ICM. 2020

Candida: un microorganisme assez rarement isolé dans les infections associées aux soins



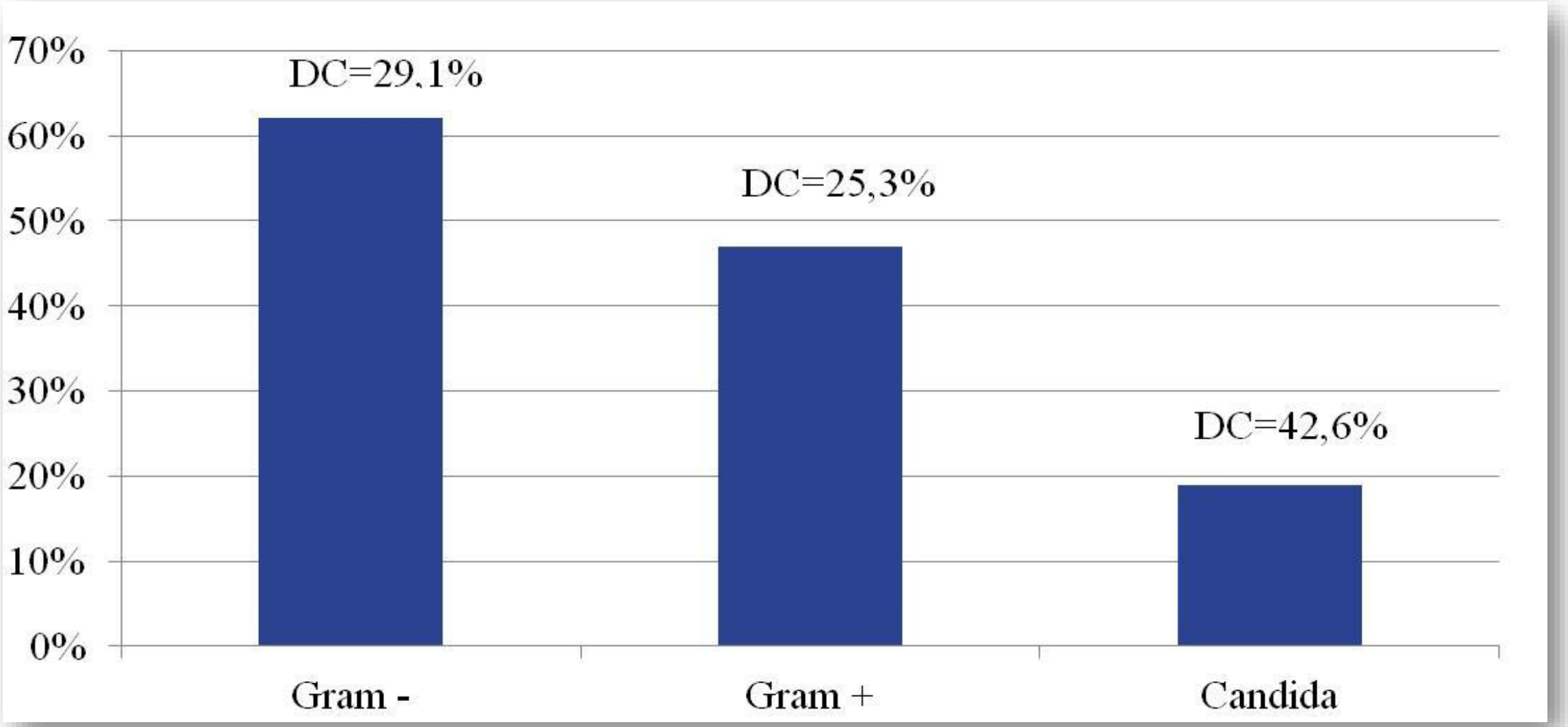
D'après RAISIN. ENP 2017. INVS

Le caractère **invasif** est lié à une **mortalité élevée**



Winsplinghoff H et al. CID 2004

En soins intensifs: candidémies moins fréquentes que bactériémies, mais **mortalité plus importante**

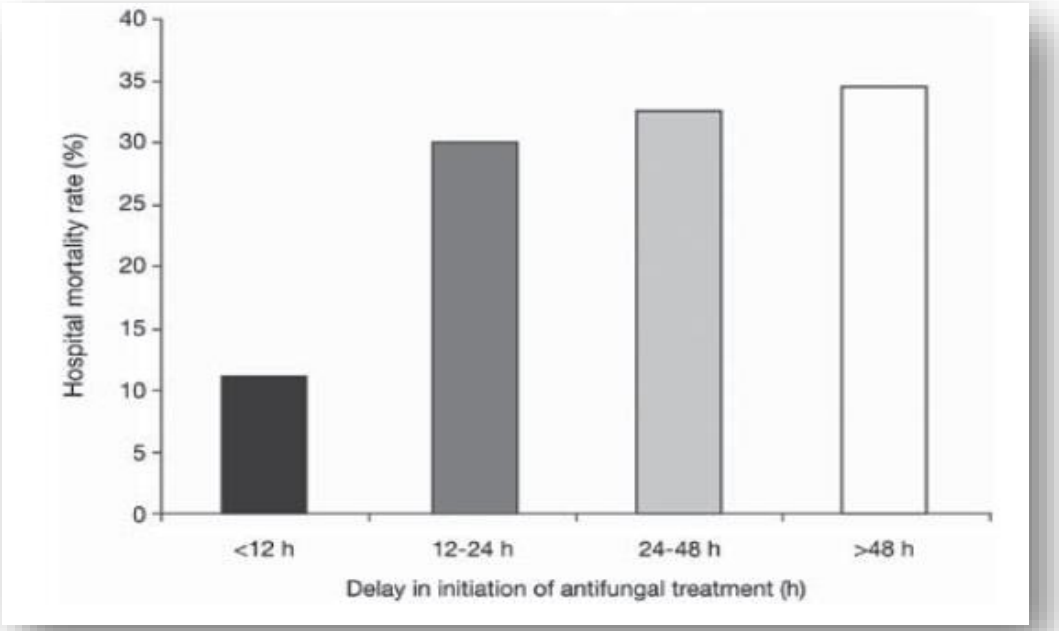


Vincent JL et al. JAMA 2009

Cette mortalité est directement influencée par le **délai d'introduction du traitement antifongique** spécifique

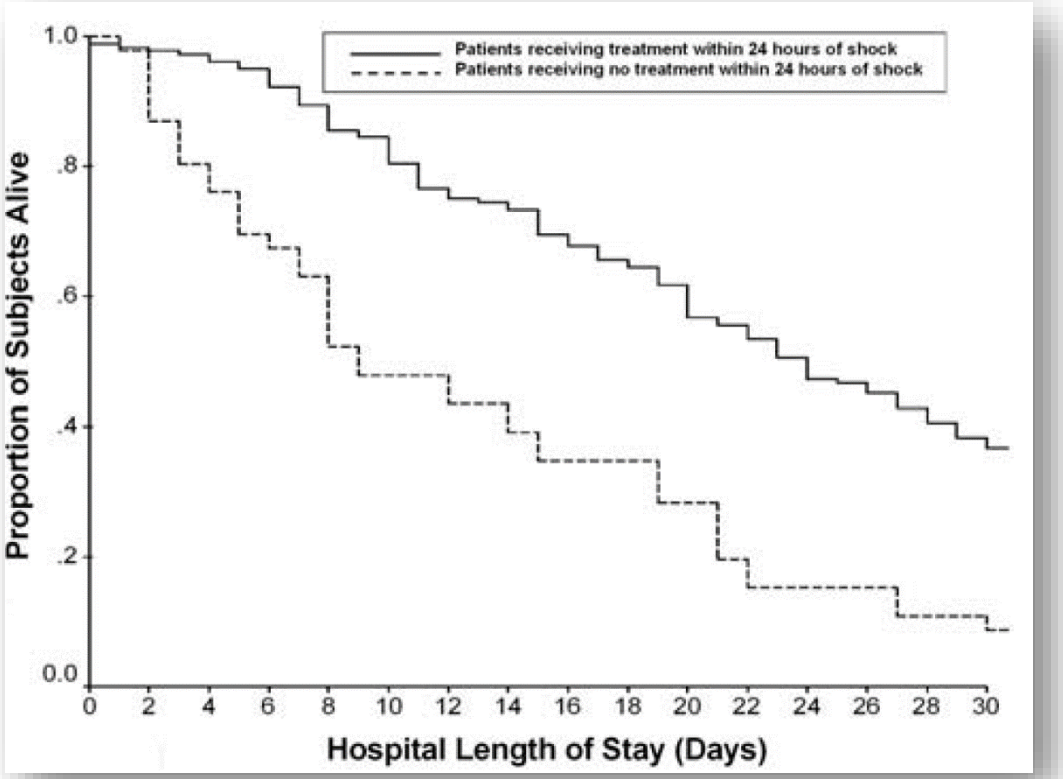
Prévalence candidémie en SI : 7/1000. Mortalité : 42,6%

Tous patients confondus



Morrell M et col. AAC. 2005

Patients en choc



Kollef M et col. CID. 2012

Les 2 facteurs impactant le plus la mortalité sont le **délai d'introduction du traitement** et le **contrôle de la source**

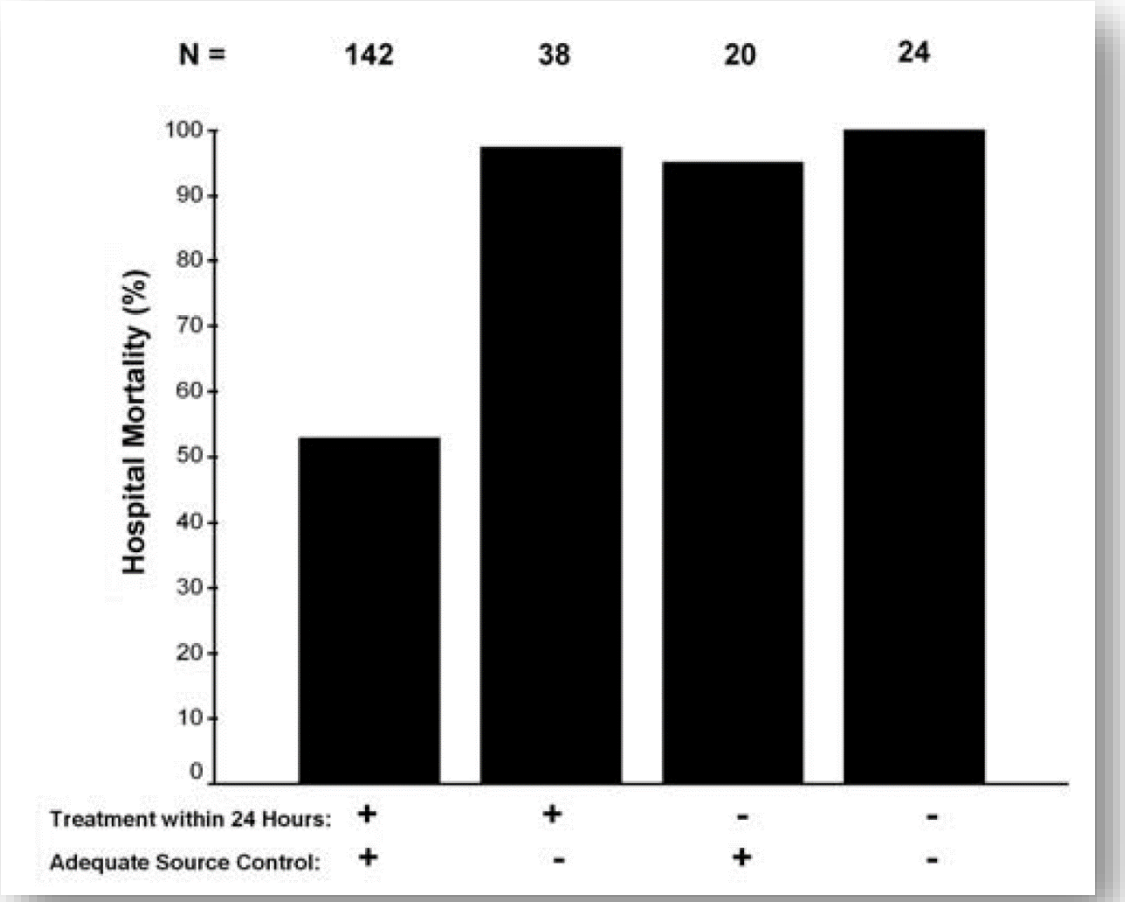
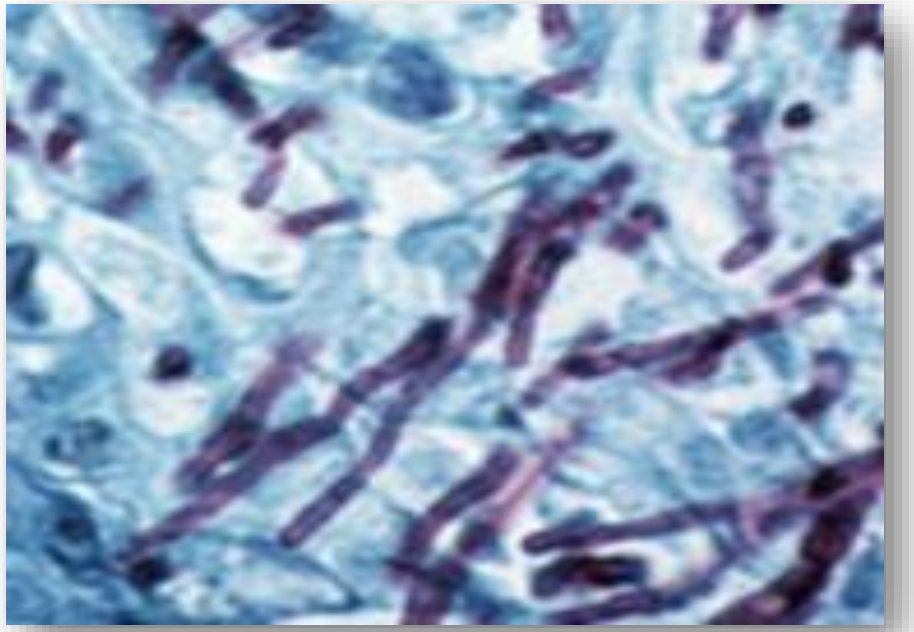


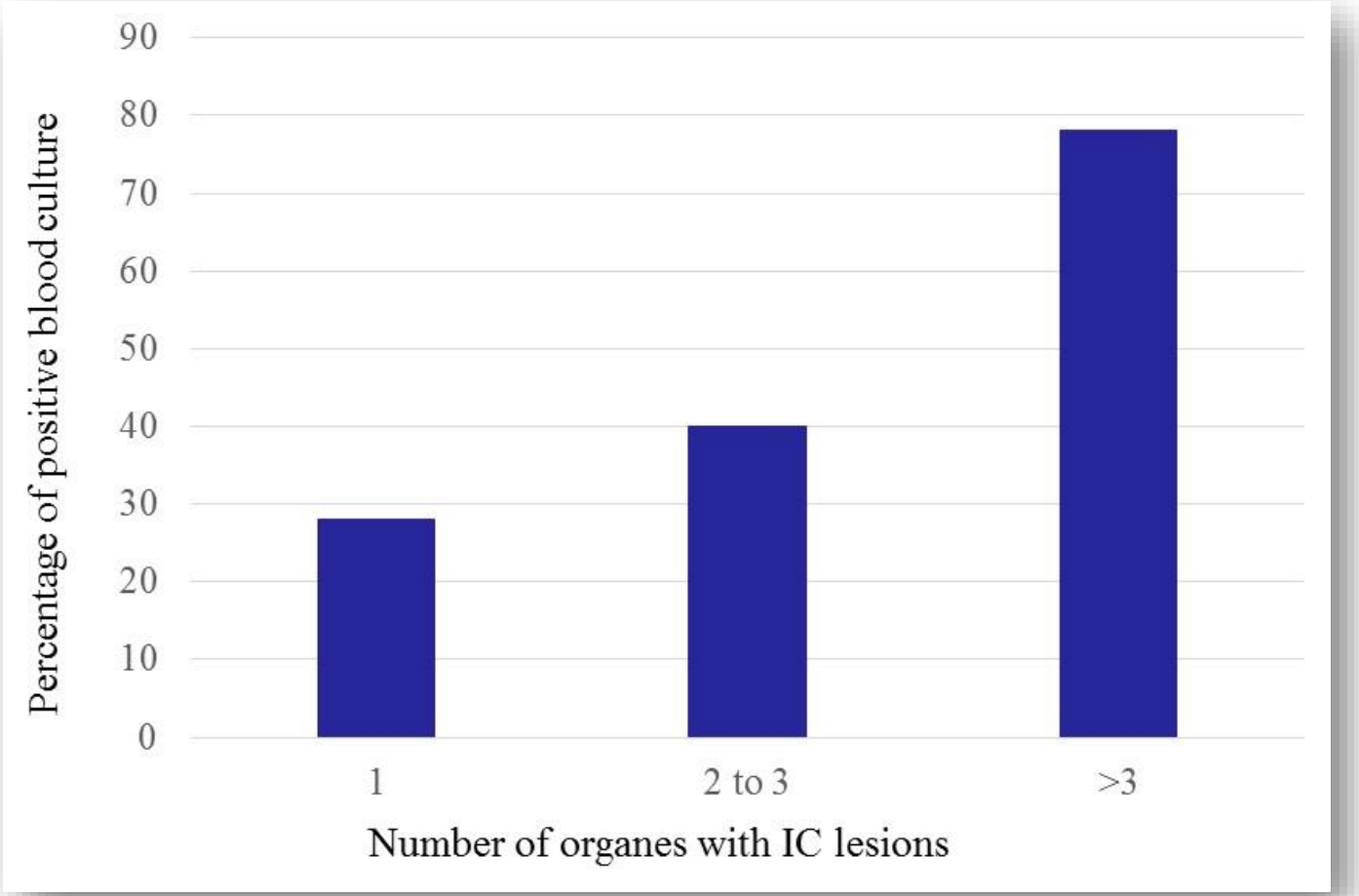
Table 3. Multivariate Analysis of Risk Factors for Hospital Mortality[a]

	AOR	95% CI	*P* value
Solid cell tumor with metastases	6.01	2.98–12.10	.010
Class IV congestive heart failure	4.95	2.53–9.68	.017
APACHE II Score (1-point increments)	1.37	1.26–1.48	<.001
Inadequate source control	77.40	21.52–278.38	.001
Red blood cell transfusion	6.49	4.06–10.38	<.001
Serum albumin (1 g/dL increments)	0.42	0.30–0.59	.012
Delayed antifungal treatment[b]	33.75	9.65–118.04	.005

Kollef M et col. CID. 2012

En pratique clinique, le **gold standard** est l'**anatomopathologie**, **l'examen de routine l'hémoculture**





Sensibilité globale de l'hémoculture pour faire le diagnostic de CI = 50%

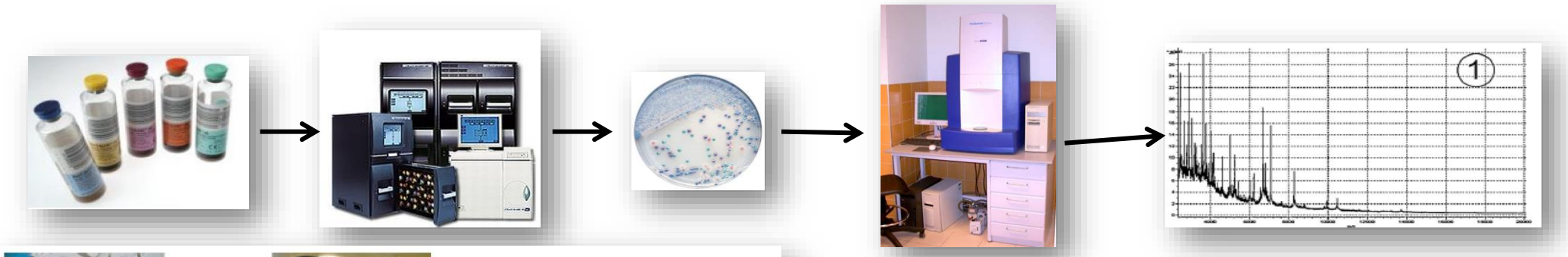
La progression des techniques de microbiologie classique améliore le **délai d'obtention des résultats** mais pas la sensibilité globale

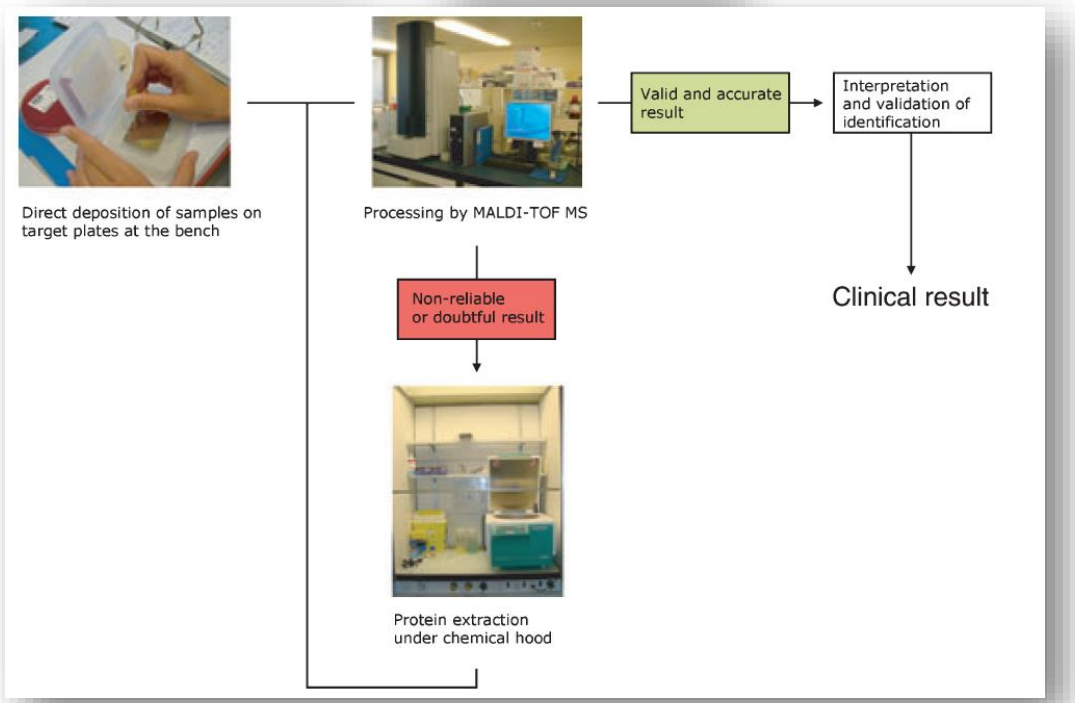
	Délai
Entre choc et DC (Délai médian) *Kollef M et al. CID. 2012*	48 heures
Entre prélèvement et résultat (Délai médian) *Kollef M et al. CID. 2012*	55,8 heures*
Mycosis IC/F vs Plus aerobic/F (Délai médian) *Meyer MH et al. JCM. 2004*	*C.albicans*: 31,1 h vs 39,9
	C.glabrata: 17,8 vs 61,5

Horvath LL et al., JCM. 2003

* Seulement 20% des patients avaient un résultat positif avant leur DC

Les techniques microbiologiques alternatives basées sur la culture améliorent le **délai d'obtention des résultats** mais pas la sensibilité globale



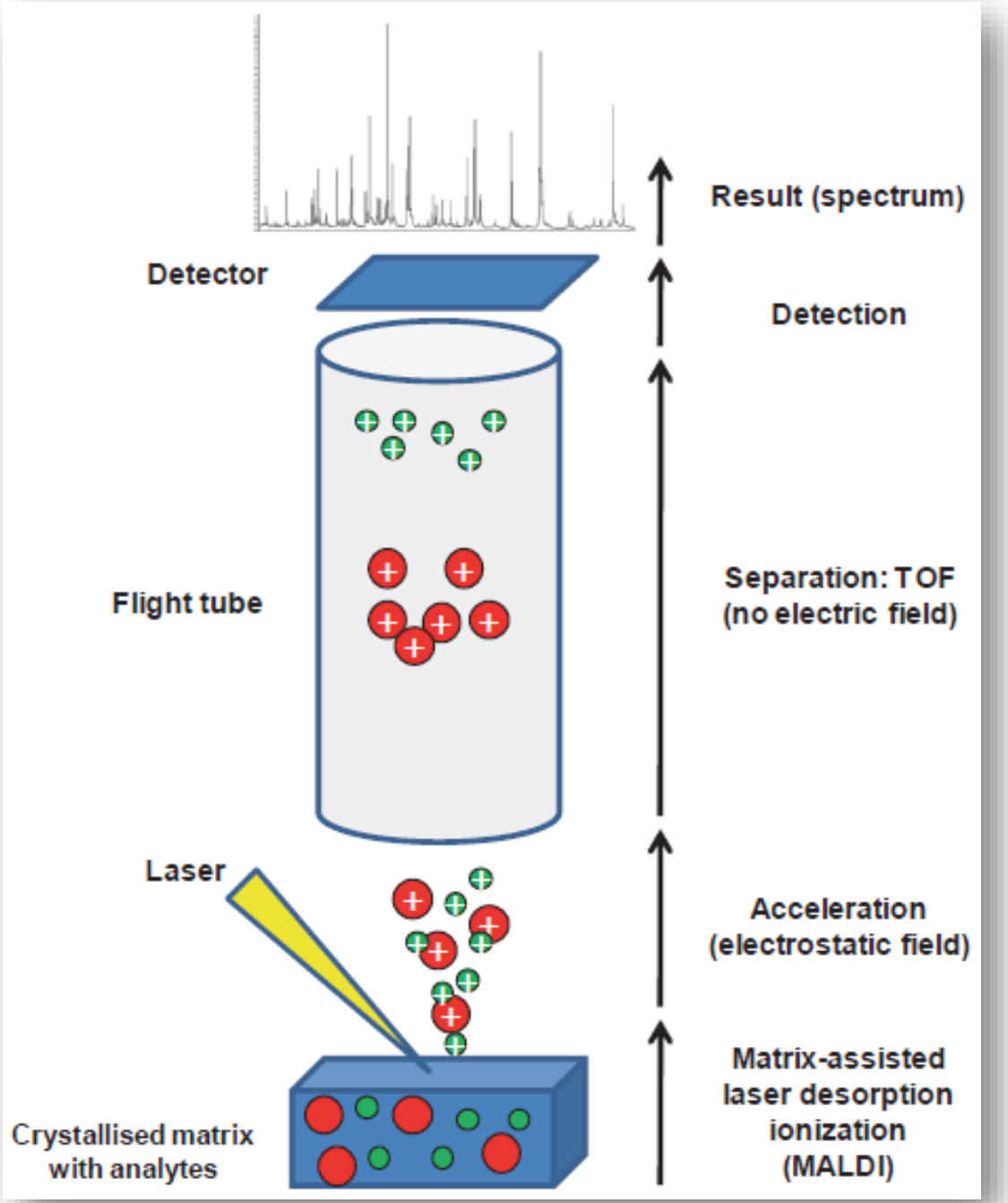


Spectrométrie de masse

Traitement pré-analytique simple

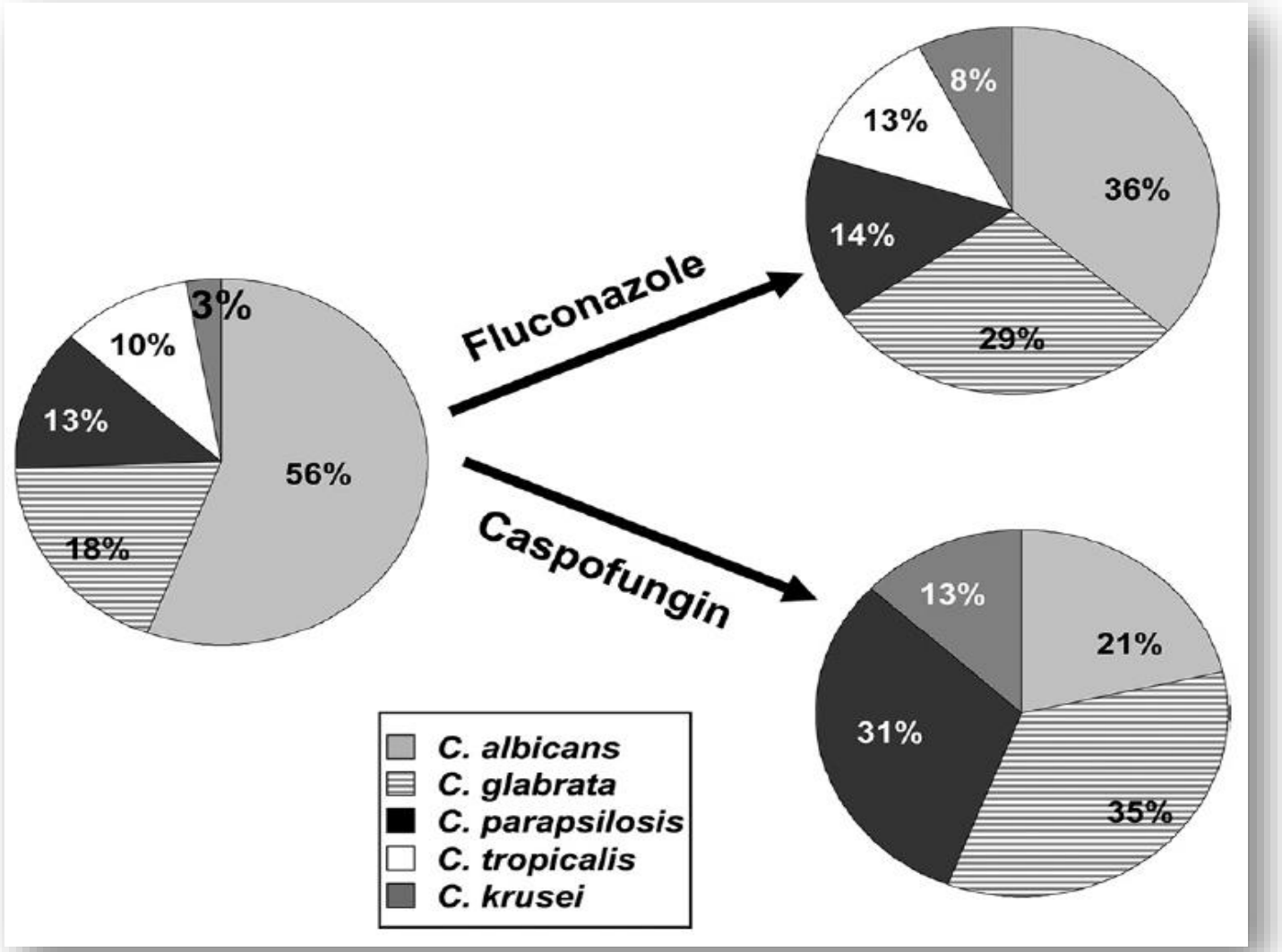
Technique automatisée

Bizzini A, Greub G. CMI 2010



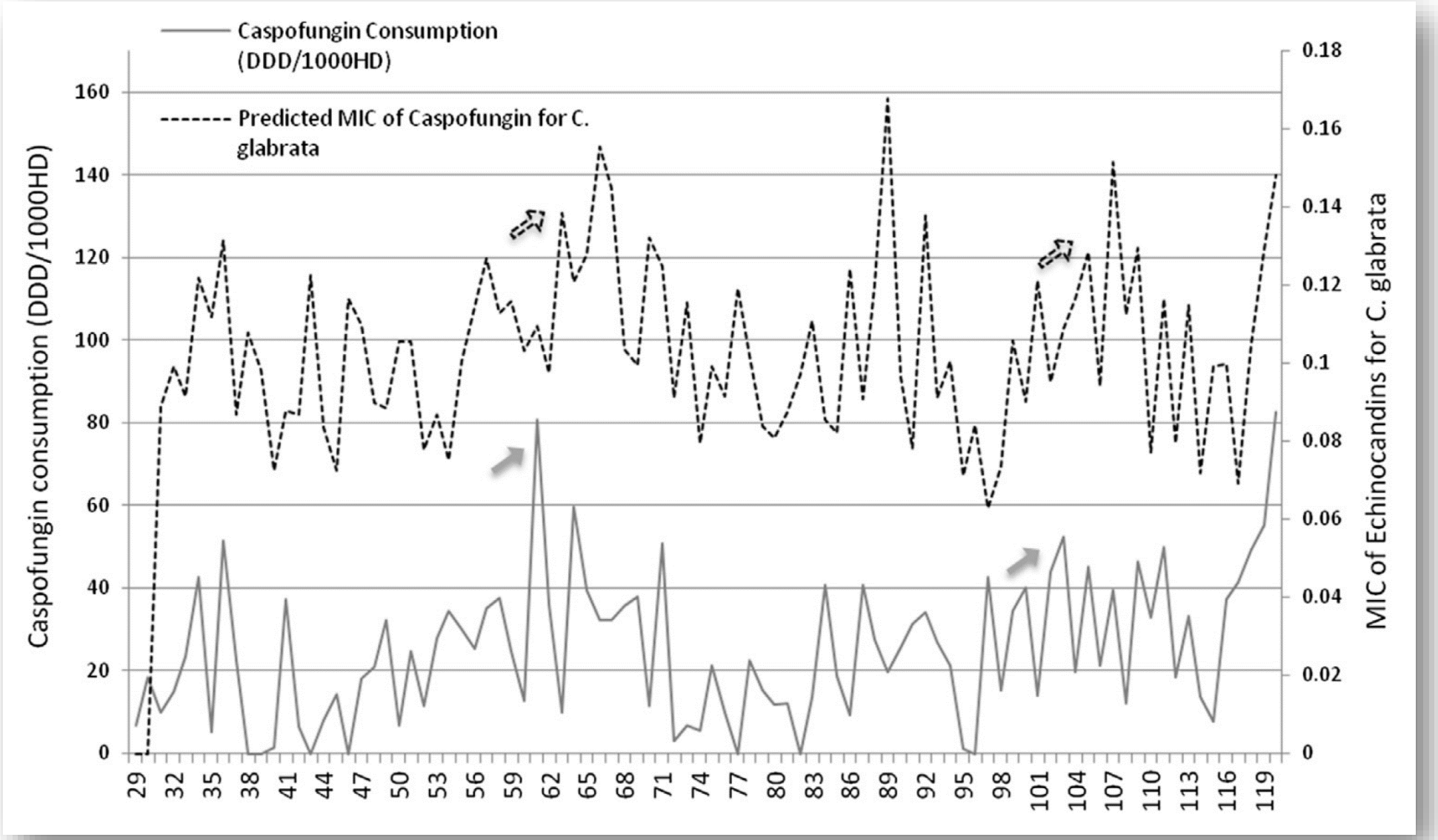
Croxatto A et al. FEMS microbiol Rev 2012.

L’identification rapide de l’espèce est cependant un enjeu épidémiologique important: pression de sélection modifiant la répartition des espèces



Lortholary O et al. AAC 2011

L’exposition aux antifongiques fait croître la CMI



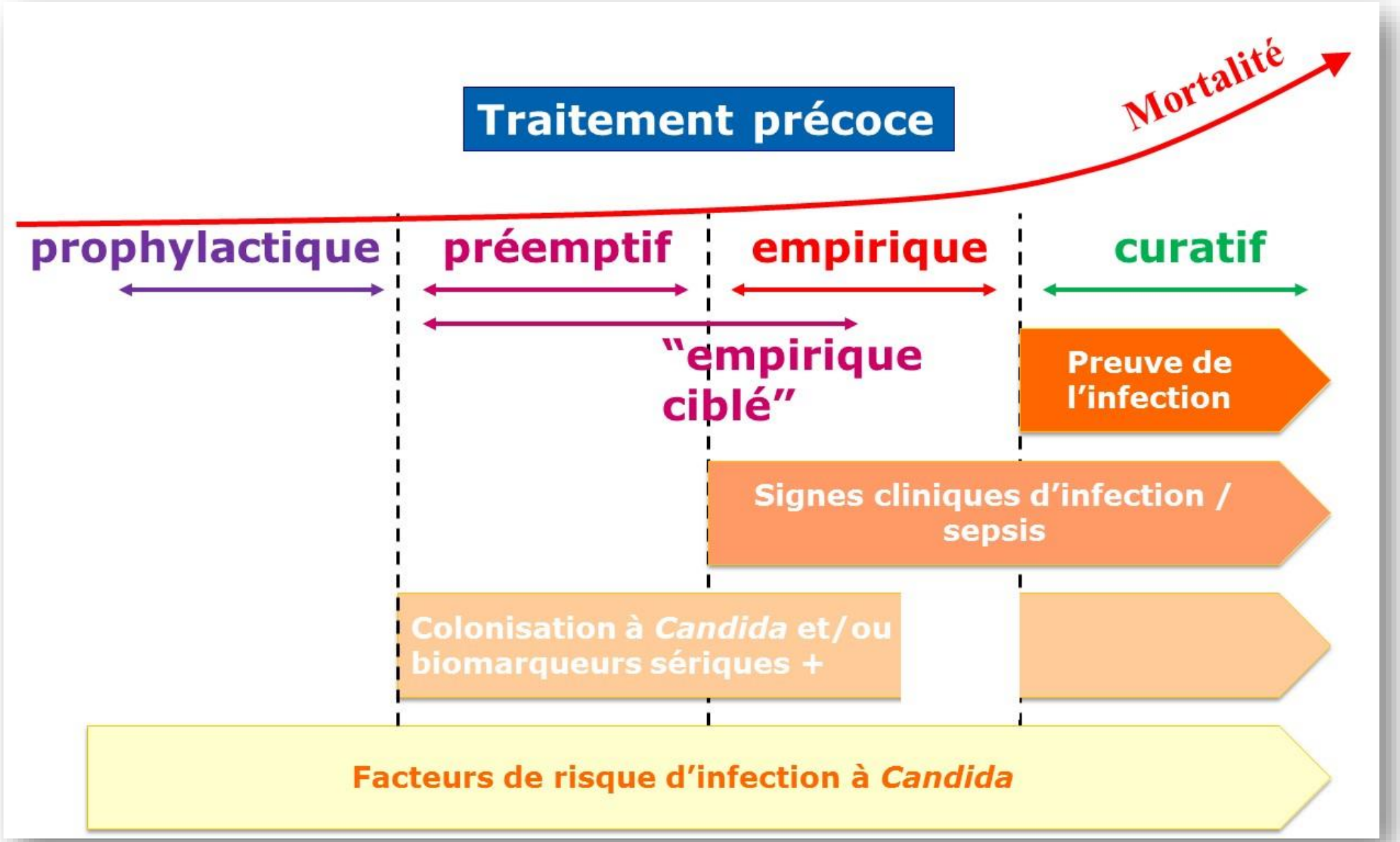
Bailly S et al. J Inf. 2016

Un volume de prescription d'antifongiques excessif

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)	

Azoulay E et al. Crit Care Med. 2012

Stratégies de traitement antifongique en réanimation



Adapté de Leon C, Intensive Care Med 2014. Schéma A Rouzé

Fluco vs placebo en stratégie empirique : 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)	–	–

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

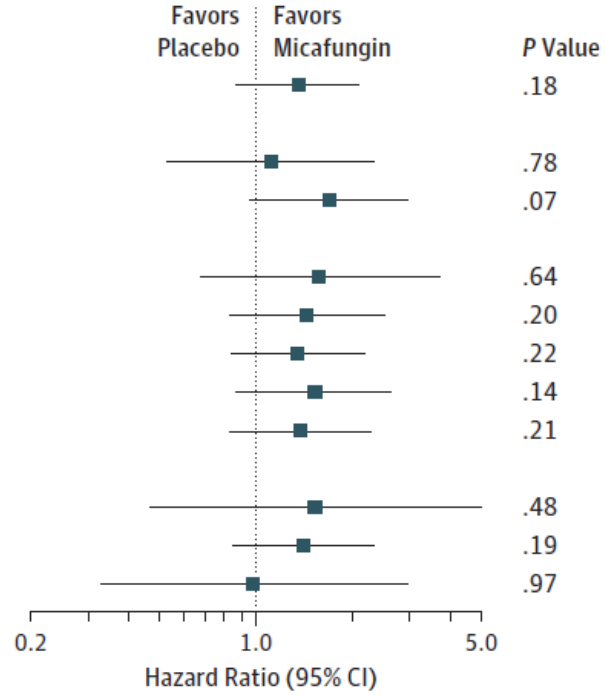
Outcome	Fluconazole Recipients (n = 122), n (%)	Placebo Recipients (n = 127), n (%)
Total failures	67 (55)	73 (57)
No resolution of fever	62 (51)	68 (54)
Documented invasive fungal infection	6 (5)†	11 (9)‡
Need for alternative antifungal agent	12 (10)	20 (16)

Schuster MG et al. Ann Intern Med. 2008

Essai Empiricus: **pas de baisse de mortalité à J28 avec micafungine**

Figure 2. Comparison of Fungal Infection–Free Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	87	128	74	123	1.35 (0.87-2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53-2.33)	.78
>8	36	62	22	55	1.69 (0.96-2.94)	.07
Admission category						
Surgical	22	34	16	31	1.56 (0.67-3.70)	.64
Medical	65	94	58	92	1.43 (0.83-2.50)	.20
Colonization index ≥0.5[a]	68	101	58	99	1.35 (0.84-2.17)	.22
Corrected colonization index ≥0.4[b]	52	76	45	80	1.52 (0.87-2.63)	.14
Candida score ≥3	64	96	47	85	1.37 (0.83-2.27)	.21
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	14	25	1.52 (0.47-5.00)	.48
>80	58	91	47	84	1.41 (0.85-2.33)	.19
≤80	29	37	27	39	0.98 (0.30-2.94)	.97



- Sepsis acquis
- MOF
- Colonisation
- VM au moins 5 j
- ATB >4j dans les derniers 7 j
- VVC ou KTart

Critère de jugement principal composite non atteint.
Bien que moins de CI dans le groupe micafungine : 3% versus 12% (p=0,008)

Timsit JF et al. JAMA. 2016

Raisonnement sur des facteurs de risque plus précis nécessaire

Table 2 Independent risk factors associated with candidemia according to hospitalization inside and outside intensive care units

Risk factors	Whole population[1, 2] (*N* = 567)			Intensive care[1, 2] (*N* = 250)			Non-Intensive care[1, 2] (*N* = 322)		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Central venous catheter[4]	6.74	2.96–15.4	< 0.001				9.77	3.72–25.7	< 0.001
Total parenteral nutrition[4]	3.92	2.28–6.73	< 0.001	6.75	2.89–15.7	< 0.001	3.29	1.52–7.13	0.003
Previous septic shock	2.29	1.33–3.96	0.003	2.39	1.14–5.01	0.02			
Acute kidney injury				4.77	1.94–11.8	< 0.001			
Heart disease	1.78	0.96–3.33	0.07	3.78	1.09–13.1	0.006			
Renal replacement therapy	2.16	1.11–4.21	0.02						
Glycopeptides[5, 6]							3.31	1.33–8.23	0.01
Nitroimidazoles[5, 6]	2.16	1.05–4.45	0.04				3.12	1.07–9.11	0.04
Aminoglycosides[5, 6]				2.28	1.01–5.13	0.05			

Poissy J et al. Crit Care. 2020

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

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

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

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

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

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

Elaboration rétrospective et validation prospective d'une **règle de prédiction clinique** d'isolement de *Candida* dans le **liquide péritonéal**

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.

Dupont H et al. Crit care med. 2003

Candida score et raisonnement probabiliste: **excellente VPN**

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

Léon C et al. Crit Care Med. 2006

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

Intensive-care unit score (N=255)	Non-intensive-care unit score (N=348)

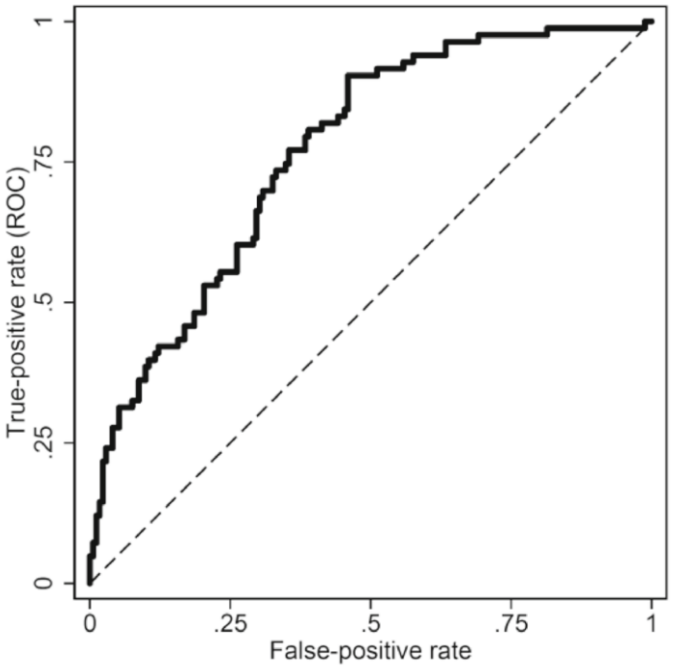
A1

Risk Factor	Points
Total parenteral nutrition	+2.5
Acute kidney failure	+1.5
Heart disease	+1.5
Previous septic shock	+1.0
Aminoglycoside	+1.0

B2

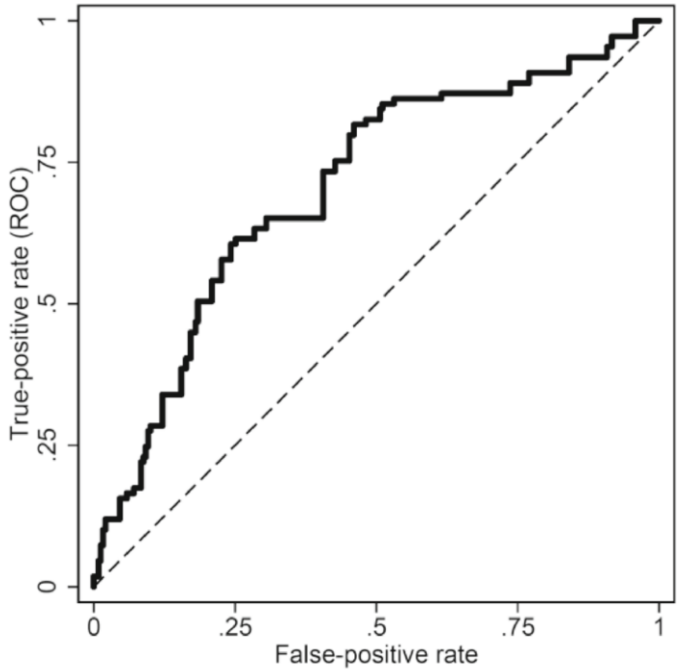
Risk Factor	Points
Central venous catheter	+2.5
Nitroimidazole	+1.0
Total parenteral nutrition	+1.0
Glycopeptide	+1.0

B1



aAUC=0.768 95% CI 0.711-0.818

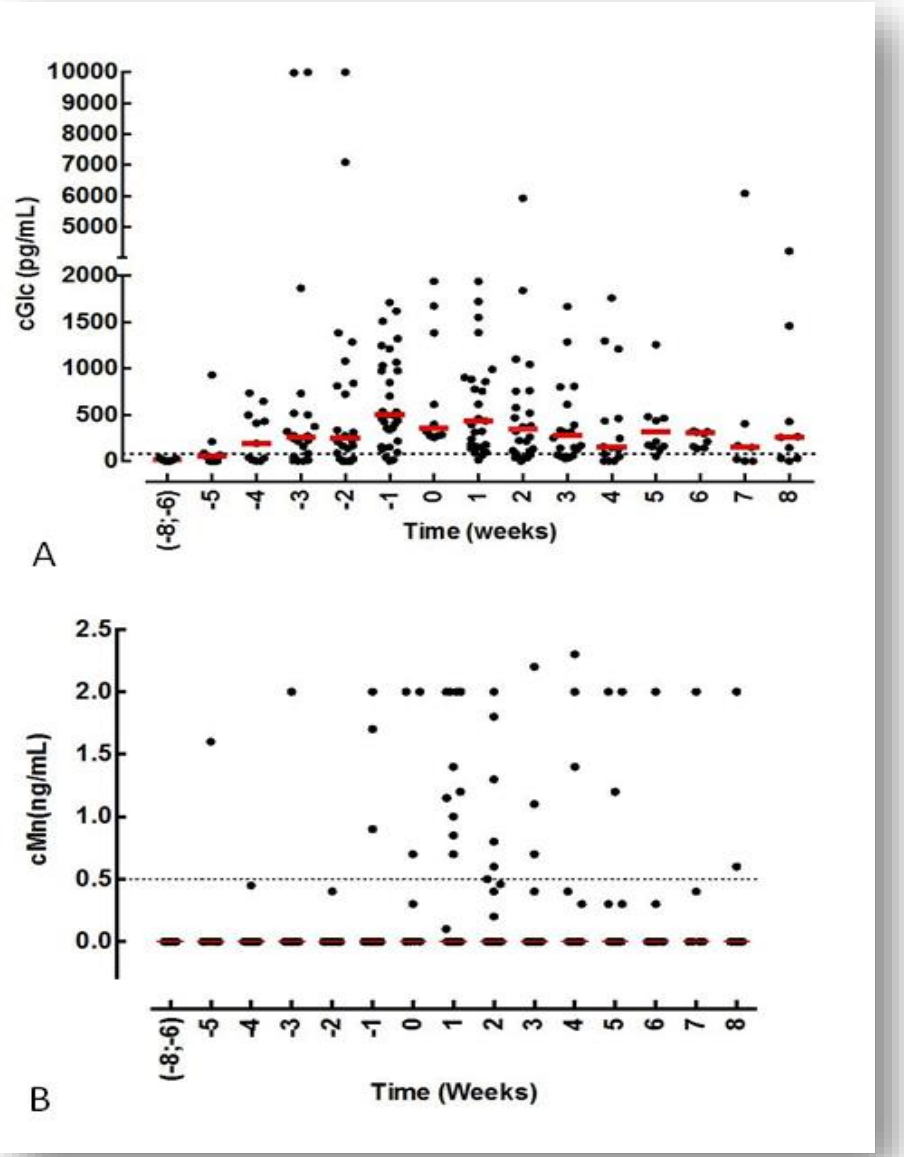
B2

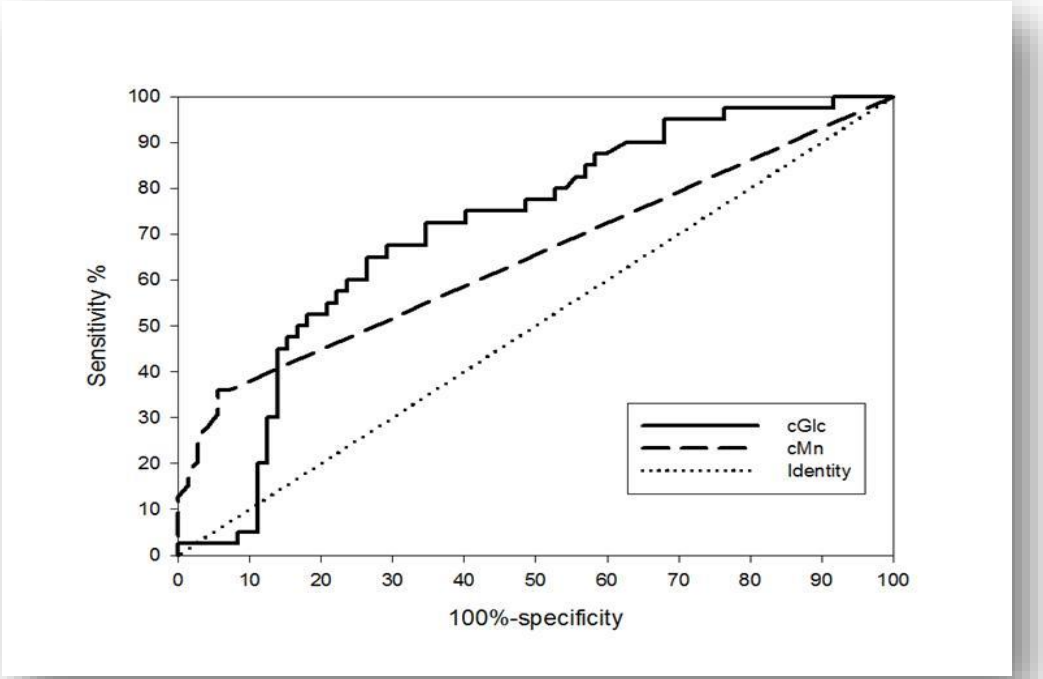


aAUC=0.717 95% CI 0.667-0.763

Poissy J et al. Crit Care. 2020

BDG biomarqueur sensible précoce, avec une longue décroissance. **Mn biomarqueur spécifique fugace**



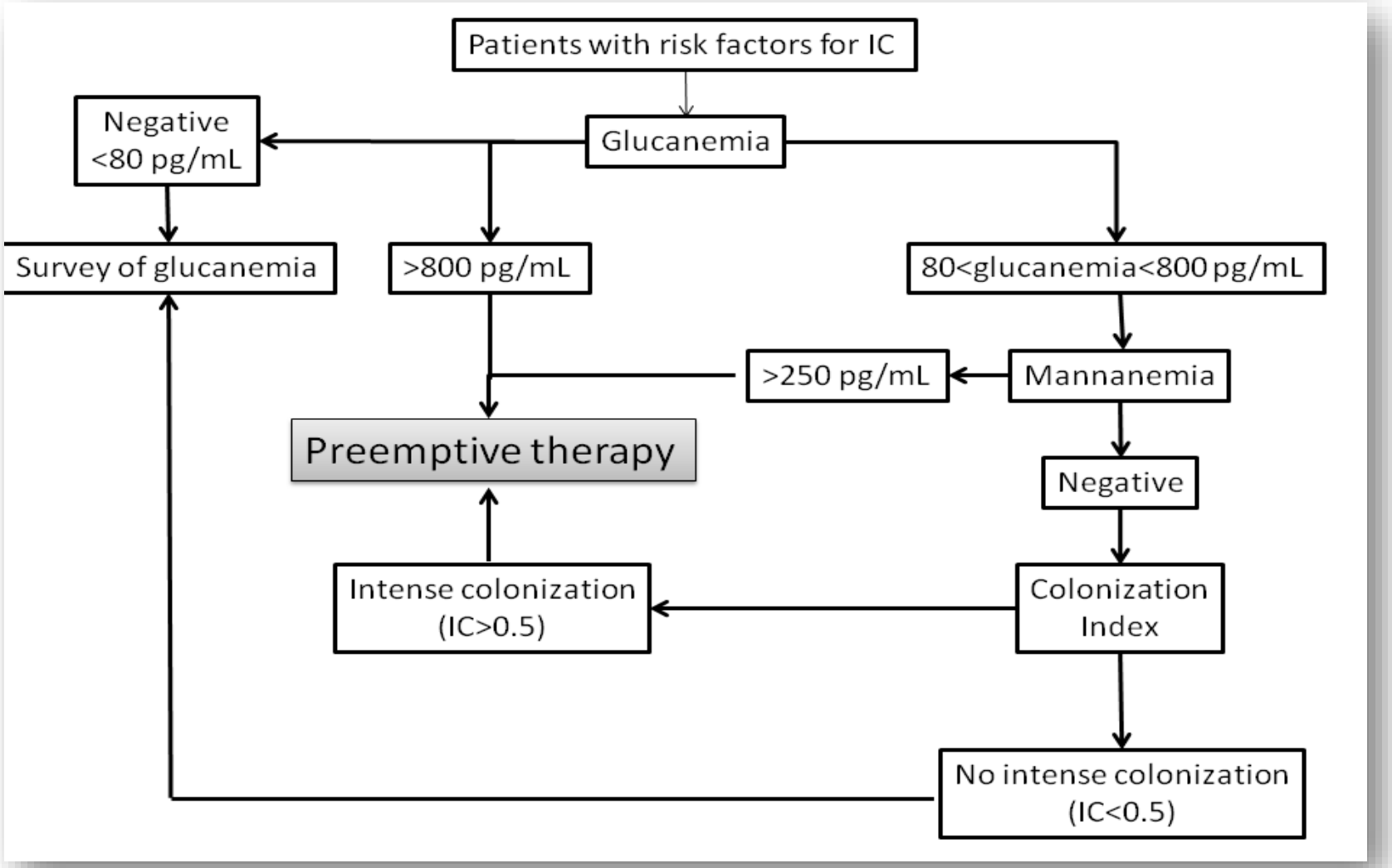


Poissy J et al.
Crit Care. 2014

	BDG (pg/mL)				Mn (ng/mL)	
	80	350*	800	1600	0.2*	0.5
Se/Sp (%)	97/31	65/74	30/86	5/90	39/96	36/94

*** Best Se/Sp**

Proposition d'un **algorithme décisionnel pour une stratégie préemptive**



Poissy J et al. Crit Care. 2014.

Les essais cliniques concernant l'utilisation de ces biomarqueurs en introduction de traitement : Candisep

Outcome	BDG-group $n=172$	Control-group $n=167$	Relative risk (95% CI)	p value
Primary outcome				
28-Day all-cause mortality—no (%)	58 (33.7)	51 (30.5)	1.1 (0.8–1.51)	0.53
Secondary outcomes				
Hospital mortality—no (%)	59 (34.5)	60 (35.9)	0.96 (0.71–1.29)	0.78
Hospital length of stay—days	25.5 (16–41)	28 (17–48)	NA	0.37
ICU mortality- no (%)	48 (27.7)	47 (27.8)	1 (0.7–1.41)	0.99
ICU length of stay—days	11 (6–20)	11 (4–22)	NA	0.70
Antifungal free survival at day 28—no (%)	52 (30.2)	87 (52.1)	2.97 (2.1–4.2)	<0.01
Time to antifungal therapy—days	1.1 (1–2.2)	4.4 (2–9.1)	NA	<0.01
Costs of antifungal therapy—Euro	4451 (1385–6923)	2800 (989–7097)	NA	0.52
Candida Colonization Index				
At randomization	0.20 (0–0.33)	0.2 (0–0.4)	NA	0.69
At day 1	0 (0–0.67)	0 (0–1)	NA	0.66
At day 7	0.25 (0–0.5)	0.25 (0; 0.5)	NA	0.22
At day 14	0.2 (0–0.33)	0.25 (0.08–0.4)	NA	0.14
Total SOFA	10.5 (8.2–14.3)	10.4 (8.2–13.4)	NA	0.42
Vasopressor free days—days	20 (3–25)	20 (3–26)	NA	0.40
Ventilator free days—days	16 (2–25)	15 (2–27)	NA	0.51
Renal replacement free days—days	27 (9–29)	27.5 (9–29)	NA	0.92

Sepsis<24h
Facteurs de risque CI :
-nutrition parentérale totale
-chirurgie abdominale <7j
-Antibiothérapie >48h <7j
-Epuration extra-rénale

Bras BDG
-ATF si au moins un dosage de BDG≥80 pg/mL sur deux dosages deux jours consécutifs

Candidémie : 4,5%
Candidose invasive : 14,5%

Prévalence attendue=28%

Bloos F et al. ICM. 2022

Stratification des niveaux de risque

Table 2. Multivariate Analysis of Risk Factors for Intensive Care Unit–Acquired Invasive Candidiasis

Variable	HR (95% CI)	*P* Value
Emergency gastrointestinal/hepatobiliary surgical procedure	2.06 (1.17–3.63)	.01
Central venous catheter (noncoated)	1.76 (1.15–2.69)	.009
Total parenteral nutrition receipt	2.24 (1.4–3.58)	.001
ICU admission source from operating theater, ED, or another hospital	1.96 (1.14–3.33)	.015
High-dose corticosteroid receipt (dose ≥50 mg prednisolone equivalent)	1.43 (.93–2.18)	.1
Blood transfusion receipt	1.83 (1.18–2.83)	.007
Carbapenem or tigecycline receipt	2.33 (1.47–3.69)	<.0001
Third- or fourth-generation cephalosporin receipt	1.94 (1.29–2.92)	.001
Prior urine culture positive for *Candida* spp	2.4 (1.58–3.63)	<.0001
Prior throat culture positive for *Candida* spp	2.22 (1.29–3.81)	.004

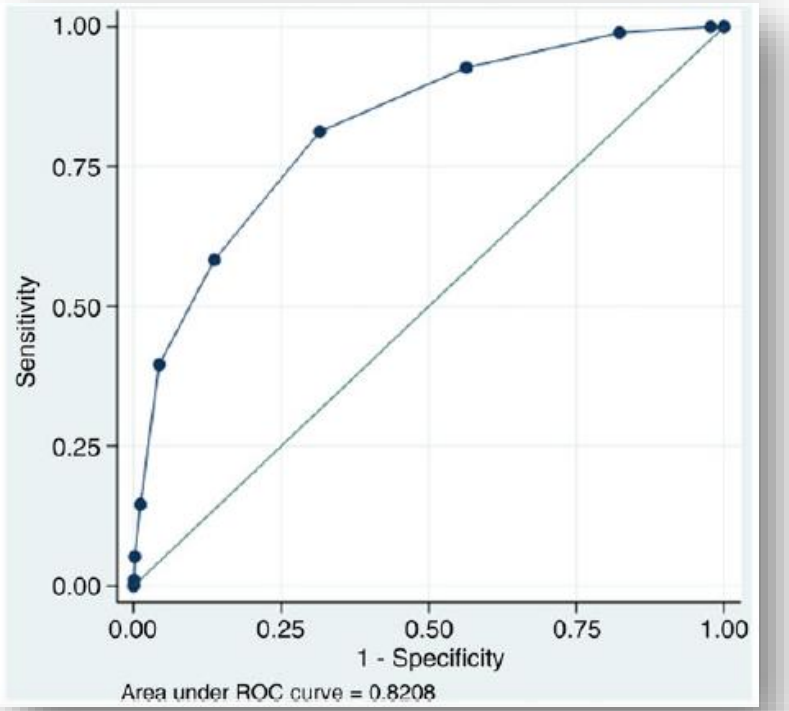


Table 5. Stratification of Predictive Scores

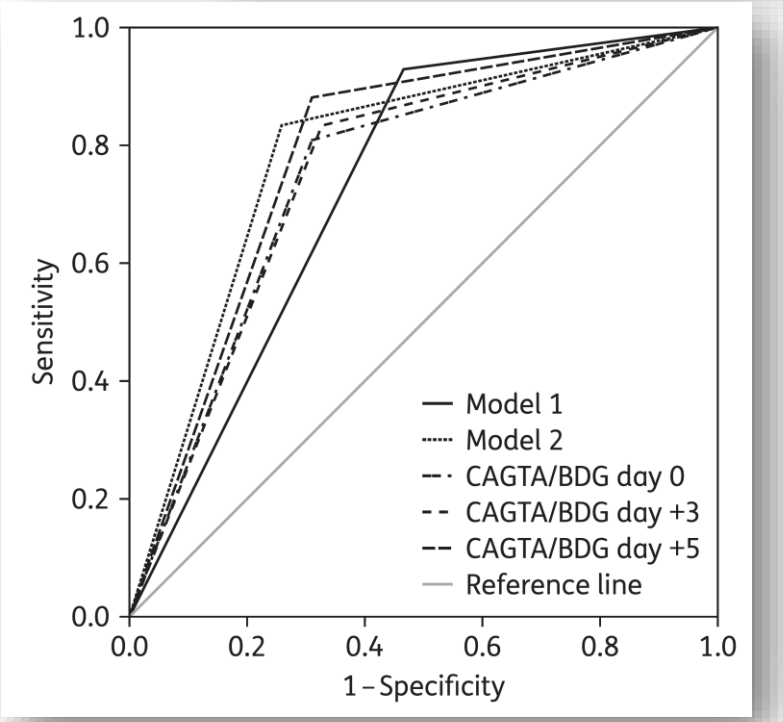
Characteristics	Patients With Predictive Scores ≤2	Patients With Predictive Scores 3–5	Patients With Predictive Scores ≥6
No. of patients within predictive score stratum (% of total cohort)	2895 (43.1)	3495 (52.1)	324 (4.8)
No. of patients with IC (% of total IC cases)	7 (7.3)	51 (53.1)	38 (39.6)
Prevalence of IC within predictive score stratum, %	0.24	1.46	11.7

Abbreviation: IC, invasive candidiasis.

Playford EG et al. CID. 2016

Et si on optait pour un arrêt précoce des traitements empiriques ?

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Model 1 CAGTA	60.0 (40.7–76.8)	85.7 (74.8–92.6)	64.3 (44.1–80.7)	83.3 (72.3–90.7)
Model 2 CAGTA	60.0 (40.7–76.8)	87.1 (76.5–93.6)	66.7 (46.0–82.8)	83.6 (72.6–90.9)
Model 1 BDG	86.7 (68.4–95.6)	52.9 (40.6–64.8)	44.1 (31.4–57.5)	90.2 (75.9–96.8)
Model 2 BDG	73.3 (53.8–87.0)	70.0 (57.1–80.1)	51.2 (35.7–66.4)	86.0 (73.6–93.3)
Model 1 CAGTA/BDG	96.7 (80.9–99.8)	47.1 (35.4–59.4)	43.9 (31.9–56.6)	97.1 (82.9–99.8)
Model 2 CAGTA/BDG	83.3 (64.5–93.7)	64.3 (51.9–75.1)	50.0 (35.7–64.3)	90.0 (77.4–96.3)

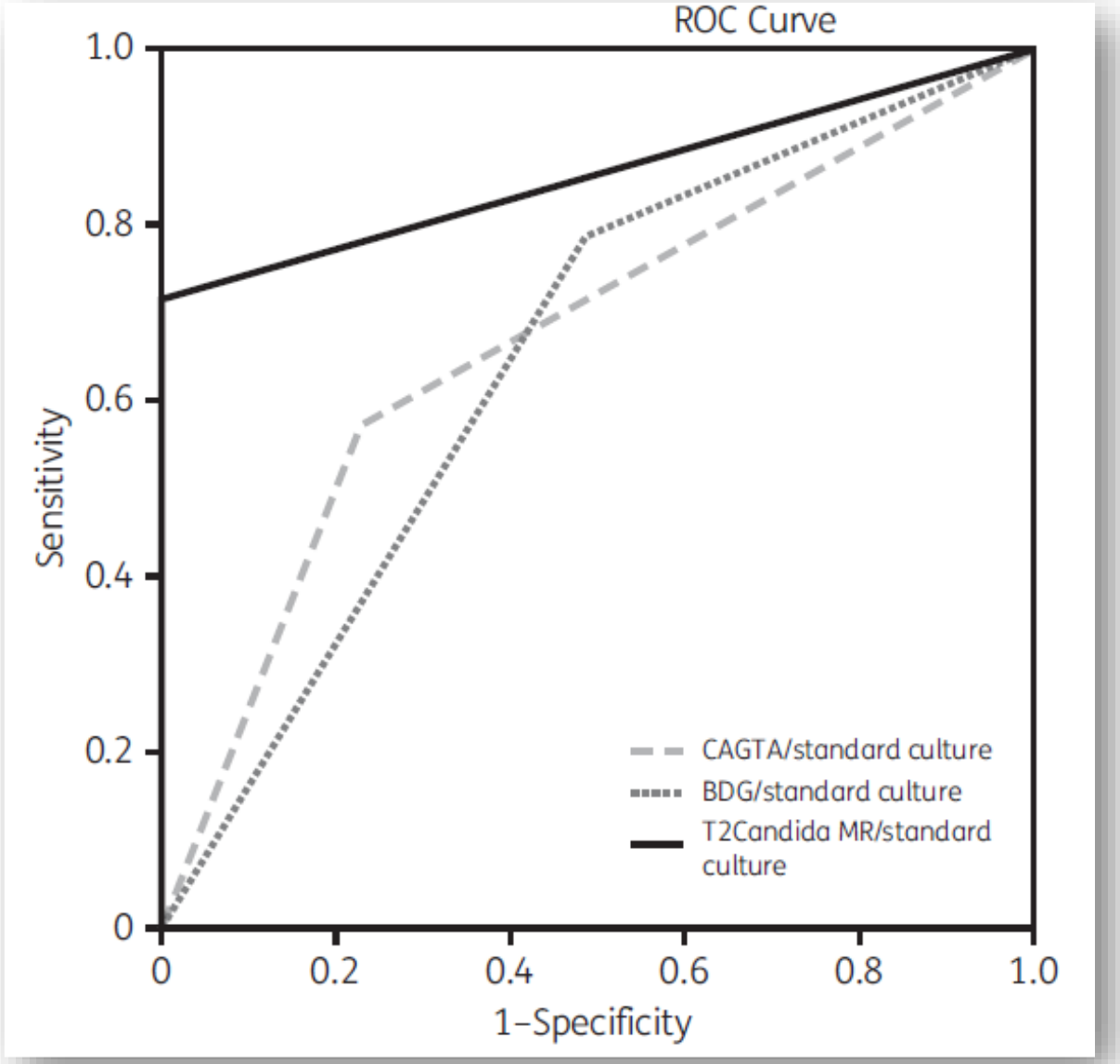


Martinez-Jimenez MC et al. JAC. 2015

	Biomarker strategy ($n = 54$)	Routine care ($n = 55$)	P
Primary outcome			
Early discontinuation of empirical antifungal treatment	29 (54)	1 (2)	<0.0001*
Secondary outcomes			
Total duration of antifungal treatment	6 (4, 13)	13 (12, 14)	<0.0001
Subsequent proven invasive *Candida* infection	2 (4)	1 (2)	0.547
Subsequent probable invasive *Candida* infection	2 (4)	0 (0)	0.243
Subsequent antifungal treatment	5 (9)	1 (2)	0.113
Subsequent resistant *Candida*	5 (9)	4 (7)	>0.999
MV-free days	4.5 (0, 9)	2 (0, 8)	0.527
Length of ICU stay, day	26 (16, 32)	25 (14, 33)	0.654
28-day mortality	15 (28)	15 (27)	0.953
ICU mortality	18 (33)	16 (29)	0.633

Rouzé A et al. ICM. 2017

Des arguments pour ne pas arrêter le traitement empirique? T2MR



Munoz P et al. JAC 2018

- Prédiction du mauvais pronostic chez des patients ayant un traitement antifongique empirique
- Rôle des marqueurs à baseline
- Mauvais pronostic : diagnostic d'IC prouvée ou décès à J7

Une innovation technologique prometteuse sensible et spécifique : T2MR

Sensitivity	No.	%	95% CI
Overall per patient[a]	233/256	91.0	86.8–94.2
Overall per assay[a]	234/257	91.1	86.9–94.2
Per *Candida* species[a]			
C. albicans/tropicalis	96/104	92.3	85.4–96.6
C. parapsilosis	49/52	94.2	84.1–98.8
C. krusei/glabrata	89/101	88.1	80.2–93.7
Per *Candida* species and per CFU/mL[b]			
C. albicans			
<1 CFU/mL	8/10	80.0	44.4–97.5
1–10 CFU/mL	18/18	100.0	81.5–100.0
11–30 CFU/mL	17/17	100.0	80.5–100.0
31–100 CFU/mL	5/5	100.0	47.8–100.0
Overall	48/50	96.0	86.3–99.5
C. tropicalis			
<1 CFU/mL	8/10	80.0	44.4–97.5
1–10 CFU/mL	16/18	88.9	65.3–98.6
11–30 CFU/mL	17/17	100.0	80.5–100.0
31–100 CFU/mL	5/5	100.0	47.8–100.0
Overall	46/50	92.0	80.8–97.8
C. parapsilosis			
<1 CFU/mL	8/10	80.0	44.4–97.5
1–10 CFU/mL	17/18	94.4	72.7–99.9
11–30 CFU/mL	17/17	100.0	80.5–100.0
31–100 CFU/mL	5/5	100.0	47.8–100.0
Overall	47/50	94.0	83.5–98.7
C. krusei			
<1 CFU/mL	6/10	60.0	26.2–87.8
1–10 CFU/mL	18/18	100.0	81.5–100.0
11–30 CFU/mL	17/17	100.0	80.5–100.0
31–100 CFU/mL	5/5	100.0	47.8–100.0
Overall	46/50	92.0	80.8–97.8
C. glabrata			
<1 CFU/mL	5/10	50.0	18.7–81.3
1–10 CFU/mL	16/18	88.9	65.3–98.6
11–30 CFU/mL	16/17	94.1	71.3–99.8
31–100 CFU/mL	5/5	100.0	47.8–100.0
Overall	42/50	84.0	70.9–92.8
Specificity			
Overall per patient[a]	1516/1545	98.1	97.3–98.7
Overall per assay[a]	5114/5146	99.4	99.1–99.6
Per species[a]			
C. albicans/tropicalis	1679/1697	98.9	98.3–99.4
C. parapsilosis	1736/1749	99.3	98.7–99.6
C. krusei/glabrata	1699/1700	99.9	99.7–100.0

Mylonakis E et al. CID. 2015

Peut être intéressante dans le suivi ? Mais quelle signification ?

Table 2. Performance of T2Candida and Companion Blood Cultures, Stratified by *Candida* Species

	Diagnostic Blood Cultures				
Candida Species	Number Detected[a]	Time to Detection, hours[b] (Median)	Time to Species Identification, hours[c] (Median)	T2Candida+ N (%)	Companion Blood Culture+ N (%)
C. albicans	46	40.4	72.7	28 (61)	10 (22)
C. glabrata	45	44.1	75.0	14 (30)	12 (27)
C. parapsilosis	43	43.1	96.1	18 (42)	12 (28)
C. tropicalis	17	26.7	71.1	10 (59)	4 (23.5)
C. krusei	4	61.6	88.1	1 (25)	0 (0)
Total	**155**	**42.5**	**81.0**	**71 (46)**	**38 (24.5)**

Table 5. Factors Associated with T2Candida-Positive/Companion Blood Culture-Negative (T2+/cBC–) Results

Factor[a]	T2+/cBC– N (%)	Other Result N (%)	Univariate *P* Value[b]	Multivariate *P* Value[c]
Neutropenia	9/37 (24)	6/115 (5)	**.002**	**.01**
Stem cell transplant	3/37 (8.1)	1/115 (0.9)	**.045**[d]	—
Prior antifungal therapy	35/37 (95)	77/115 (67)	**<.0001**	**<.0001**
Candida albicans	28/37 (76)	18/115 (16)	**.007**	**<.0001**
C. glabrata	5/37 (13.5)	40/115 (35)	**.01**	.3

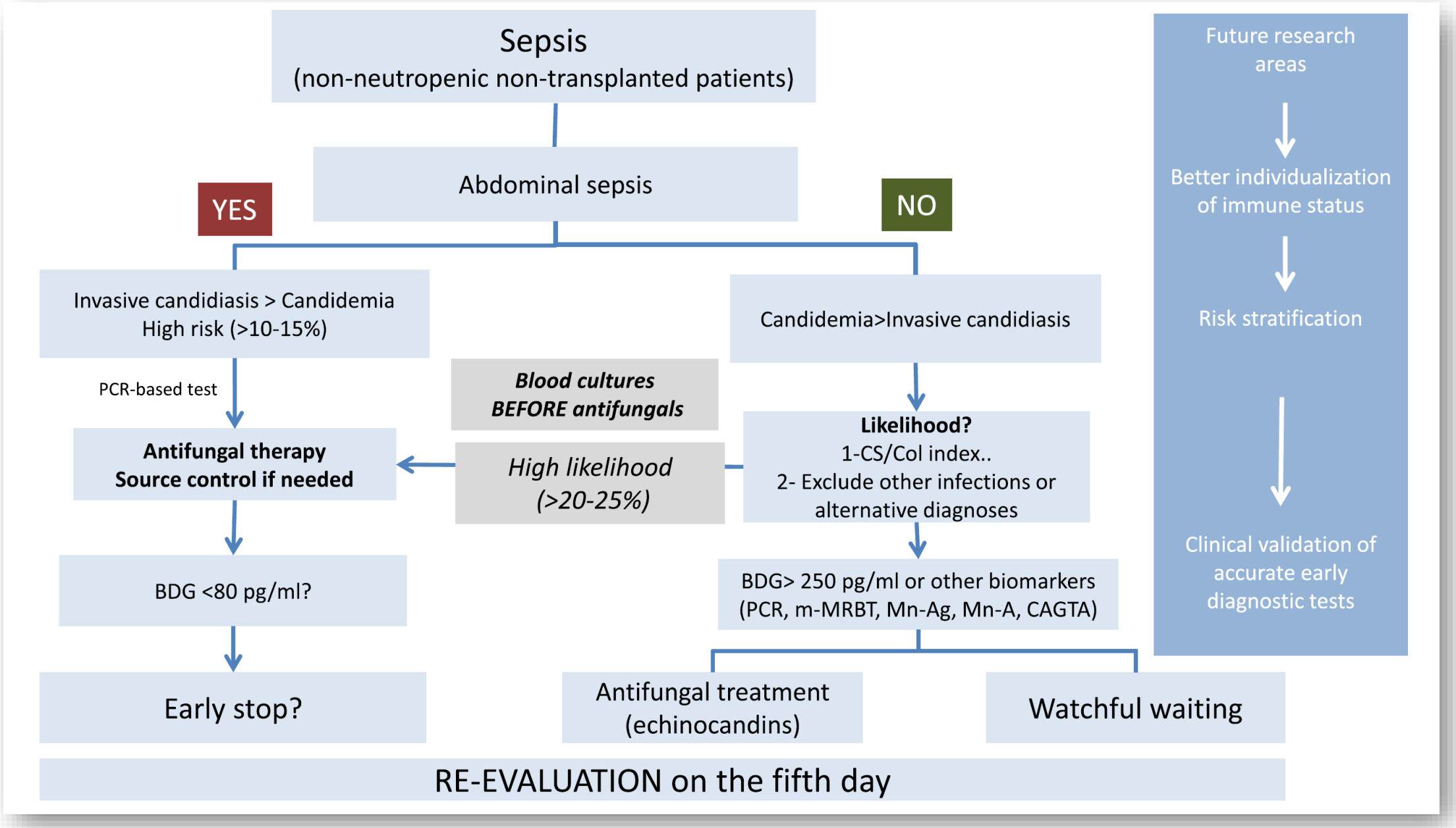
Clancy CJ et al. CID. 2018

Un outil qui va modifier le paysage des outils diagnostiques ?

Table 1. Anticipated positive and negative predictive values of T2Candida, based on prevalence of candidaemia

		90% Sensitivity/ 98% specificity	
Prevalence	Representative patient	PPV	NPV
0.4%	Any hospitalized patient in whom a blood culture is collected.[7]	15%	>99.9%
1%	Patient admitted to critical care unit.[19,20]	31%	99.9%
2%	Patient with febrile neutropenia, baseline rate of candidaemia prior to empirical antifungal treatment.[21–24]	47%	99.8%
3%	Patient with sepsis, shock or >3–7 day stay in critical care unit.[20,25–27]	67%	99.7%
10%	Patient at increased risk of candidaemia based on clinical prediction models.[4,28,29]	82%	99%
20%	Neutropenic bone marrow transplant recipient or leukaemia patient not receiving antifungal prophylaxis.[30–33]	92%	98%

Clancy CJ. JAC. 2018

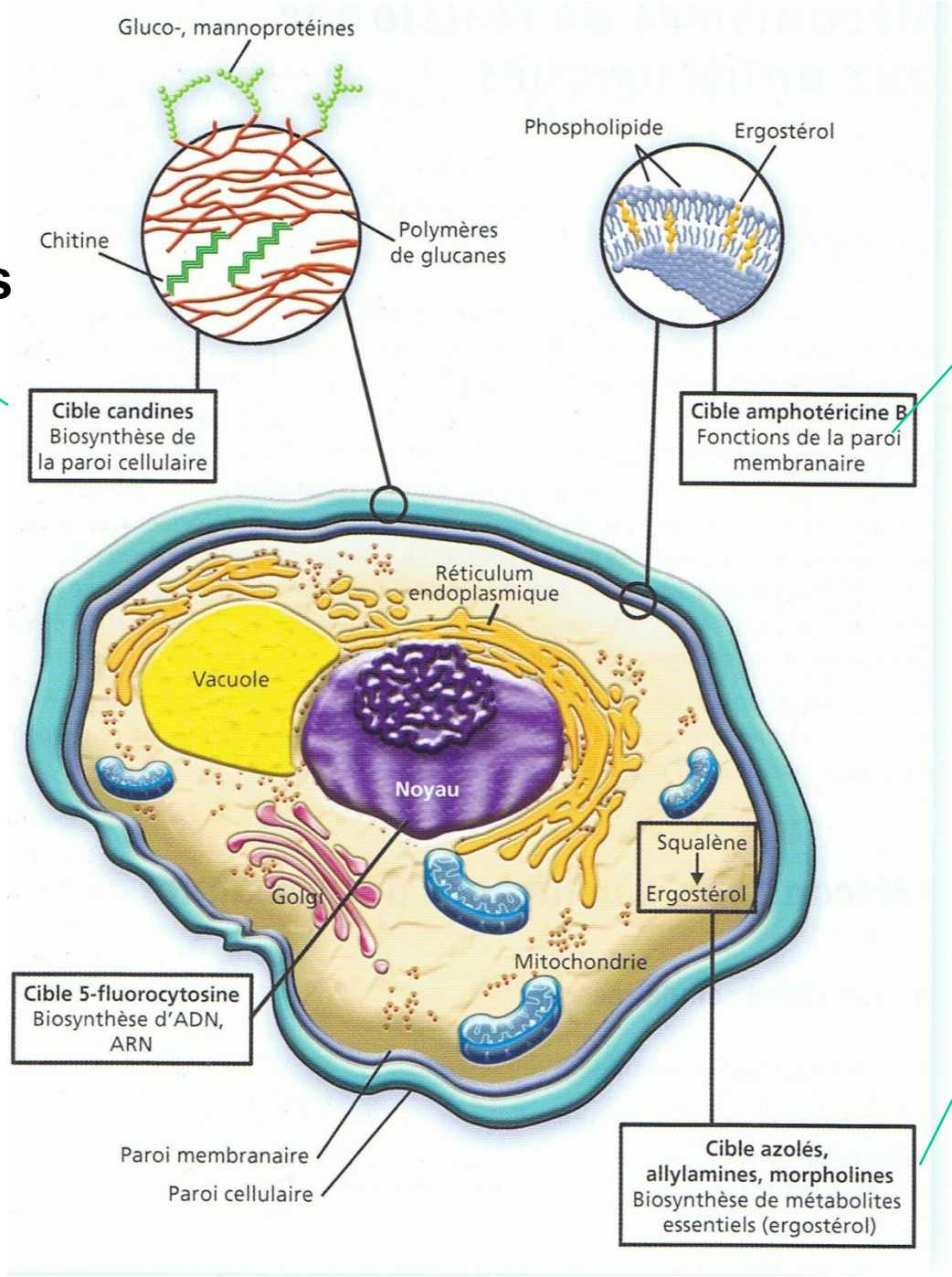


Martin-Loeches I et al. ICM. 2019

Les molécules antifongiques disponibles

Echinocandines

Amphotéricine B



5-FU

Azolés

Spectre antifongique

	Polyènes	*Fluco*	*Itraco*	*Vorico*	*Posaco*	*Candines*
C. albicans	+	+	+	+	+	+
Cryptococcus neof	+	+	+	+	+	-
***Aspergillus* spp**	+	-	+	+	+	+
***Zygomycetes* spp**	+	-	-	-	+	-
***Fusarium* spp**	+	-	-	+/-	+/-	-

- Polyènes fongicides
- Azolés fongicides sur aspergillus et statique sur *Candida*
- 5 FU active et fongistatique sur *Candida*
- Candines fongistatiques sur *Aspergillus*, fongicides sur *Candida*

Activités in-vitro sur les espèces de *Candida*

Souches	Amb	Fluco	Vorico	Caspo
C. albicans	+	+	+	+
C. tropicalis	+	+	+	+
C. parapsilosis	+	+	+	+/-
C. glabrata	+/-	+/-	+/-	+
C. krusei	+/-	-	+	+

Journal of Antimicrobial Chemotherapy (2007) **60**, 613–618
doi:10.1093/jac/dkm212
Advance Access publication 18 June 2007

JAC

Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive *Candida* species infections

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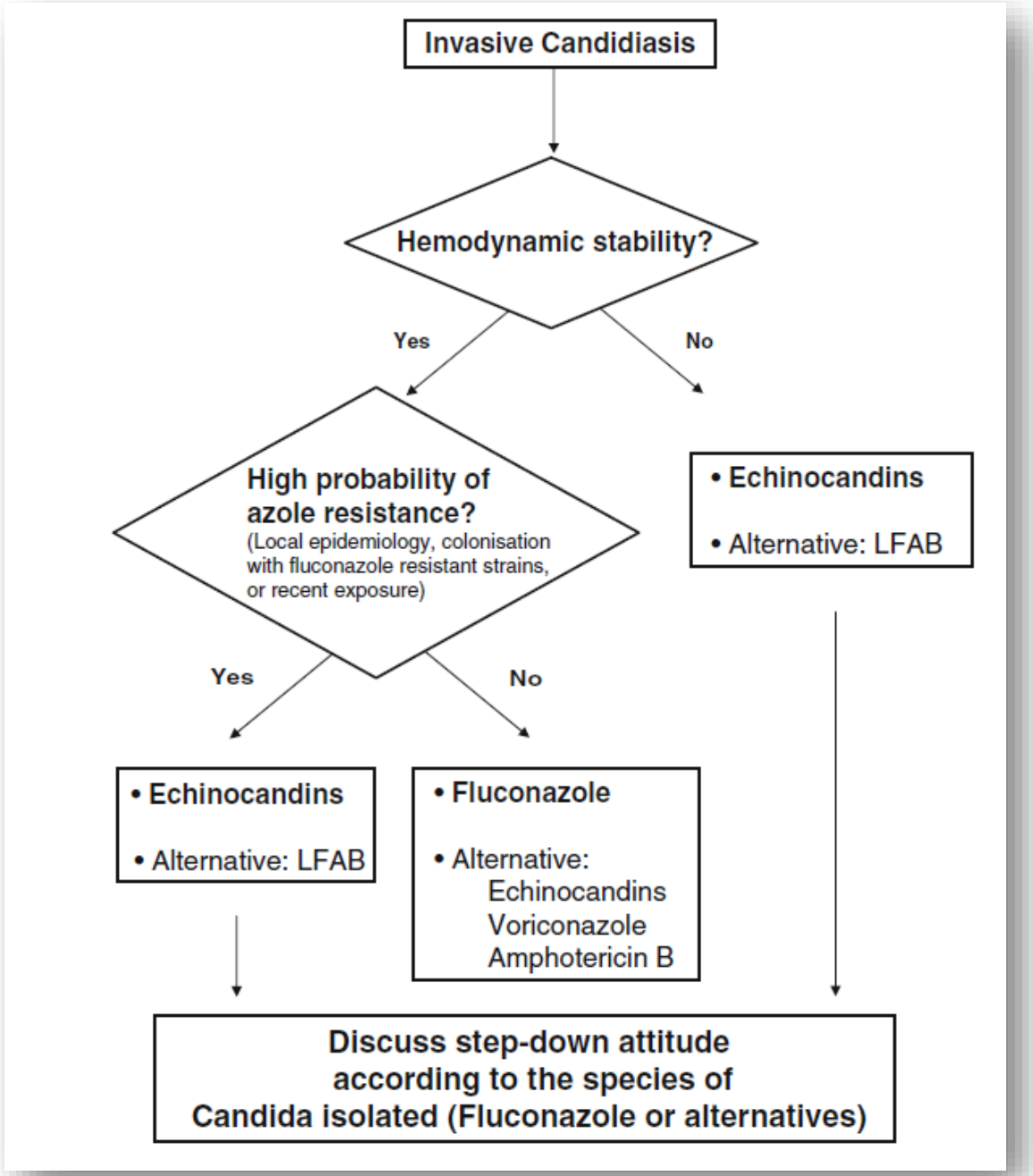
Variable	RR (IC 95%)	p
18-64 ans	4 (1,3-12,5)	0,01
65-79 ans	9 (2,8-29,4)	<0,001
≥80 ans	21 (5,3-83,7)	<0,001
Réanimation	3,8 (1,9-7,4)	<0,001
Tt initial adéquat	0,46 (0,22-1,00)	0,05



Guéry B et al. Int Care Med. 2008

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David Andes,[4] Daniel K. Benjamin, Jr.,[5] Thierry F. Calandra,[11] John E. Edwards, Jr.,[6] Scott G. Filler,[6] John F. Fisher,[7] Bart-Jan Kullberg,[12] Luis Ostrosky-Zeichner,[8] Annette C. Reboli,[9] John H. Rex,[13] Thomas J. Walsh,[10] and Jack D. Sobel[3]

Clin Infect Dis 2009;48:53

- Soit fluco soit échinocandines avant identification de l’espèce

- Candines préférées si (A3)
  - Critères de gravité
  - Exposition antérieure aux azolés

- Remplacer candines par fluco si patient stable et infecté par une espèce sensible

- Candidémie à *glabrata* (B3)
  - Candines recommandées
  - Si azolés et bonne évolution, on peut ne pas changer

- Candidémie à parapsilosis (B3)
  - Fluco
  - Si candines et bonne évolution, on peut ne pas changer

- Amb+fluorocytosine reste le traitement de référence
  - Endocardites
  - Ostéomyélites
  - Endophtalmie

Candines fortes doses?

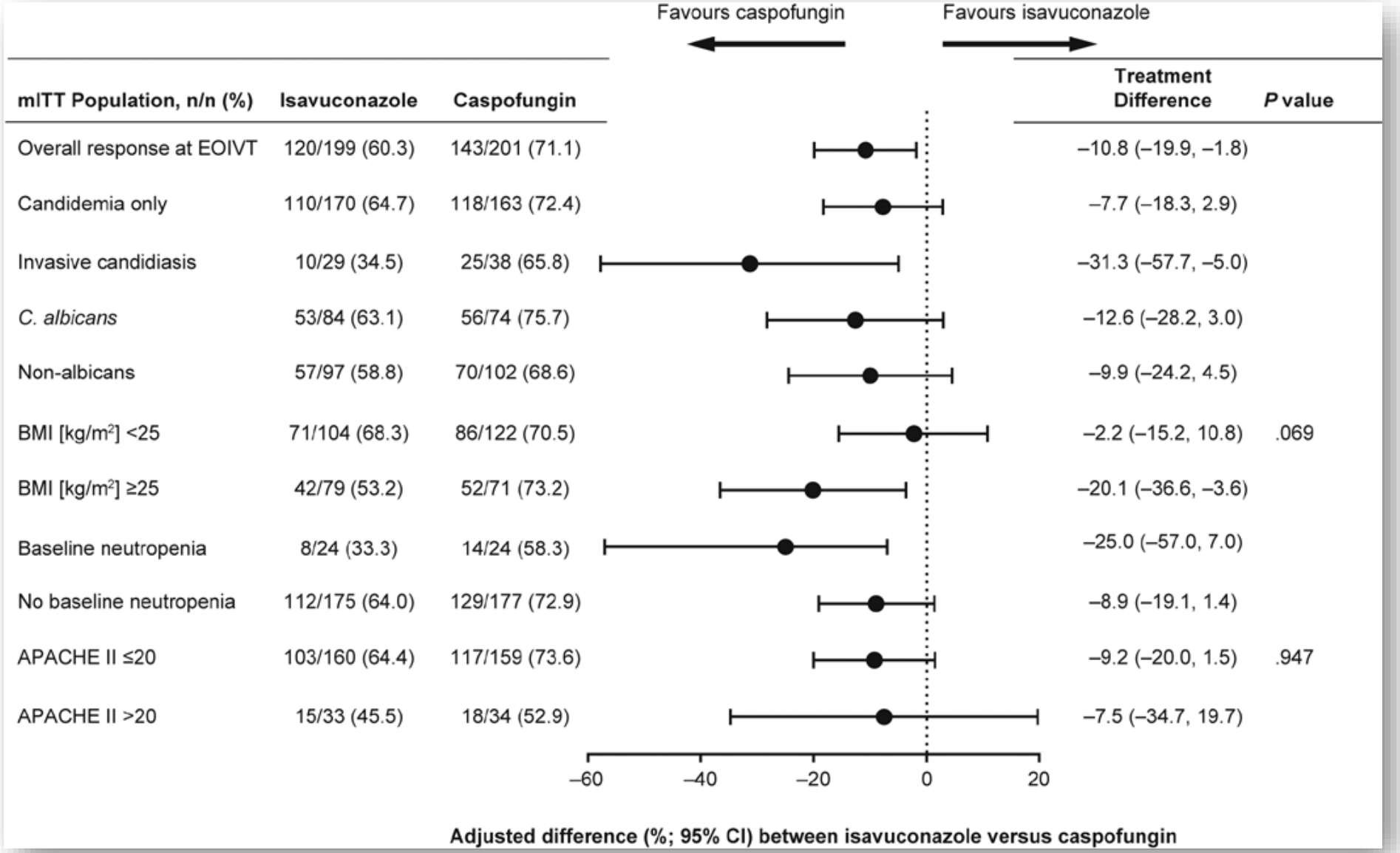
Durée du traitement

The recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms attributable to candidemia (A-III)

Reco ESCMID 2012

- A consulter, mais si on se résume
  - Échinocandines chez le malade de réanimation en première intention
  - Sauf localisation particulière: œil, méninges, endocardite, prothèses…
  - Prophylaxie sur population à haut risque

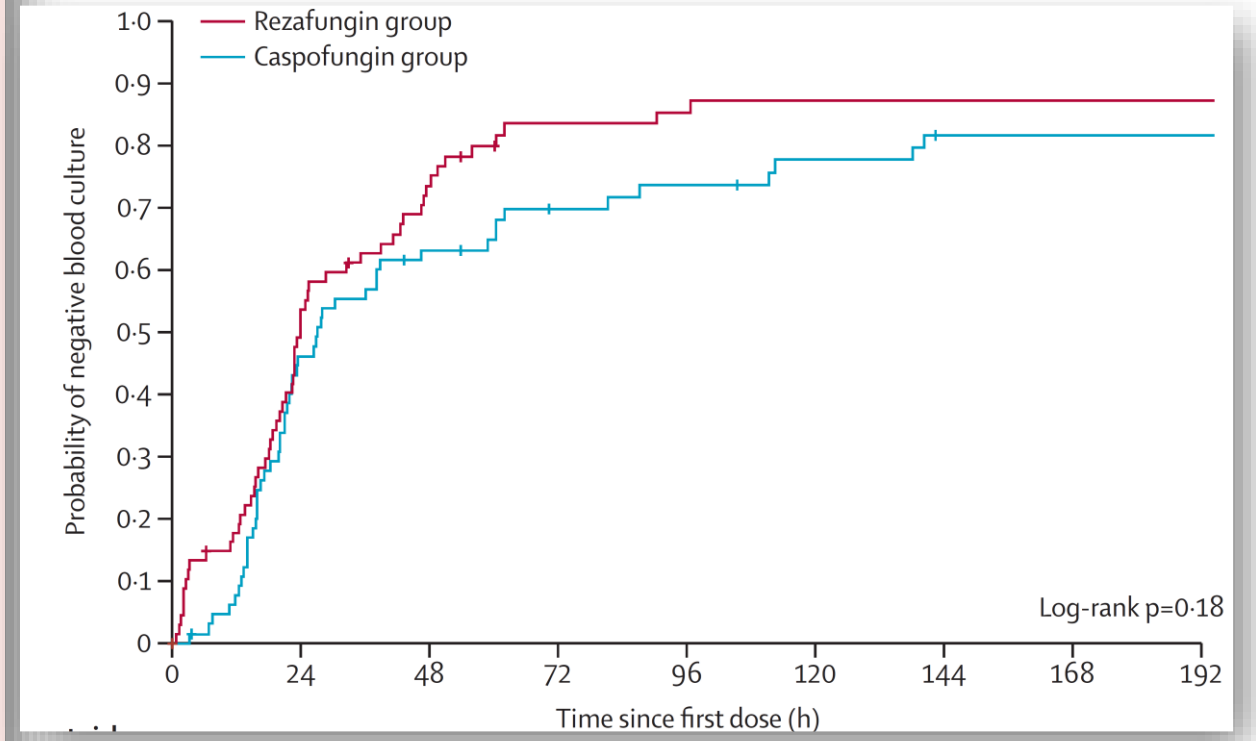
Essai Active: Isavuco vs Caspo



Kullberg BJ et al. CID. 2018

Rezafungine vs caspo: essai Restore

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)
All-cause mortality at day 30 (US FDA primary outcome)			
Died	22 (24%)	20 (21%)	2·4 (−9·7 to 14·4)*
Known to have died	19 (20%)	17 (18%)	..
Unknown survival	3 (3%)	3 (3%)	..
All-cause mortality at day 30 by diagnosis			
Candidaemia only	18/64 (28%)	17/67 (25%)	2·8 (−12·5 to 18·0)*
Invasive candidiasis	4/29 (14%)	3/27 (11%)	2·7 (−16·7 to 21·7)*
Global response at day 14 as assessed by DRC (EMA primary outcome)			
Cure	55 (59%)	57 (61%)	−1·1 (−14·9 to 12·7)†
Failure	28 (30%)	29 (31%)	..
Indeterminate	10 (11%)	8 (9%)	..
Global response at day 14 as assessed by DRC by diagnosis			
Candidaemia only			
Cure	39/64 (61%)	43/67 (64%)	−3·2 (−19·6 to 13·3)*
Failure	21/64 (33%)	19/67 (28%)	..
Indeterminate	4/64 (6%)	5/67 (7%	..
Invasive candidiasis			
Cure	16/29 (55%)	14/27 (52%)	3·3 (−22·4 to 28·6)*
Failure	7/29 (24%)	10/27 (37%)	..
Indeterminate	6/29 (21%)	3/27 (11%)	..



Thompson Ill GR et al. Lancet.. 2023

Résumé

- Candidémies
  - Techniques de microbiologie classique prises en défaut par manque de sensibilité et délai trop long
  - Techniques alternatives plus ou moins prometteuses
  - A confronter à la stratégie thérapeutique

- Candidoses invasives sans candidémie
  - Stratégie préemptive permet d'anticiper
  - Problématique du gold standard pour l'évaluation

- Les échinocandines restent le traitement de choix chez les patients instables selon les reco
  - Mais les patients stables ?
  - Penser à la désescalade
  - Arrêt précoce des traitements empiriques non justifiés