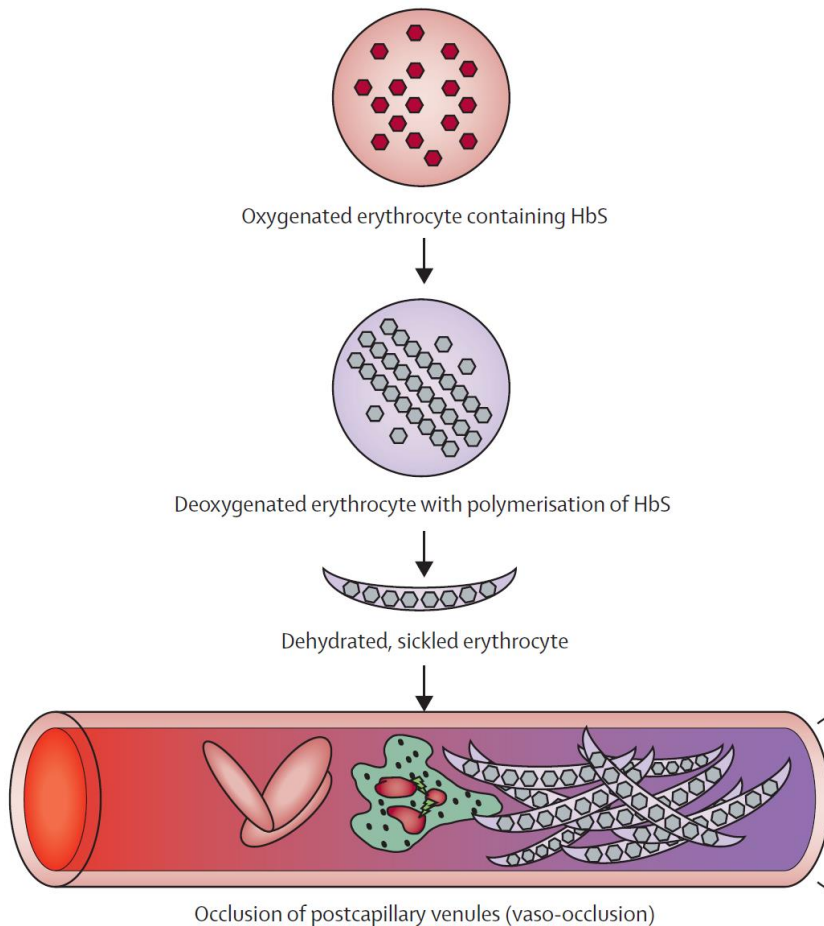


Drépanocytose en réanimation

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Réanimation Médicale, Hôpitaux Universitaires Henri Mondor
Groupe de Recherche Clinique CARMAS, Université Paris Est Créteil

Bases moléculaires et classification



Severe sickle-cell disease

HbS/S ($\beta 6\text{Glu}>\text{Val}/\beta 6\text{Glu}>\text{Val}$); sickle-cell anaemia

HbS/ β^0 thalassaemia

Severe HbS/ β^+ thalassaemia

HbS/OArab ($\beta 6\text{Glu}>\text{Val}/\beta 121\text{Glu}>\text{Lys}$)

HbS/D Punjab ($\beta 6\text{Glu}>\text{Val}/\beta 121\text{Glu}>\text{Gln}$)

HbS/C Harlem ($\beta 6\text{Glu}>\text{Val}/\beta 6\text{Glu}>\text{Val}/\beta, \beta 73\text{Asp}>\text{Asn}$)

HbC/S Antilles ($\beta 6\text{Glu}>\text{Lys}/\beta 6\text{Glu}>\text{Val}, \beta 23\text{Val}>\text{Ile}$)

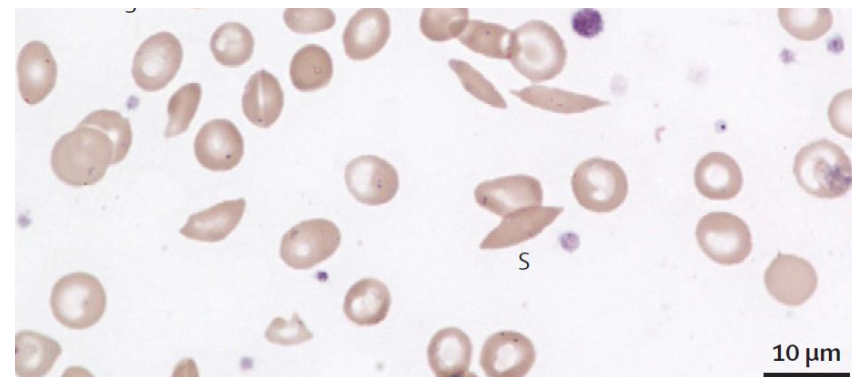
HbS/Quebec-CHORI ($\beta 6\text{Glu}>\text{Val}/\beta 87\text{Thr}>\text{Ile}$)

Moderate sickle-cell disease

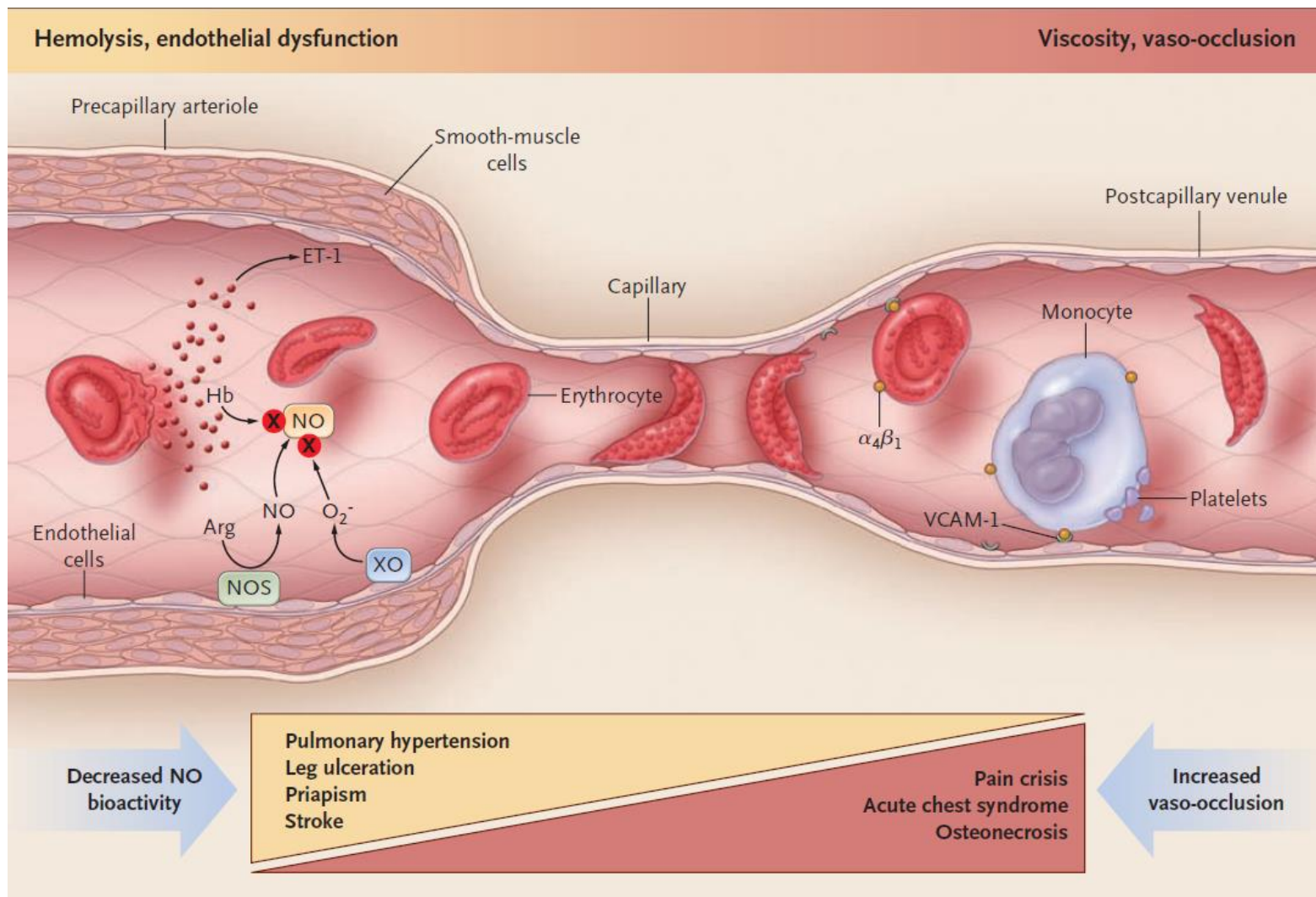
HbS/C ($\beta 6\text{Glu}>\text{Val}/\beta 6\text{Glu}>\text{Lys}$)

Moderate HbS/ β^+ thalassaemia

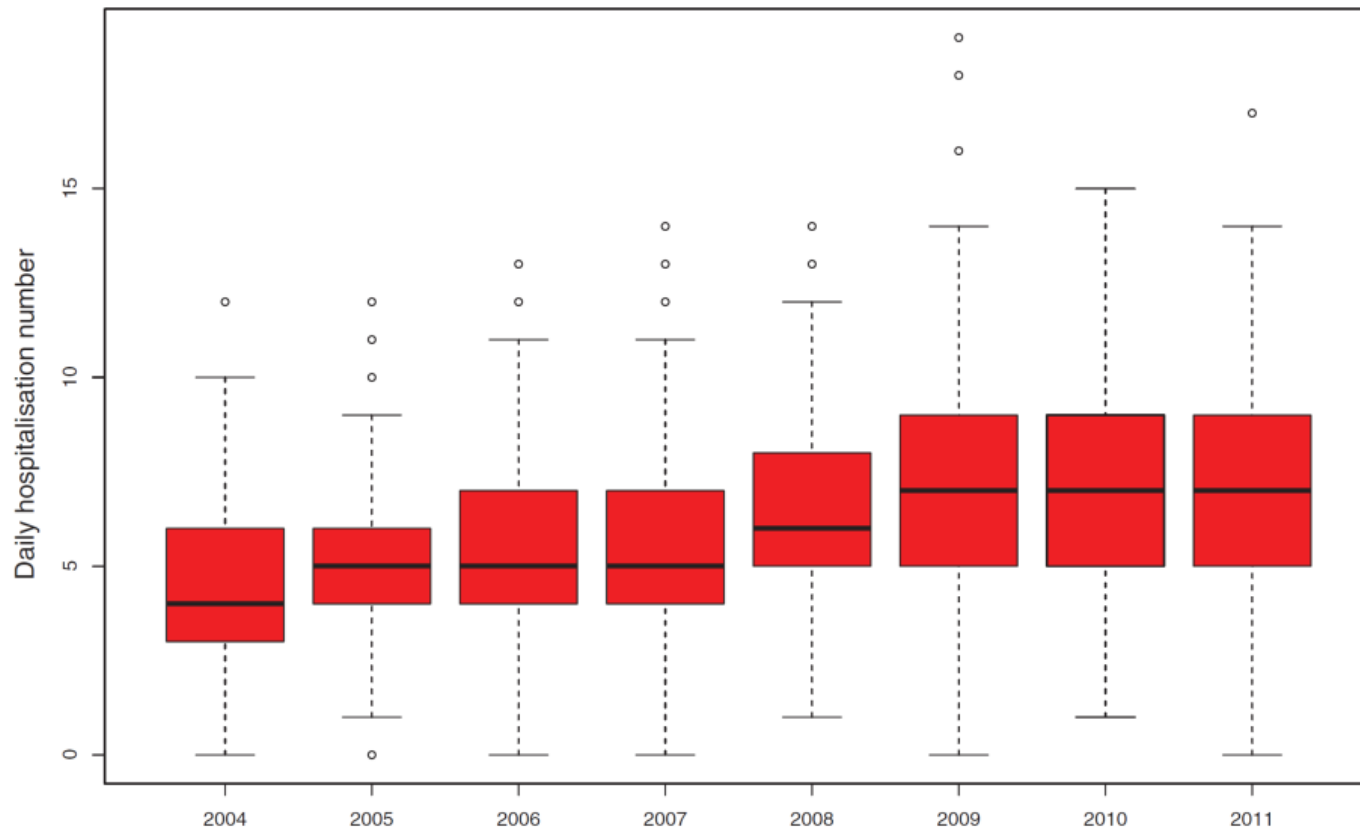
HbA/S Oman ($\beta^+/\beta 6\text{Glu}>\text{Val}, \beta 121\text{Glu}>\text{Lys}$)



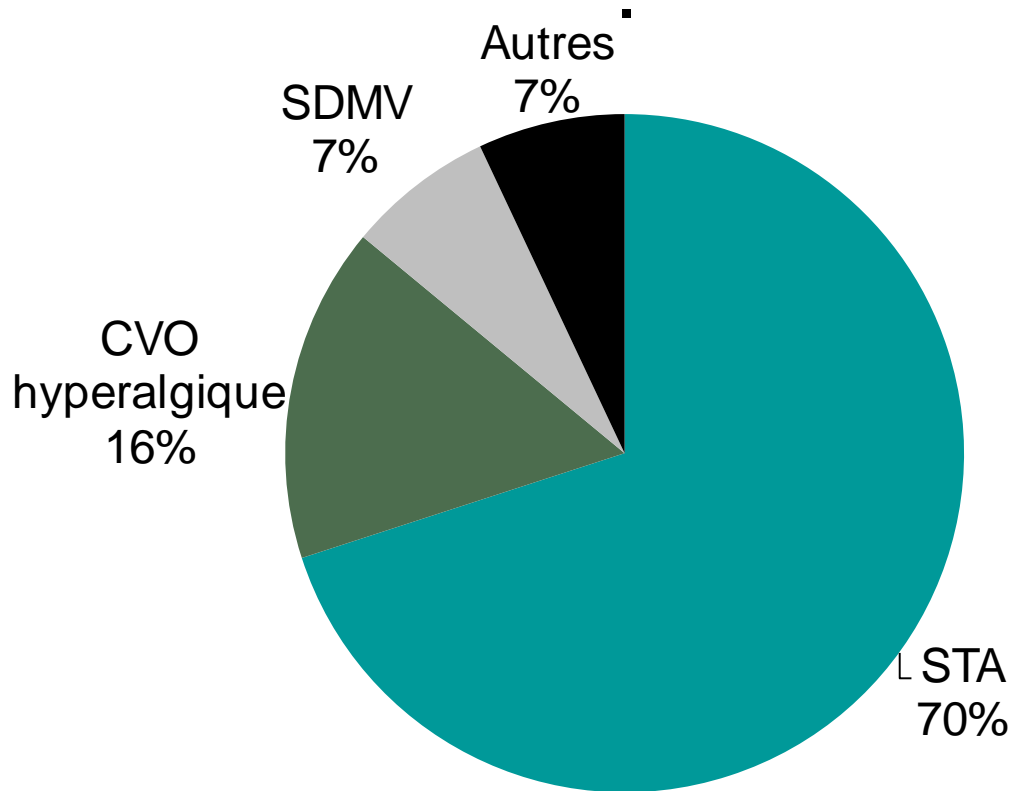
Phénotypes cliniques



Incidence croissante des complications aigues graves



Motifs d'admission en réanimation



Critères d'admission en réanimation

TABLE 6. Predictors of Complicated Course in Sickle Cell Disease Patients

Variable	n	Complicated Course, n (%)	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	p	OR (95% CI)	p
Sex						
Male	69	10 (14)	1	0.1	Variables not entered in the multivariate model	
Female	67	17 (25)	0.5 (0.2–1.2)			
Age, yr						
< 32	118	21 (18)	1	0.1	Variables not entered in the multivariate model	
≥ 32	18	6 (33)	2.3 (0.8–6.9)			
Homozygous hemoglobinopathy						
No	19	5 (26)	1	0.4	Variables not entered in the multivariate model	
Yes	117	22 (19)	0.6 (0.2–1.9)			
Respiratory rate, cycles/min						
< 32	92	11 (12)	1	0.001	5.6 (1.8–17.2)	0.003
≥ 32	25	11 (44)	5.8 (2.1–15.9)			
Hemoglobin, g/dL						
> 7.8	63	5 (8)	1	0.002	3.6 (1.1–11.9)	0.04
≤ 7.8	73	22 (30)	5.0 (1.8–14.2)			
Acute kidney injury						
No	122	17 (14)	1	0.0001	11.5 (2.5–52.6)	0.002
Yes	14	10 (71)	15.4 (4.3–54.9)			

STA: regroupe les complications pulmonaires aiguës de la drépanocytose

'Acute Chest Syndrome' in Adults
With Sickle Cell Anemia

Microbiology, Treatment, and Prevention

Samuel Charache, MD; Jean C. Scott, RN;
Patricia Charache, MD

(*Arch Intern Med* 139:67-69, 1979)

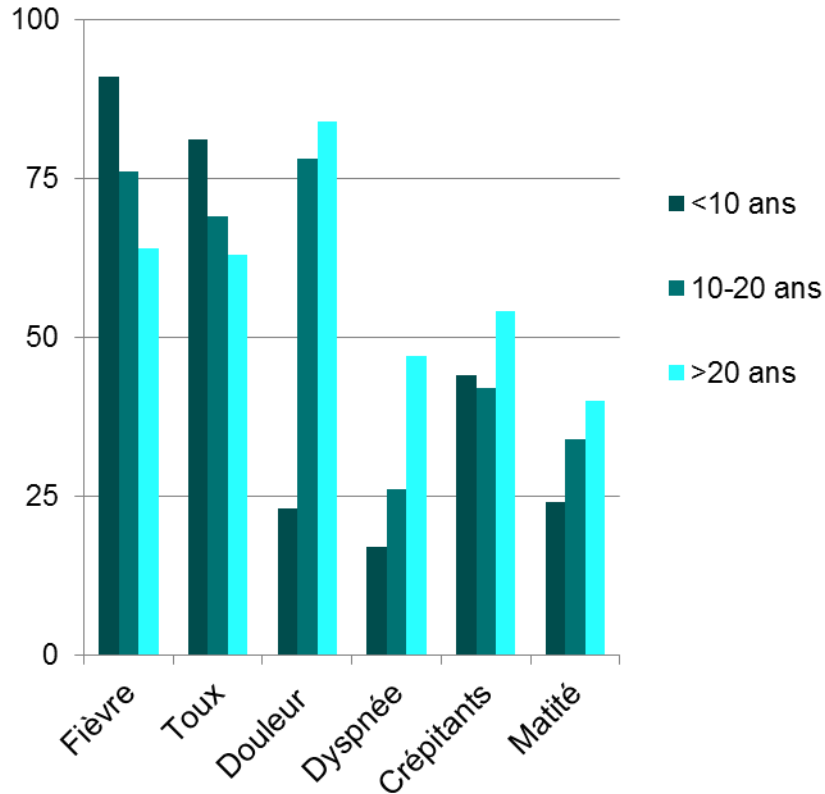
● **Fifty-two episodes of fever, chest pain, increased leukocytosis, and pulmonary infiltrate (“acute chest syndrome”) were studied in 28 adults with sickle cell anemia. Possible bacterial pathogens were identified in sputum cultures from less than half of the episodes; no pneumococci were found**

Much disease diagnosed as “pneumonia” in adults with sickle cell anemia is probably pulmonary infarction. Many of these patients will recover with no more than modest supportive care; if

STA: critères diagnostiques non

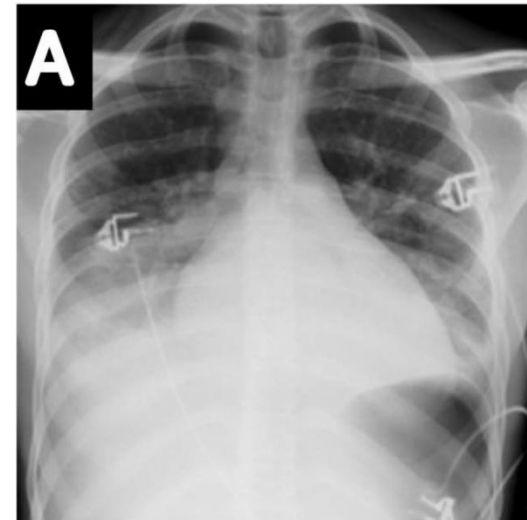
consensuels

SIGNE CLINIQUE



NOUVEL INFILTRAT RADIOLOGIQUE

- Consolidation
 - \geq segmentaire
 - \neq atélectasie

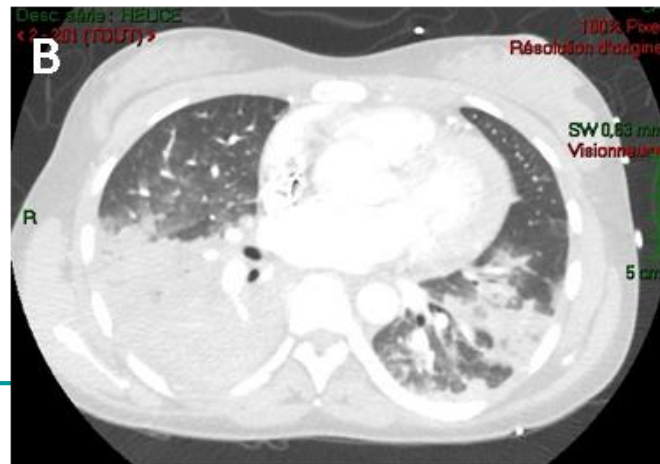


Vichinsky, NEJM 2000
Gladwin, NEJM 2008

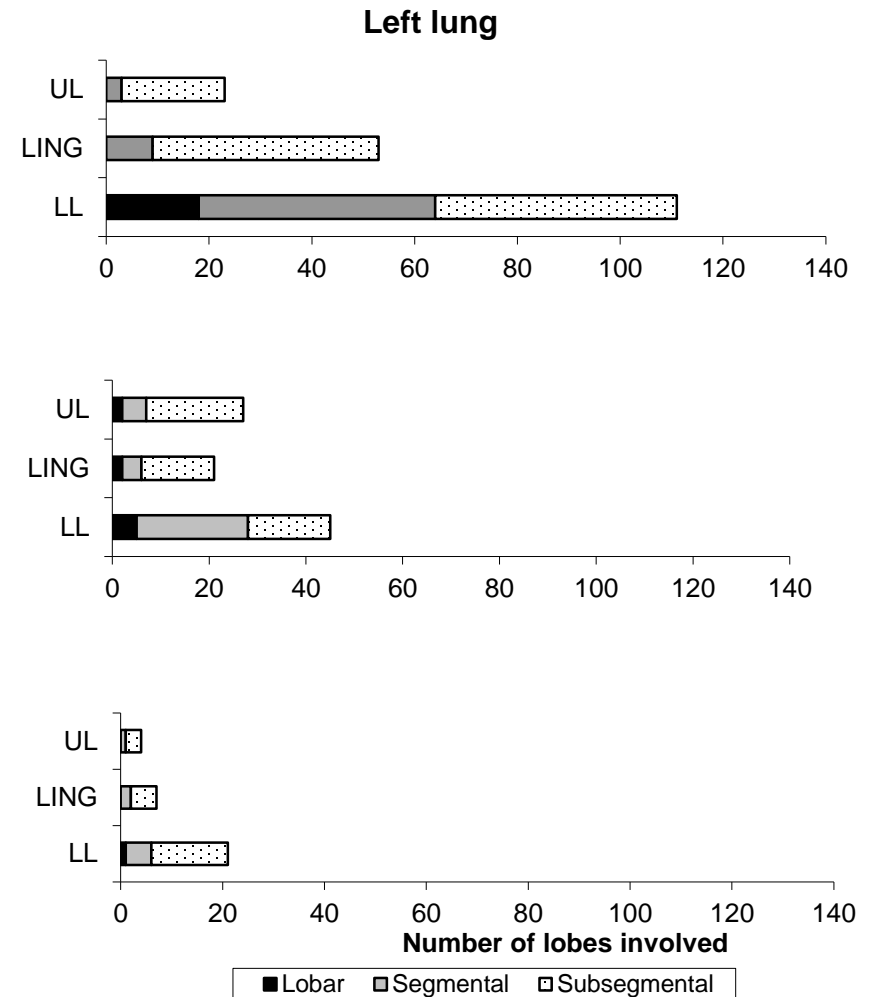
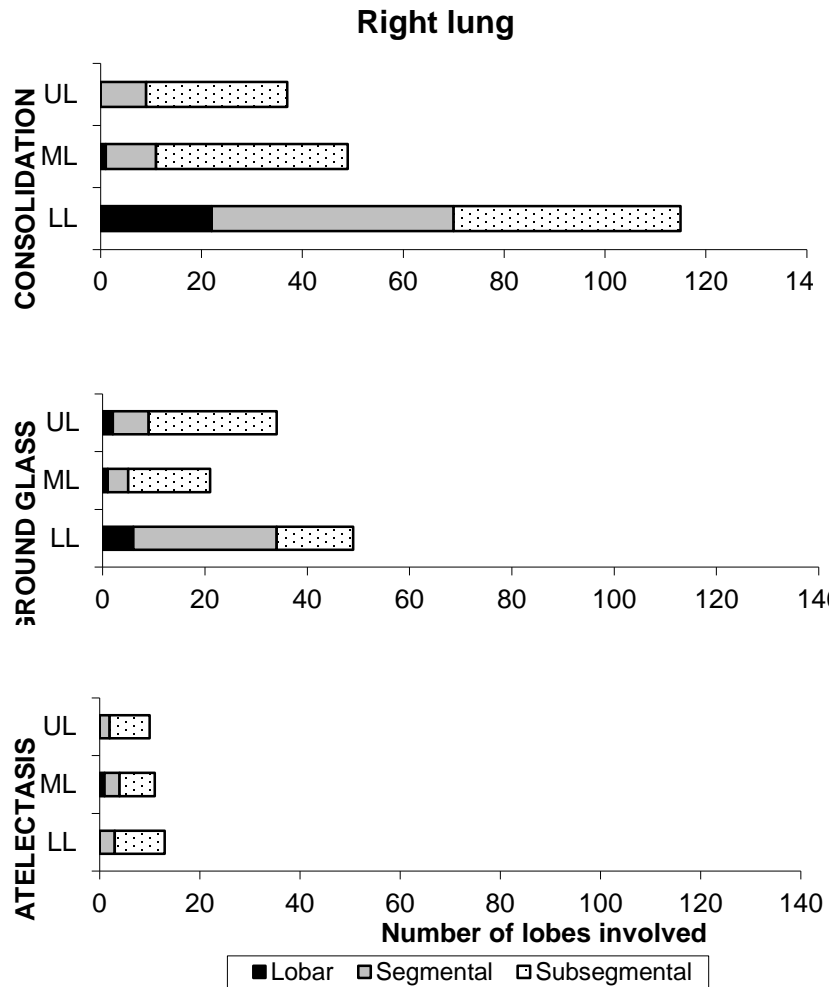
Vichinsky, Blood 1997
Mekontso Dessap, Thorax 2013

STA: prédominance basale

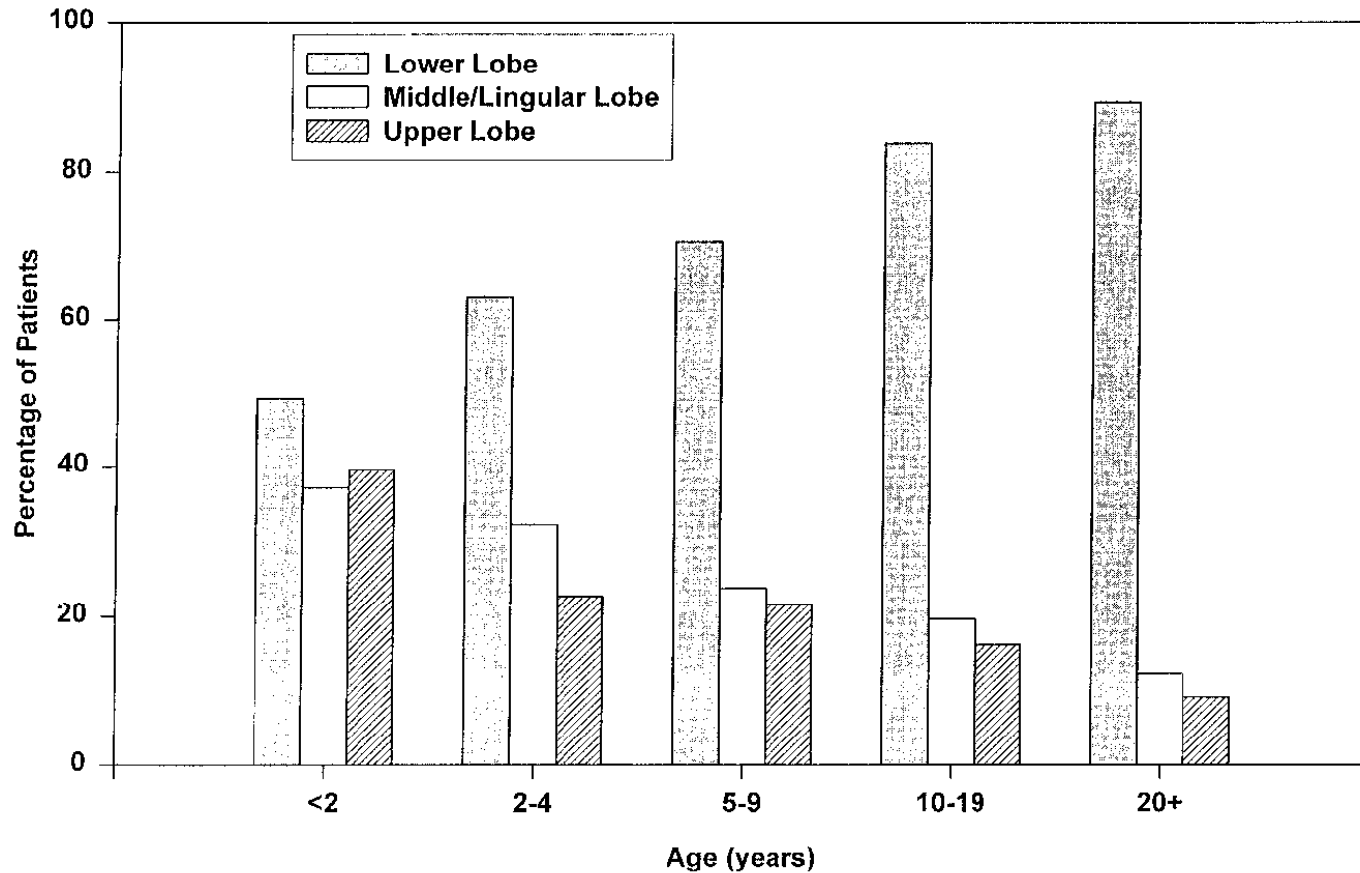
- Epanchement pleural dans $\frac{1}{4}$ des cas
- Atteinte lobe inférieur dans $> 95\%$ des cas
 - Son absence élimine le diagnostic chez l'adulte



STA: prédominance consolidations basales

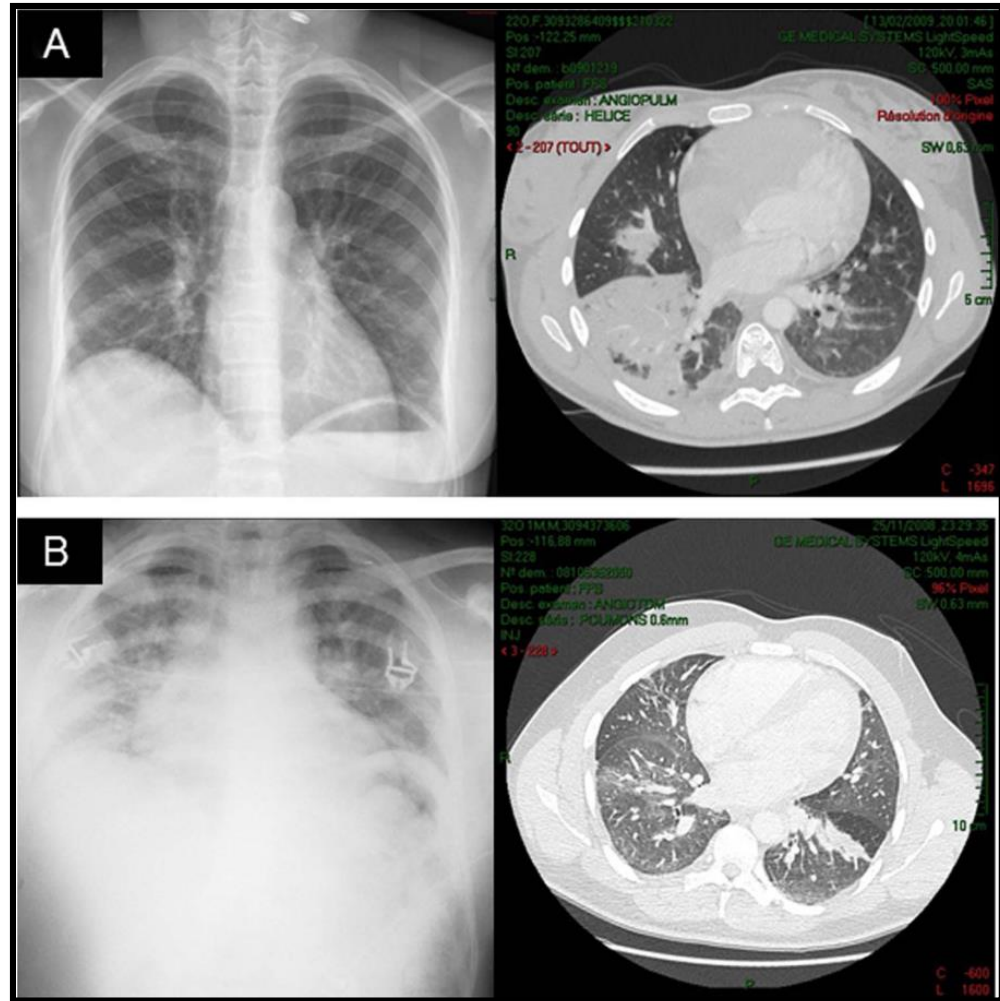


Aspect radiologique STA: effet de l'âge



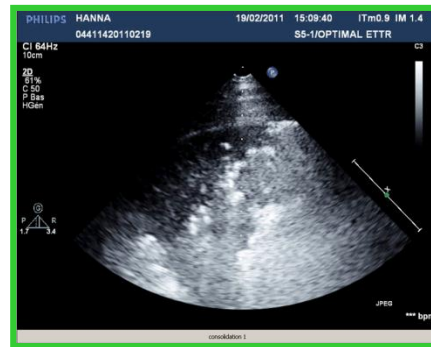
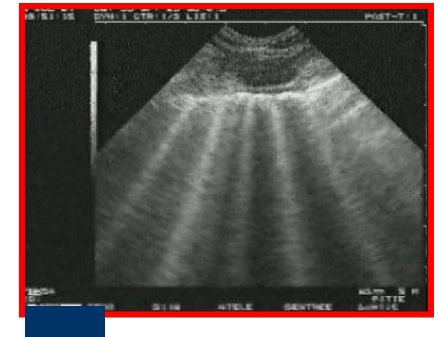
Diagnostic radiologique STA

- Radio au lit
 - Se >85%
 - Sp <60%

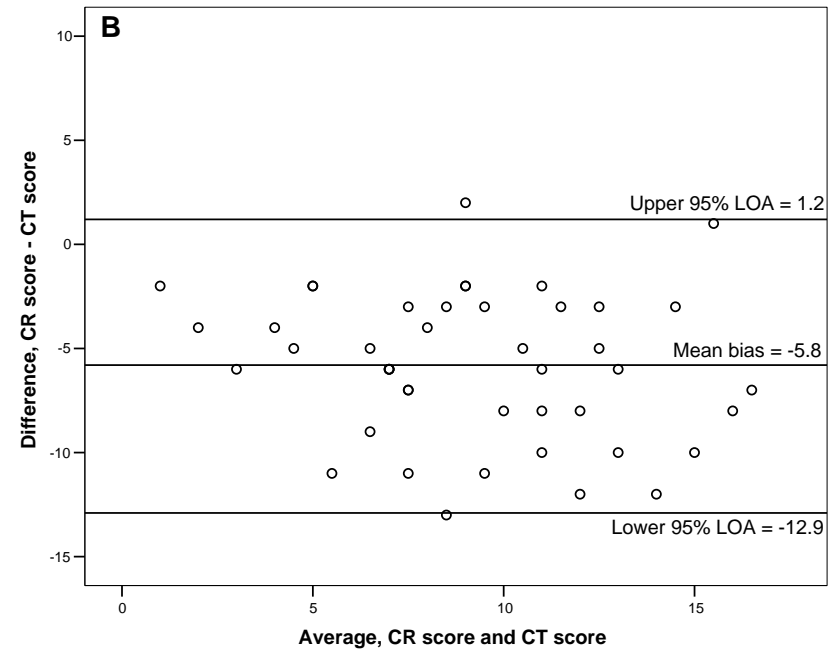
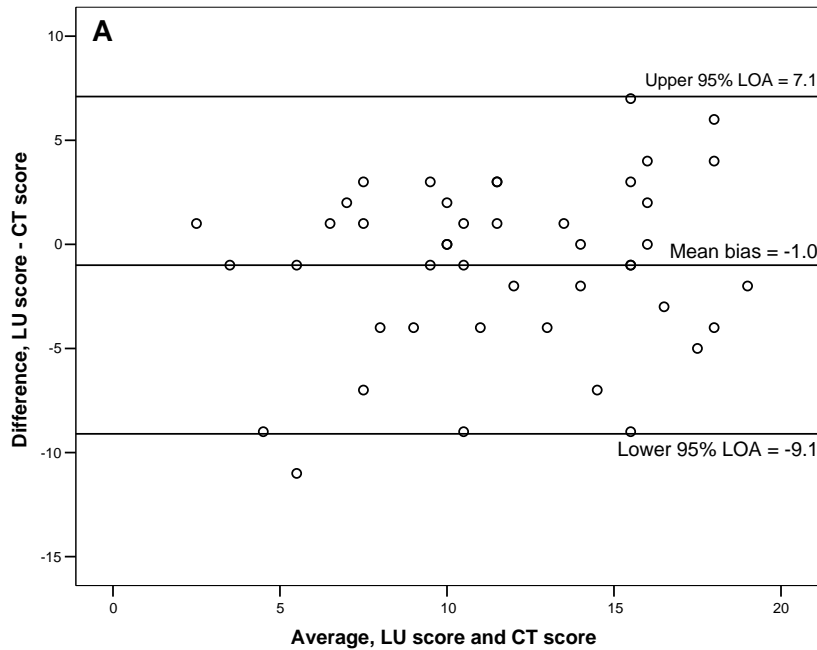


Echographie pulmonaire

- Aération normale
- Syndrome interstitiel
- Consolidation
- Épanchement

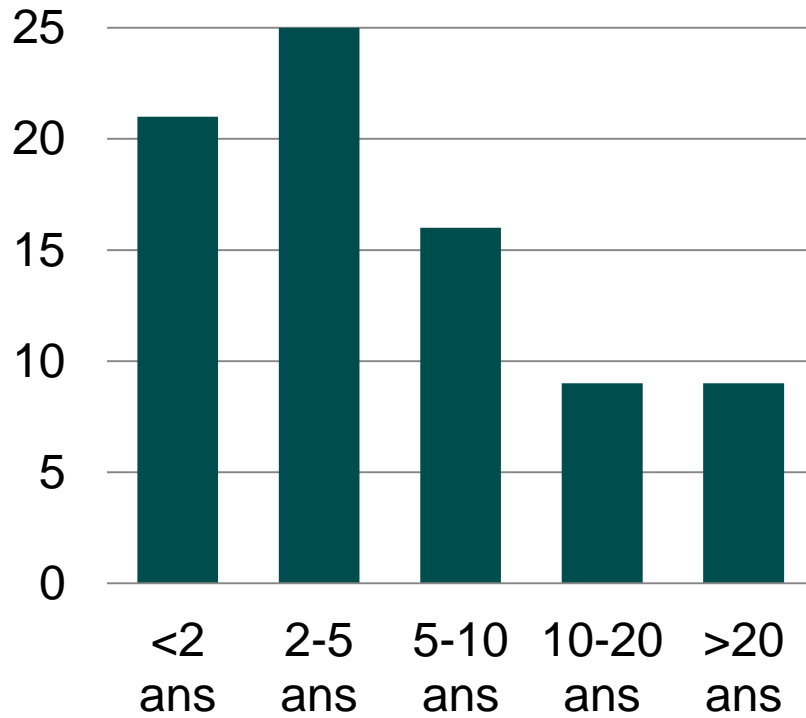


Echographie pulmonaire



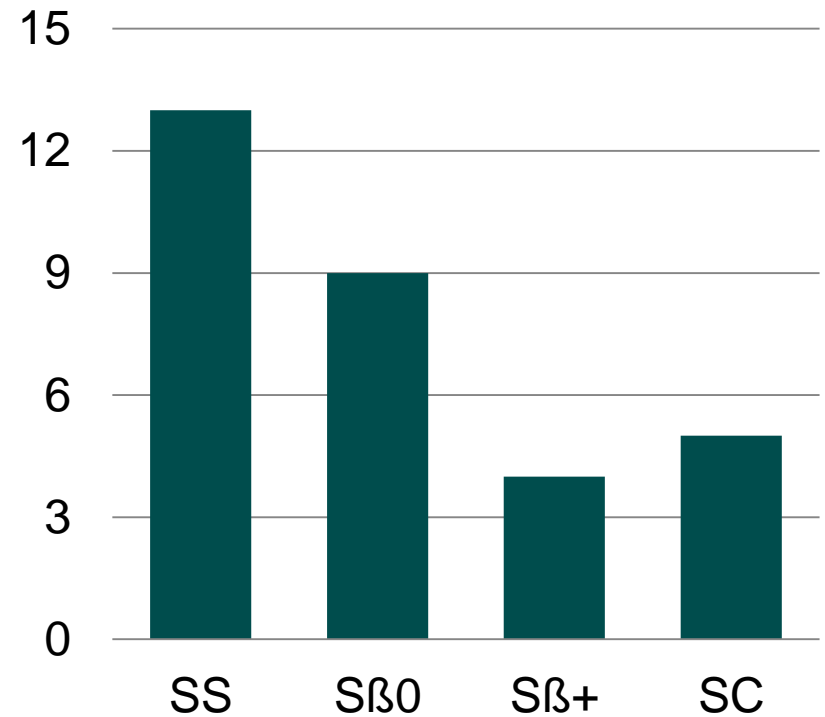
Facteurs de risque STA

Jeune âge



■ Incidence (/100 patients-années)

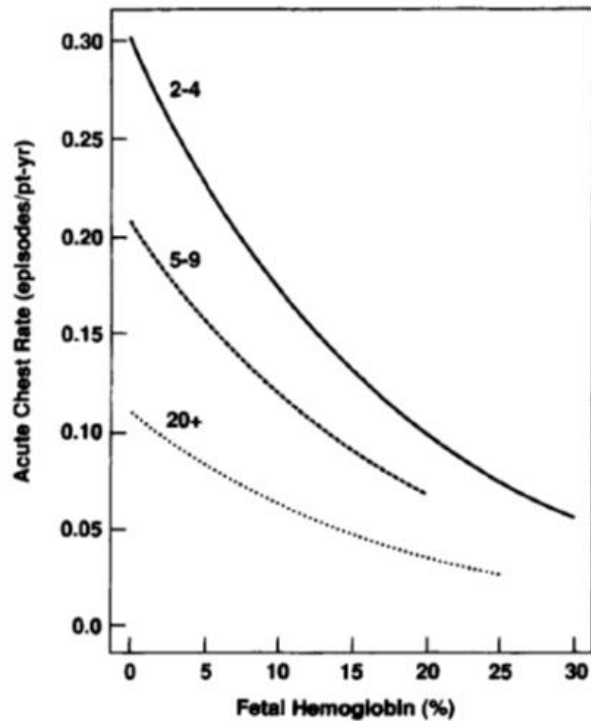
Génotype SS et S-β⁰



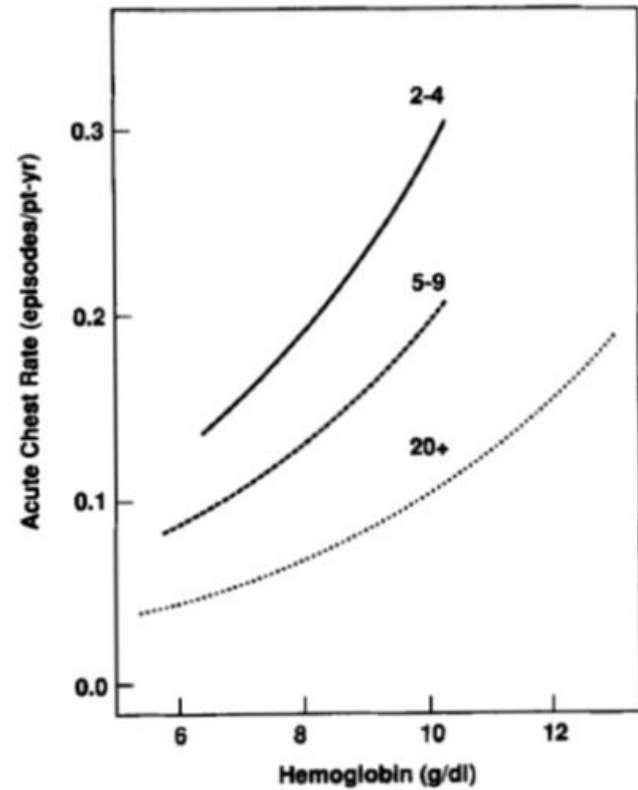
■ Incidence (/100 patients-années)

Facteurs de risque STA

↓ Hb F



↑ Hb totale et leucocytes



Facteurs déclenchants STA

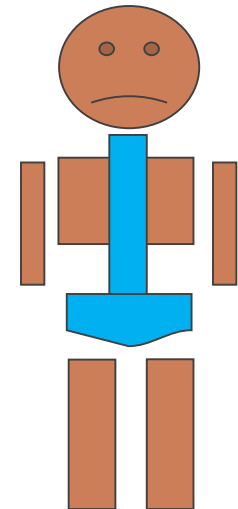
- Le STA peut inaugurer la maladie drépanocytaire
 - Près de la moitié des patients avec STA sont admis pour une autre raison
 - Facteurs déclenchants classiques
 - Grossesse, postpartum
 - Chirurgie
 - CVO
 - Environnement
-

CVO: score PRESEV

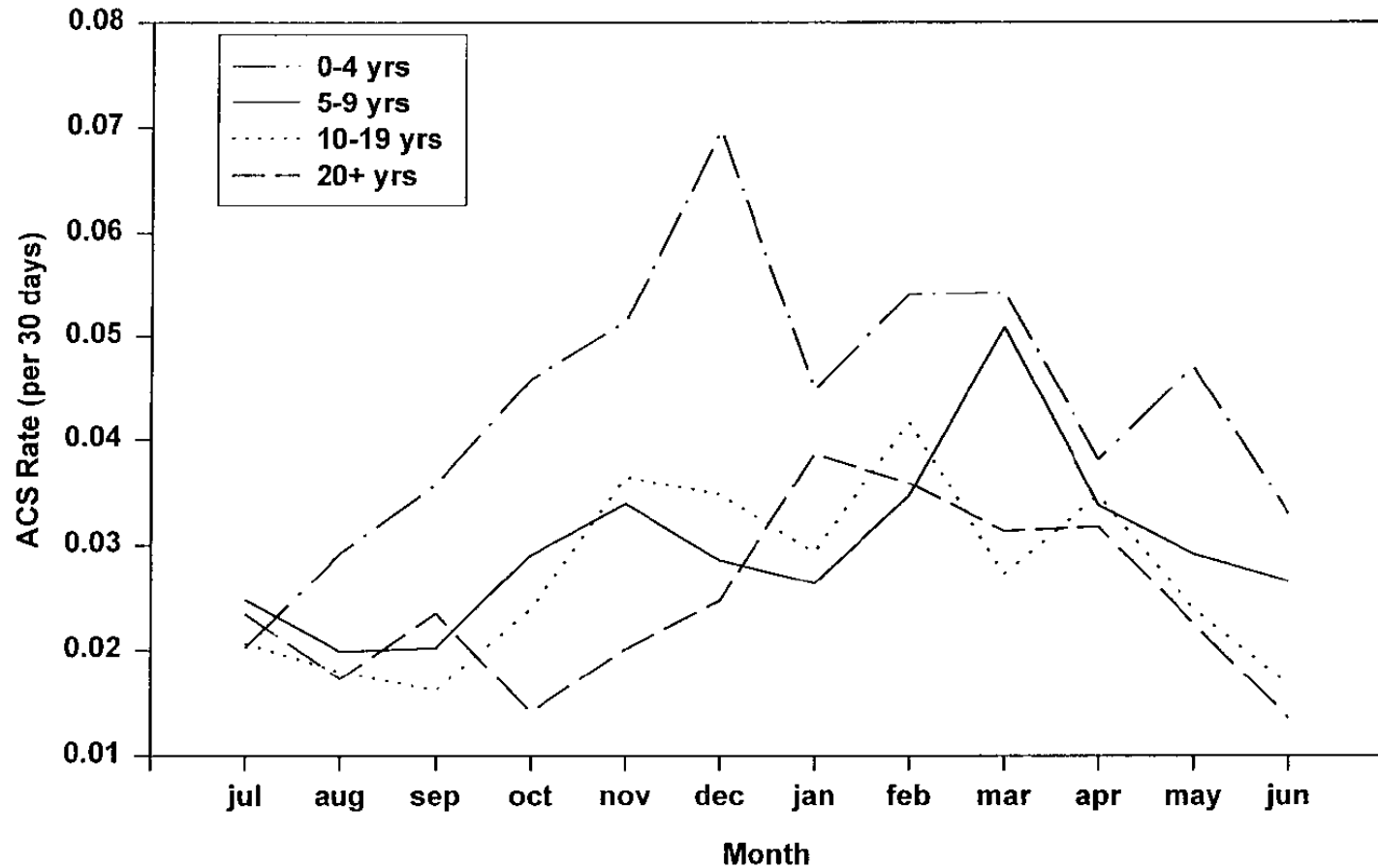
Table 3

ACS-predictive model derived from the multivariate analysis.

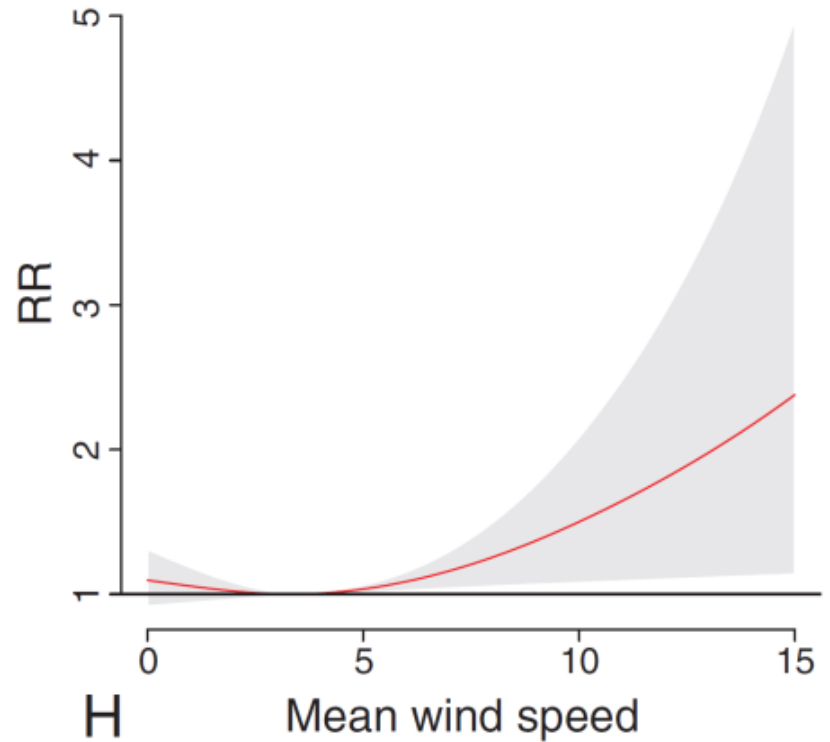
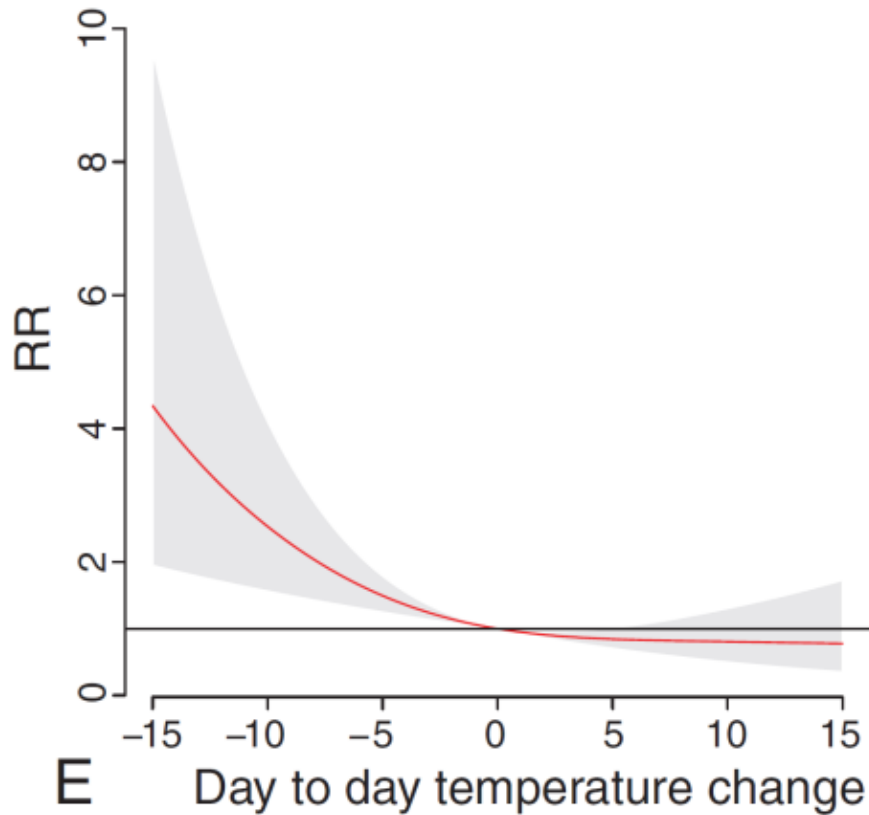
Day-1 variable	β -Coefficient	aOR [95% CI]	<i>p</i>	Points ^a	
Reticulocytes ($10^9/L$)					
≤ 216	0	1		0	
> 216	2.153	8.613 [3.01–24.69]	< 0.001	6	
Spine and/or pelvis CPS				0	
0 or 1	0	1			
2	1.401	4.060 [1.46–11.26]	0.007	4	
3	1.852	6.371 [2.37–17.15]	< 0.001	6	
Leukocytes ($10^9/L$)					
≤ 11	0	1		0	
> 11	1.160	3.190 [1.17–8.72]	0.024	3	
Hemoglobin (g/dL) ^b					
> 9	0	1		0	
≤ 9	0.246	1.279 [0.55–2.96]	0.567	1	
Predictive model performance on the study population					
Predictive score ^c	ACSs	VOCs	Total		Risk
≥ 11	21	26	47	PPV = 44.7%	High
6–10	15	75	90		Intermediate
≤ 5	1	88	89	NPV = 98.9%	Low
Total	37	189	226		



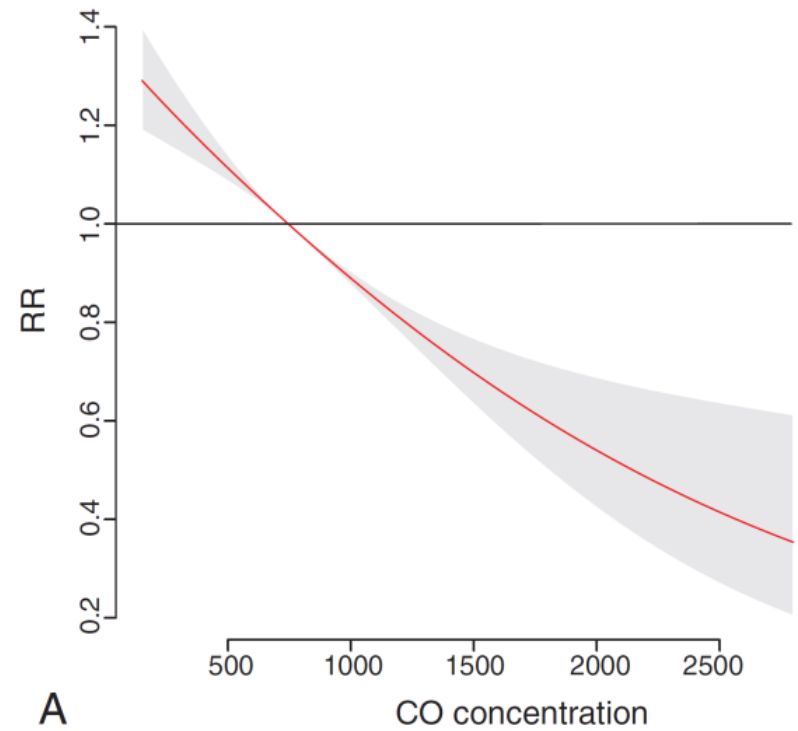
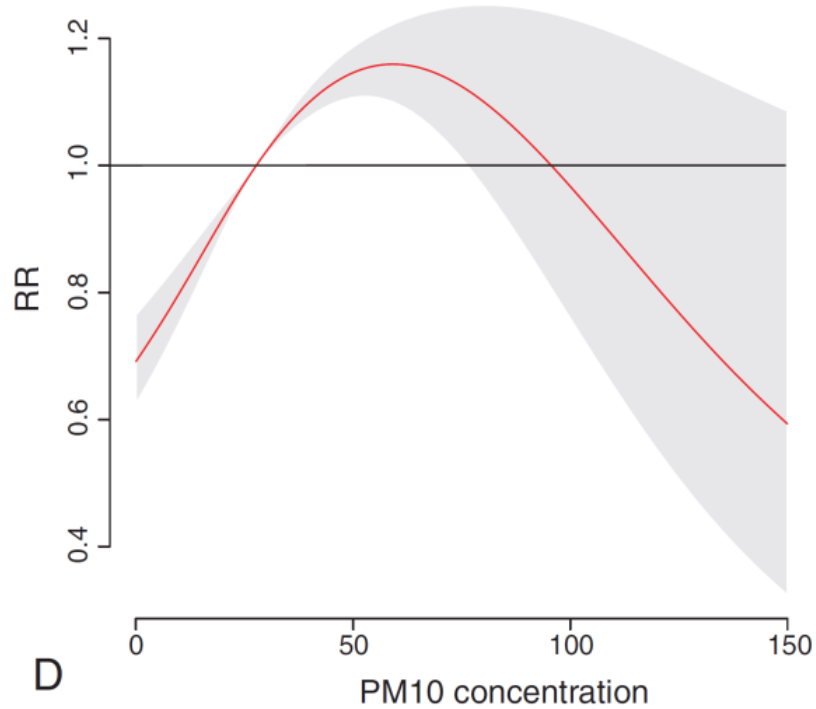
Saisonnalité STA



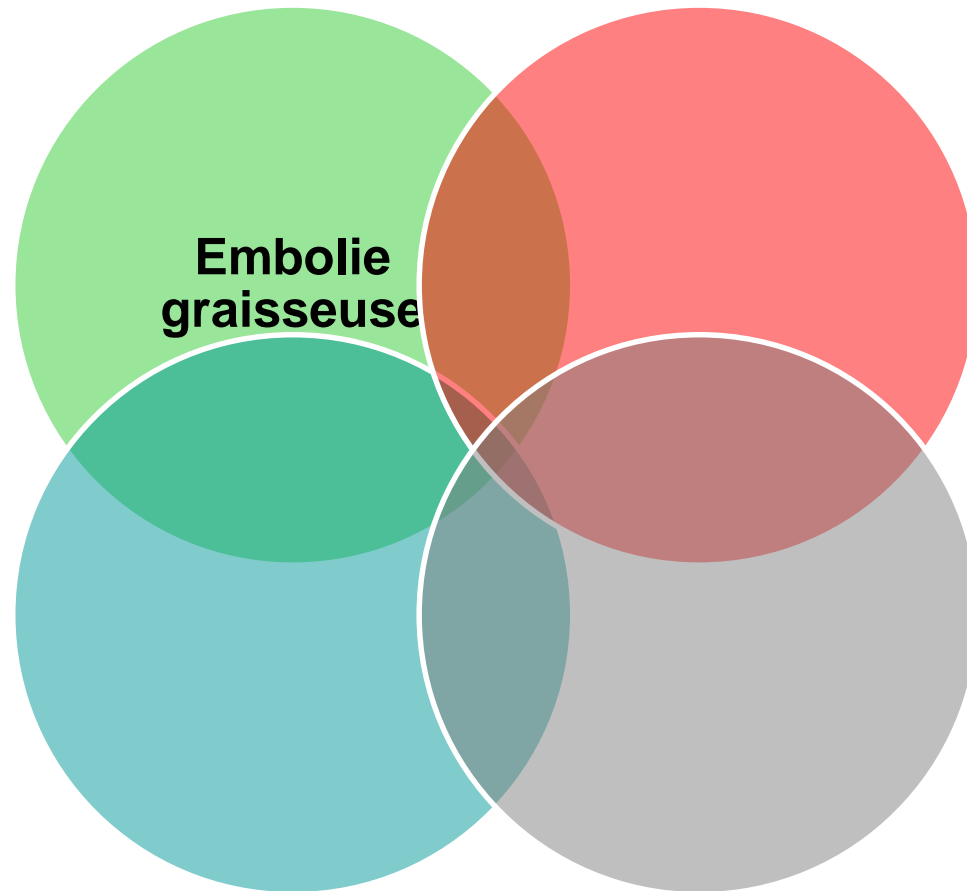
STA et environnement



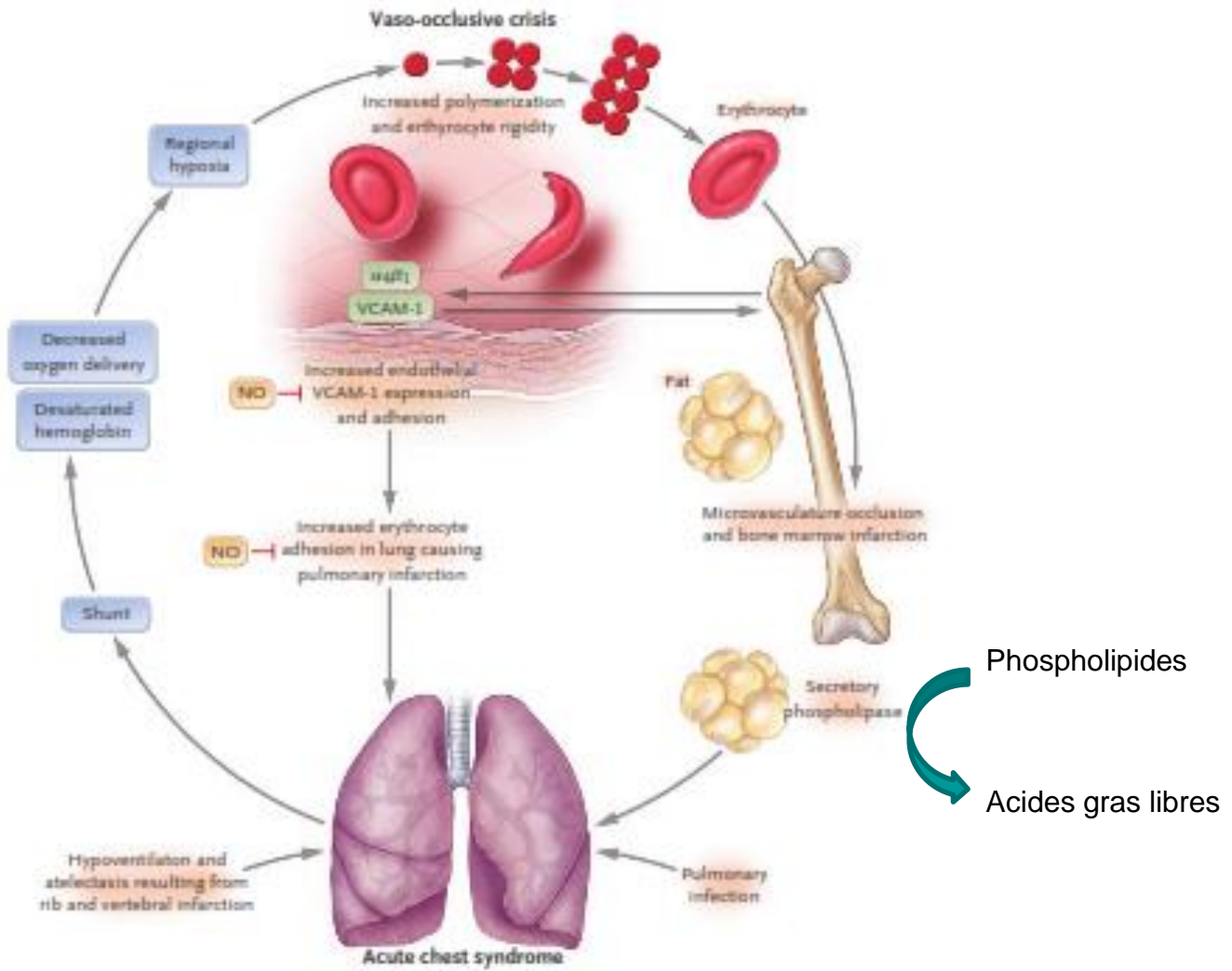
STA et environnement



Physiopathologie STA

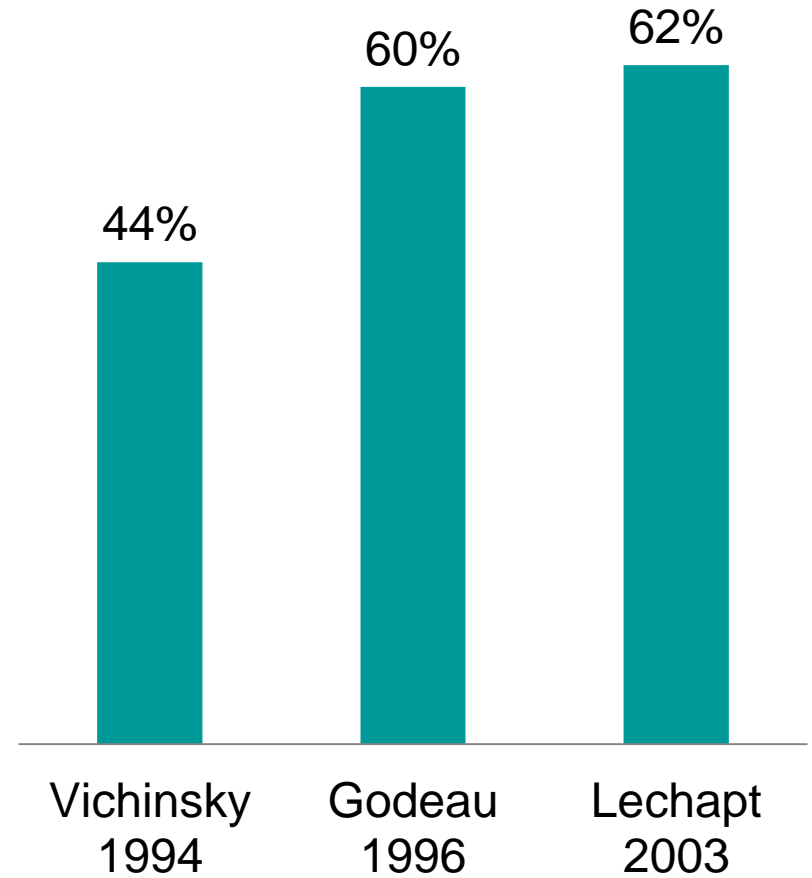
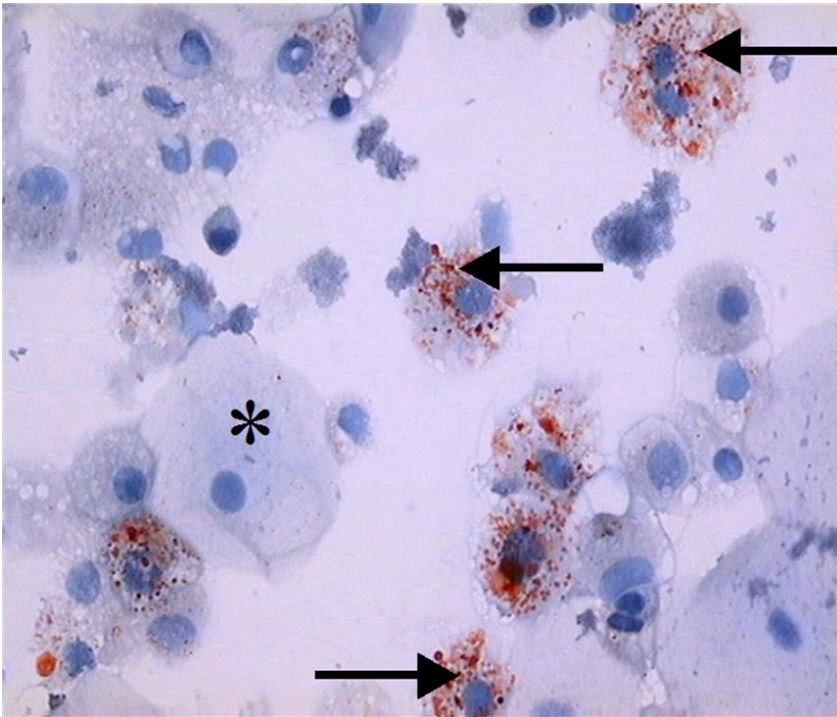


Embolie graisseuse STA



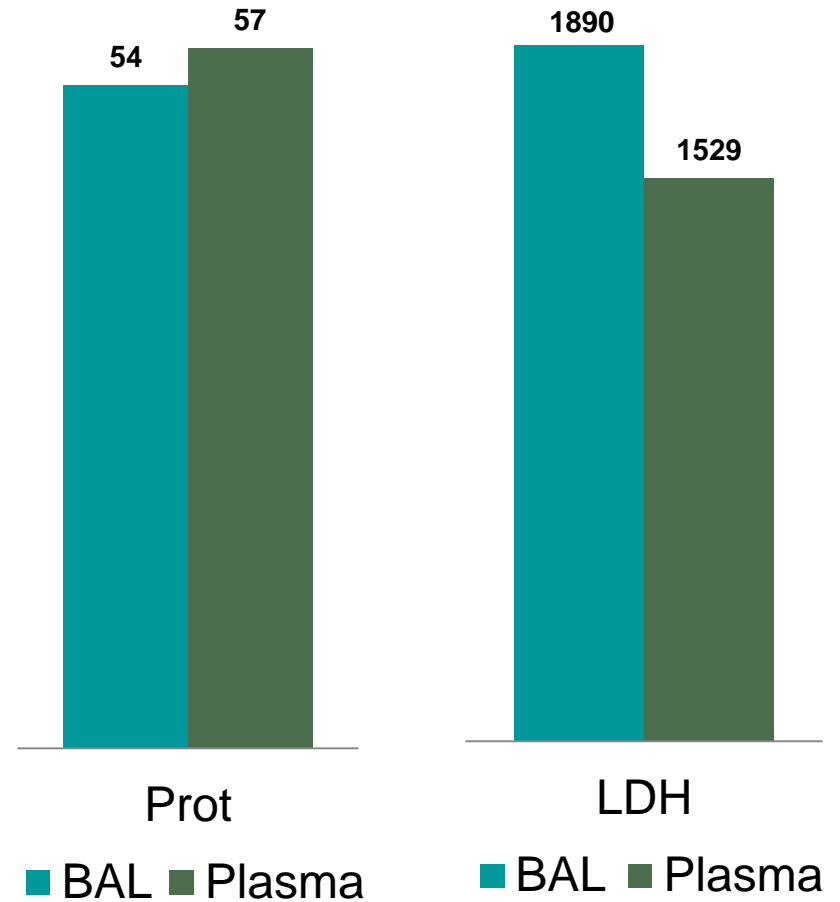
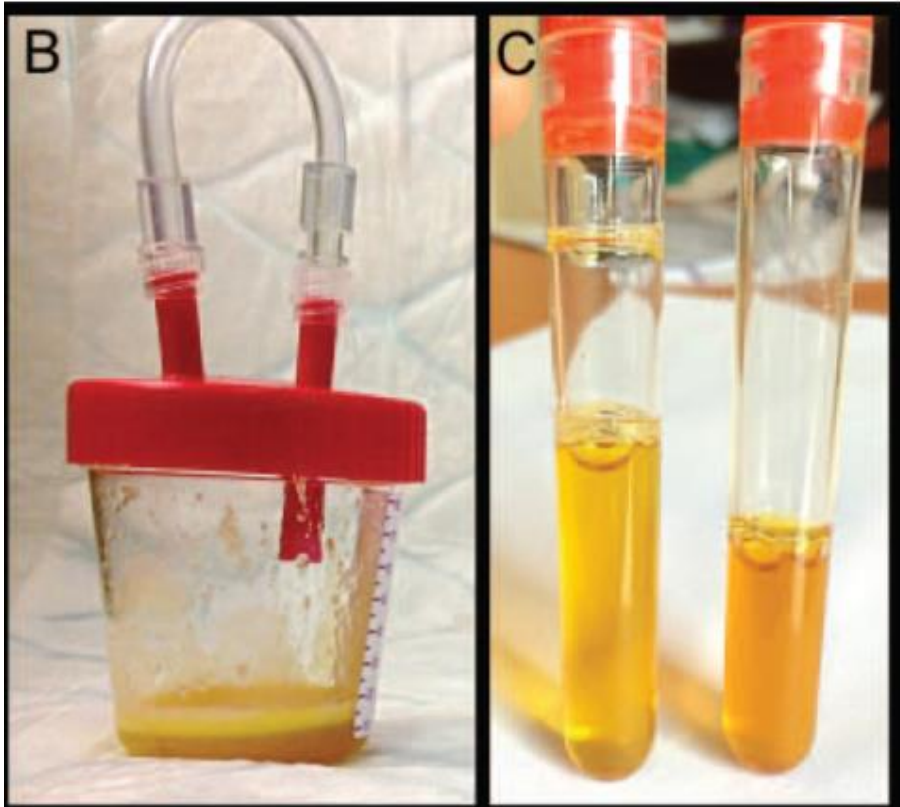
Godeau AJRCCM 1996
Maitre, Chest 2000
Lechapt, AJRCCM 2003

Embolie graisseuse STA

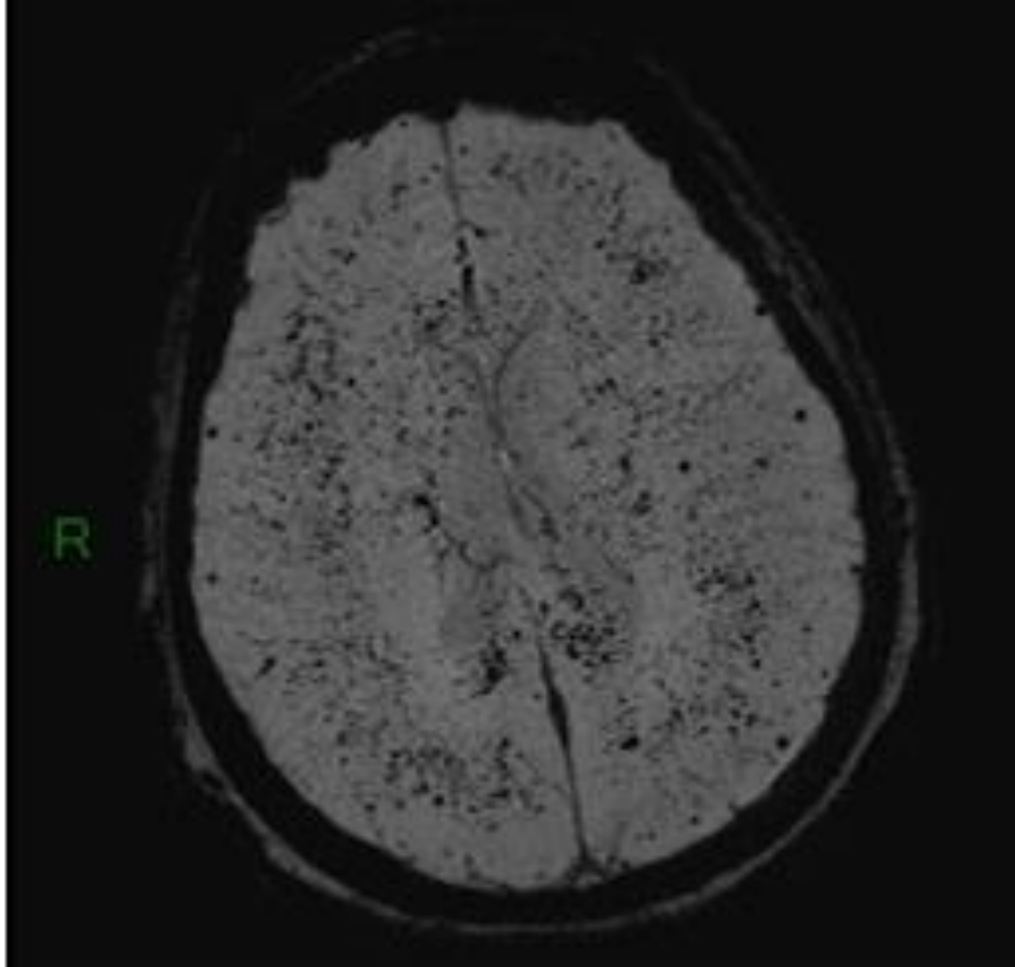


Maitre et al, Chest 2000
Lechapt, AJRCCM 2003

Expectoration jaune d'or

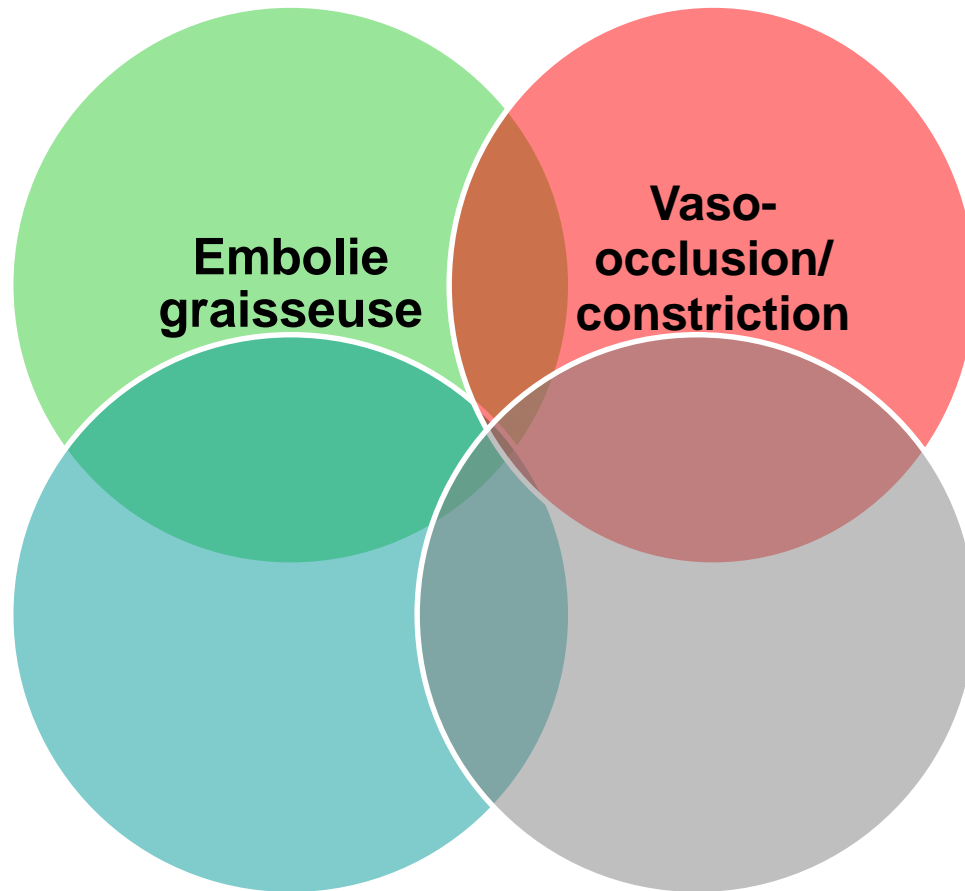


Embolie graisseuse systémique

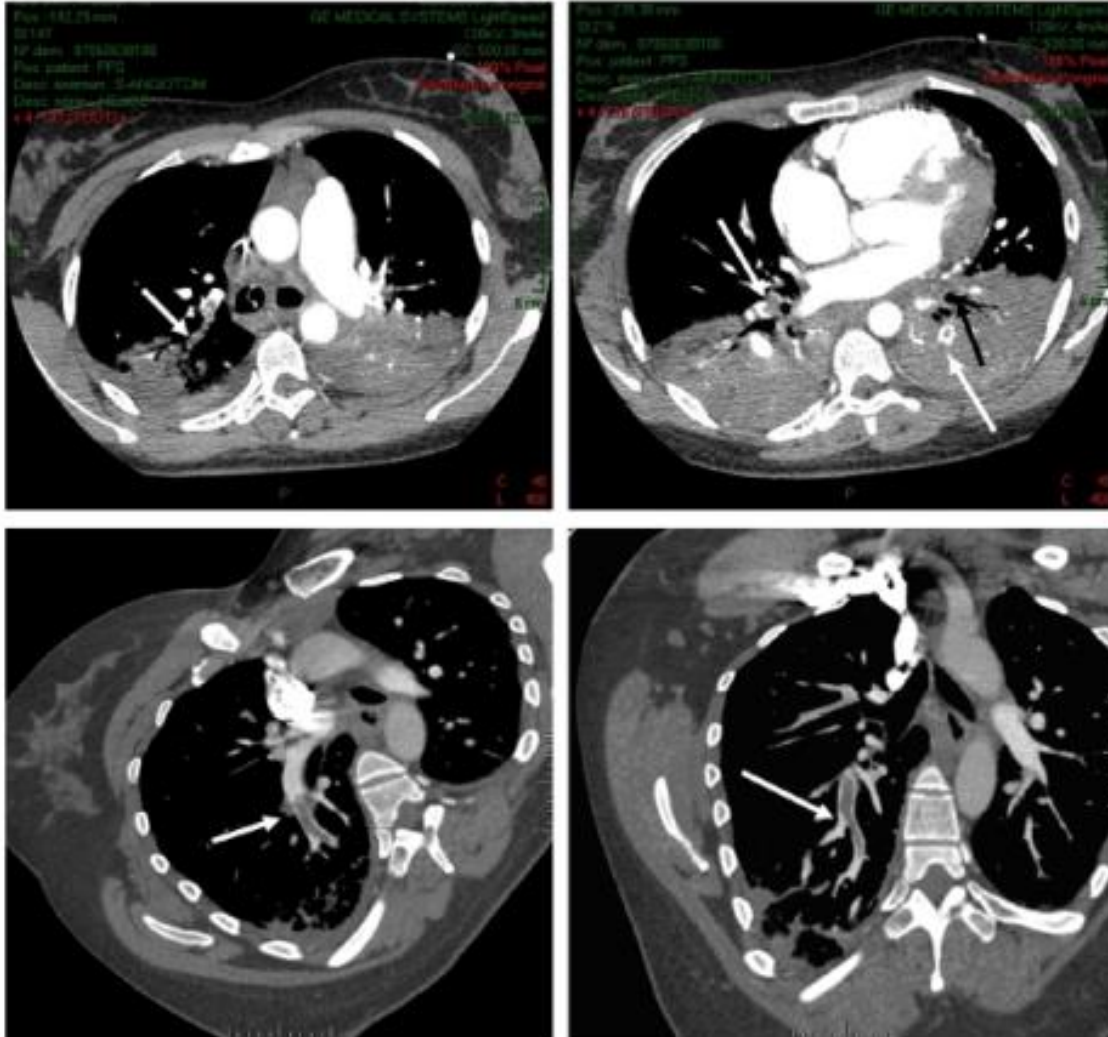


Intérêt SWI phase mapping ?

Physiopathologie STA

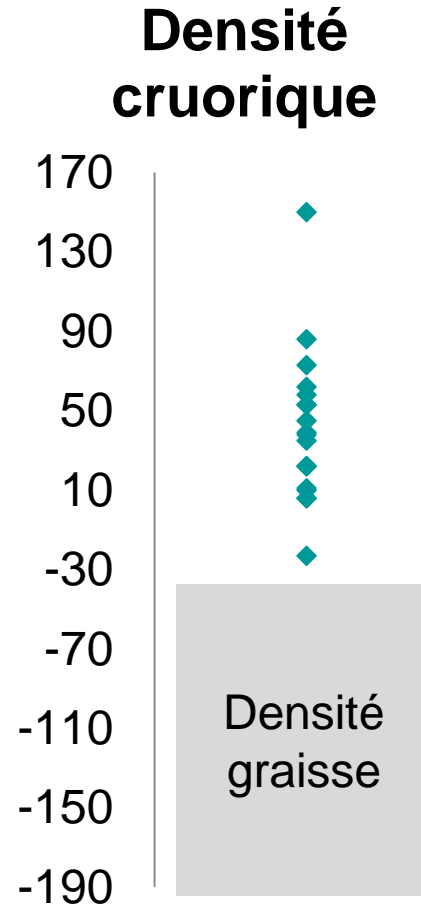


Thrombose artérielle pulmonaire

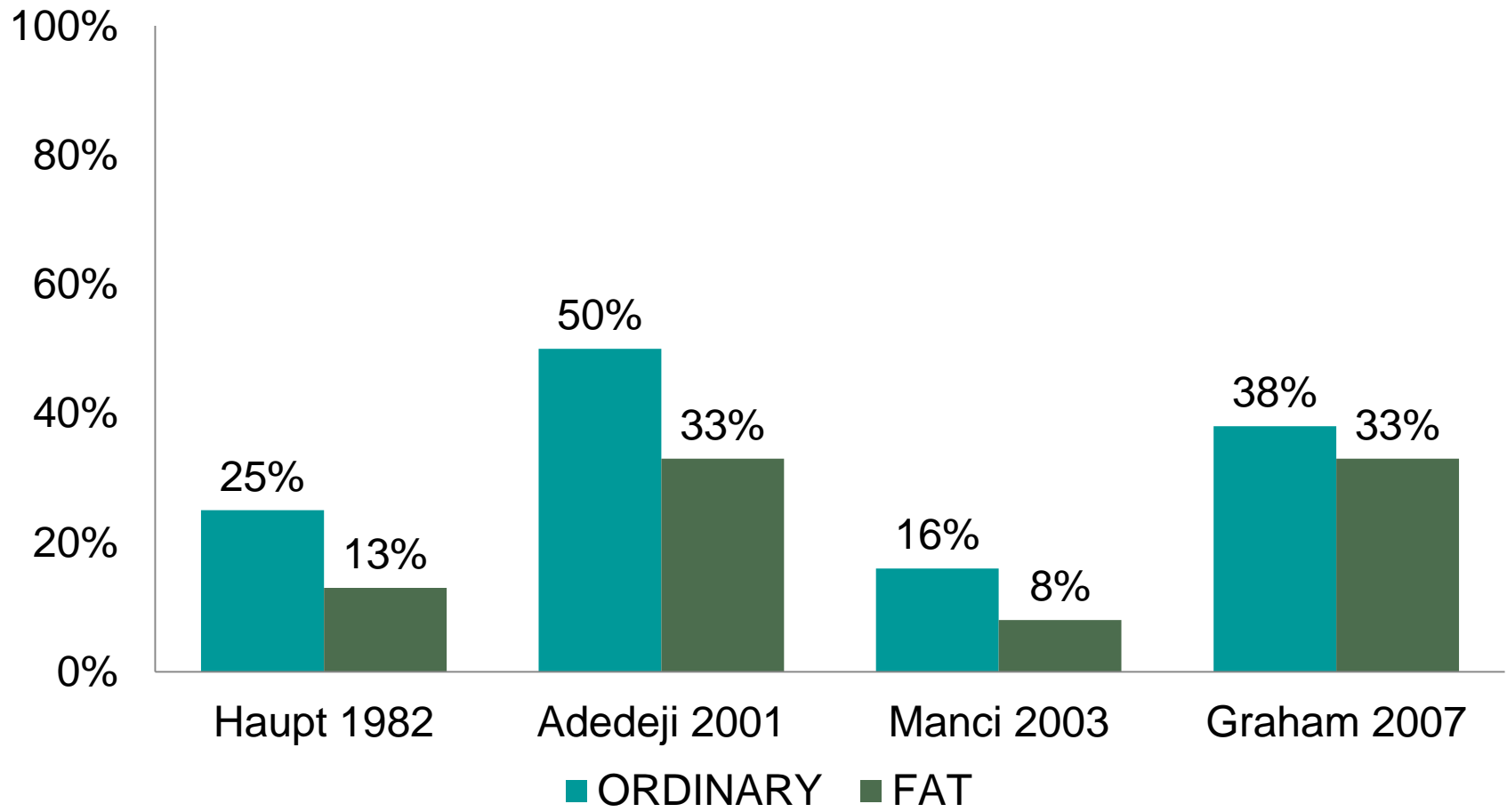


- 17% des STA

Thrombose artérielle pulmonaire non graisseuse



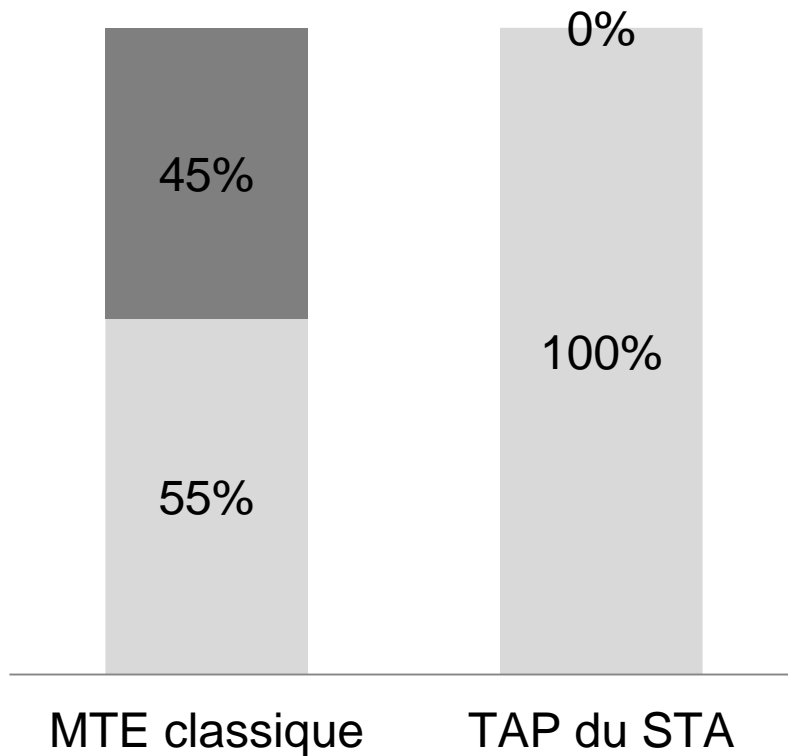
Obstruction pulmonaire à l'autopsie



MTE classique ?

Sans TVP

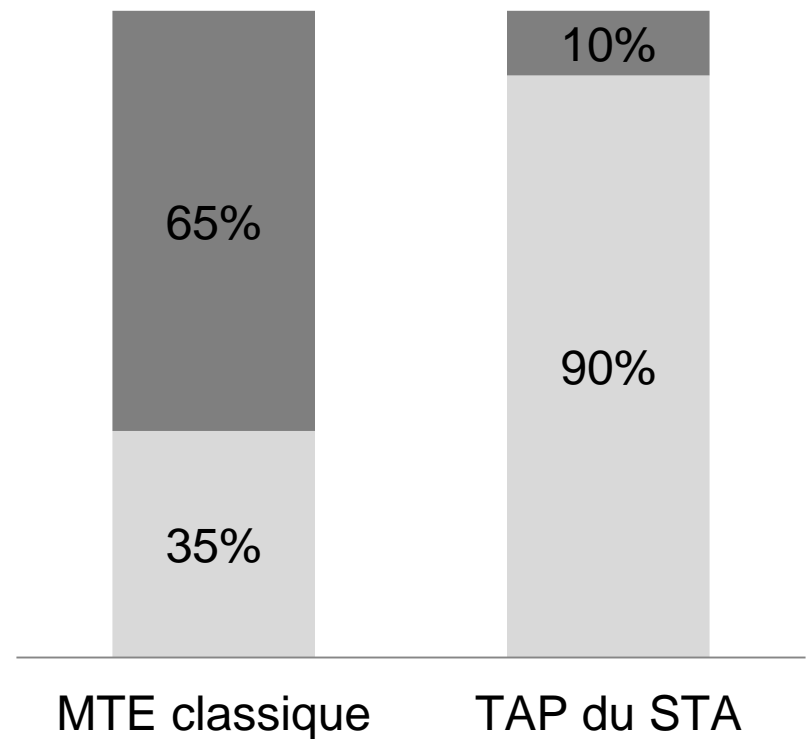
■ Absence TVP ■ Présence TVP



Girard, Chest 2005

In situ

■ SS/S ■ L/T



Righini, Lancet 2008

Score de risque de thrombose pulmonaire

FACTEURS DE RISQUE

Hb de base >82 g/L

Pas de facteur déclenchant identifié de STA

Numération plaquettaire >440 G/L

PaCO₂ <38 mmHg au diagnostic de STA

Score de risque de thrombose pulmonaire

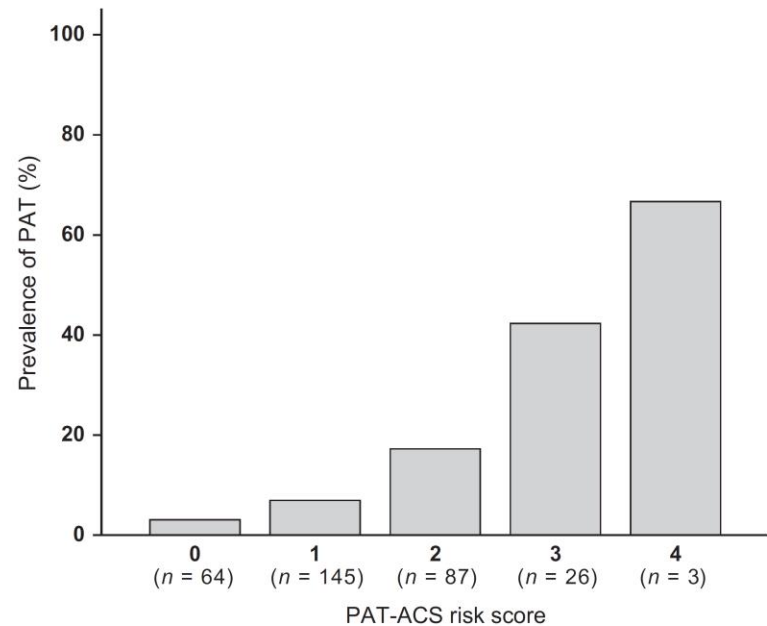
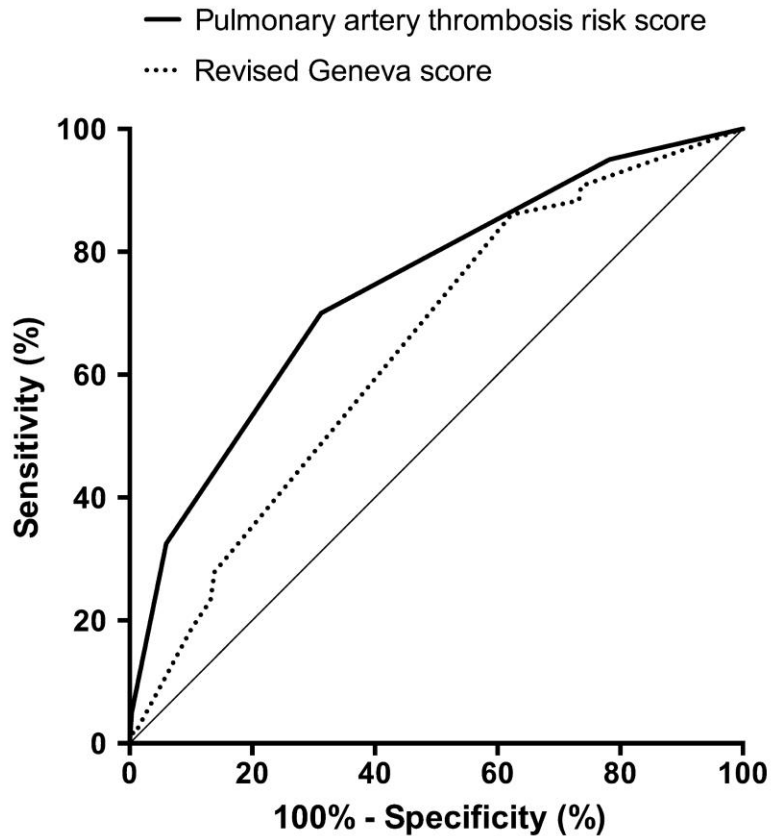
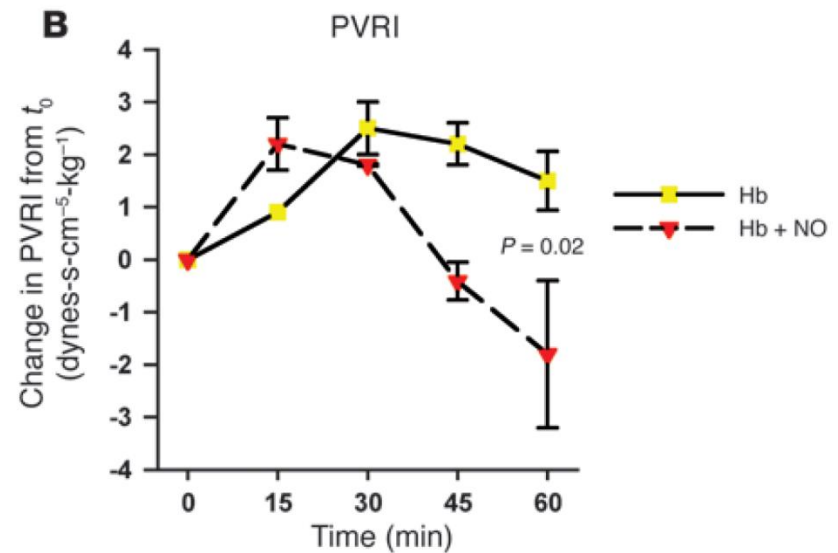
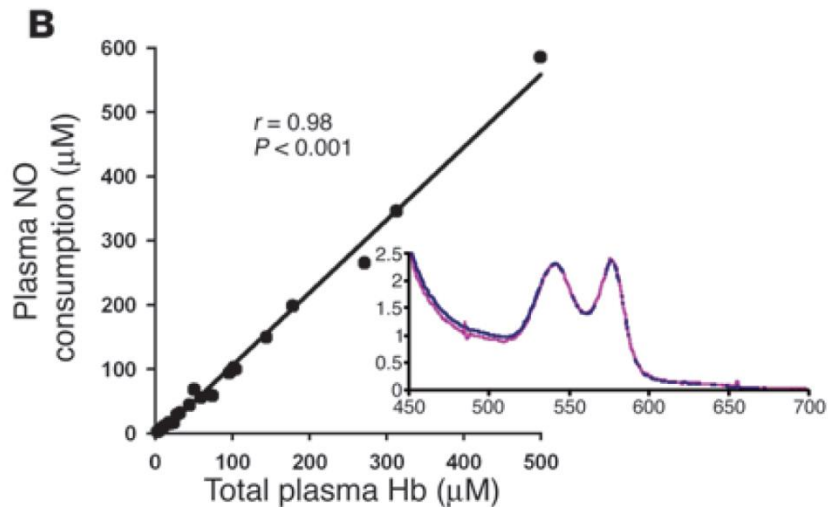


Fig 2. Prevalence of pulmonary artery thrombosis (PAT) according to the risk score for PAT during acute chest syndrome (PAT-ACS risk score).

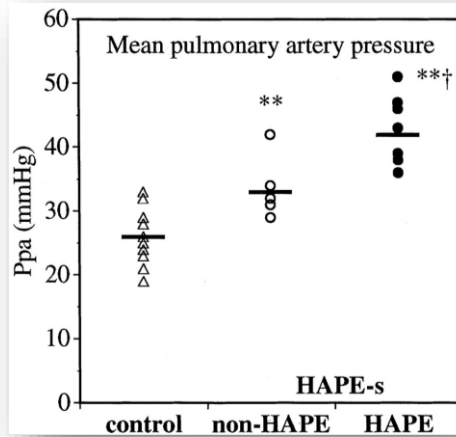
Vasoconstriction pulmonaire



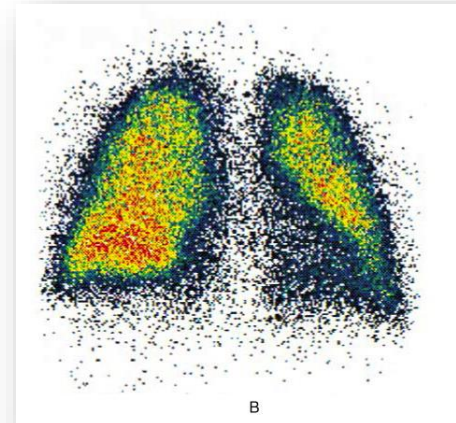
Œdème pulmonaire d'altitude

Vasoconstriction pulmonaire hypoxique

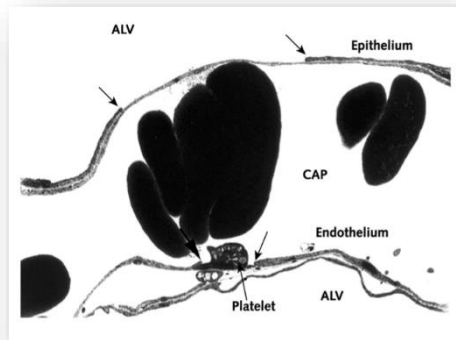
Excessive



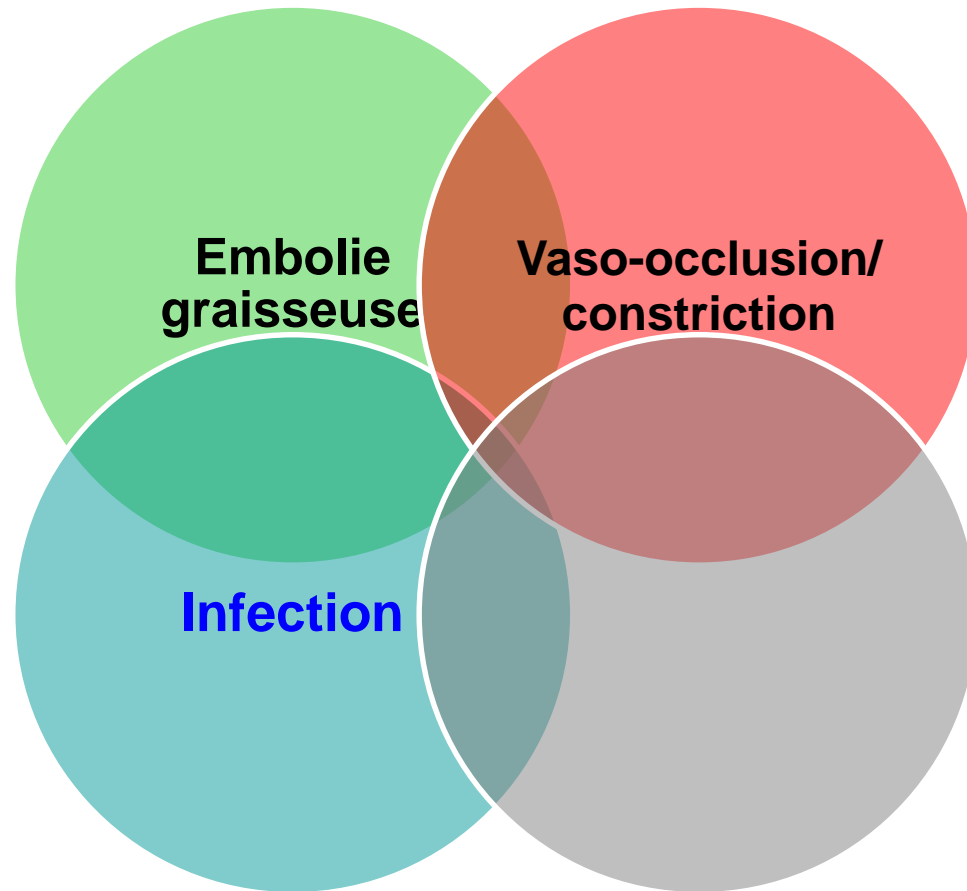
Inhomogène



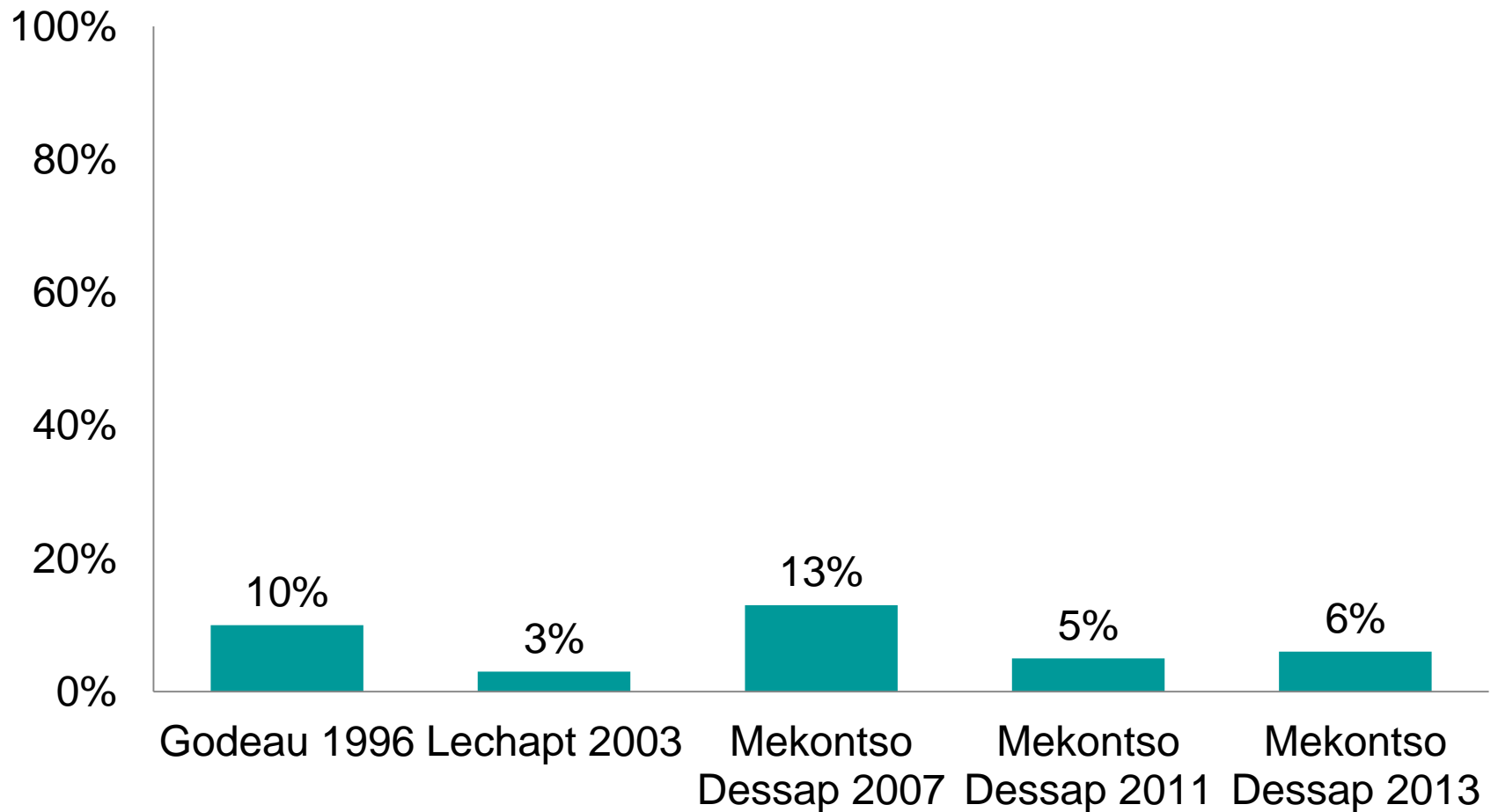
Hyper-perfusion régionale et rupture membrane alvéolo-capillaire



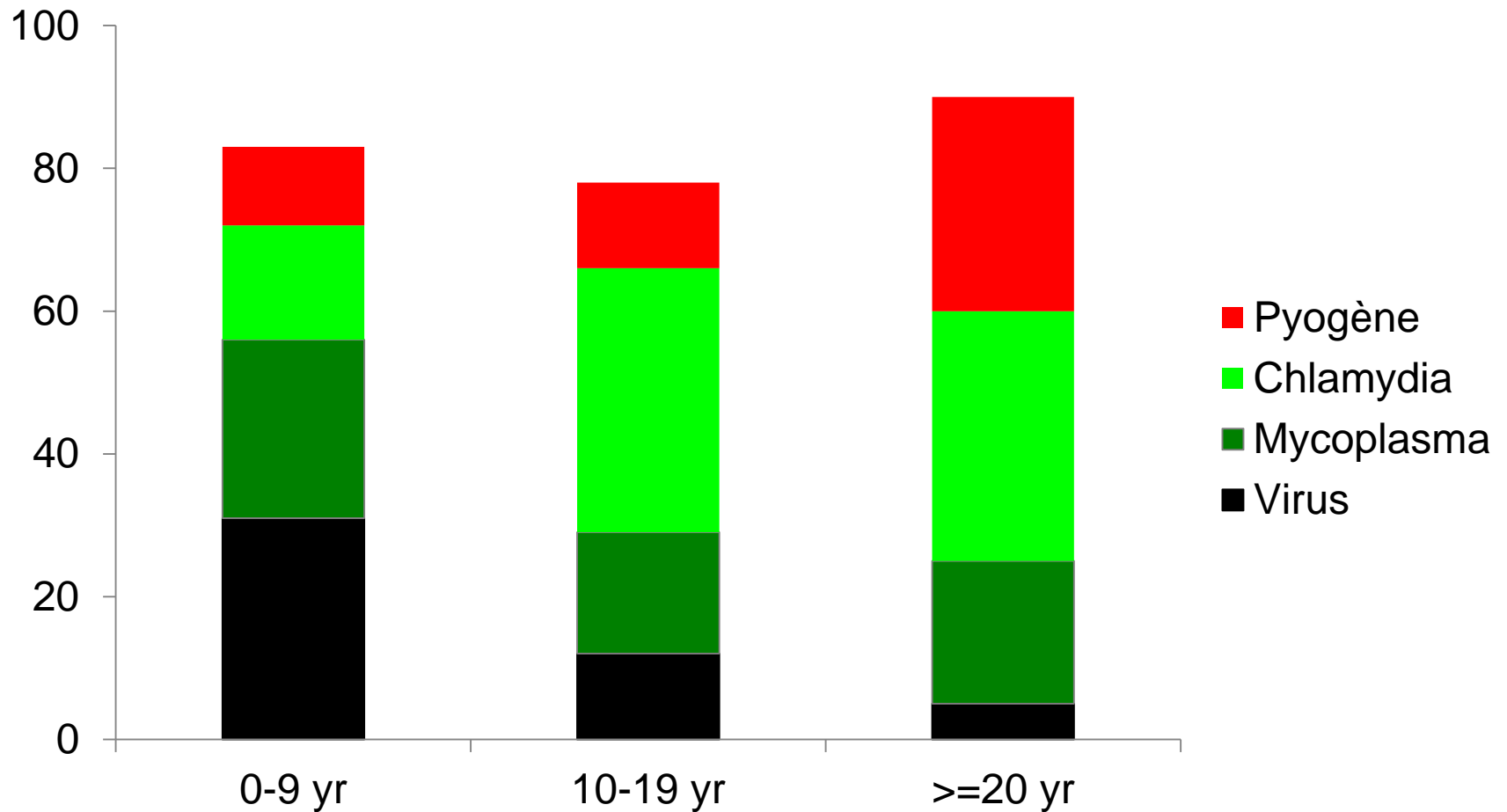
Physiopathologie STA



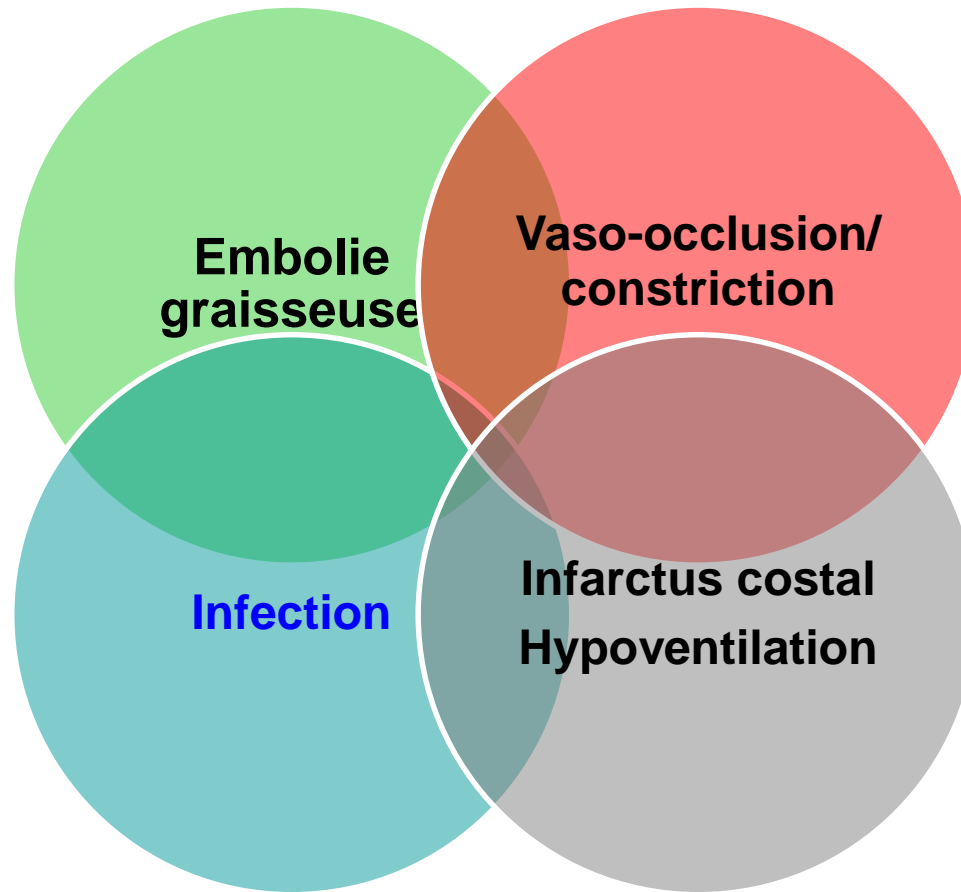
Infection et STA



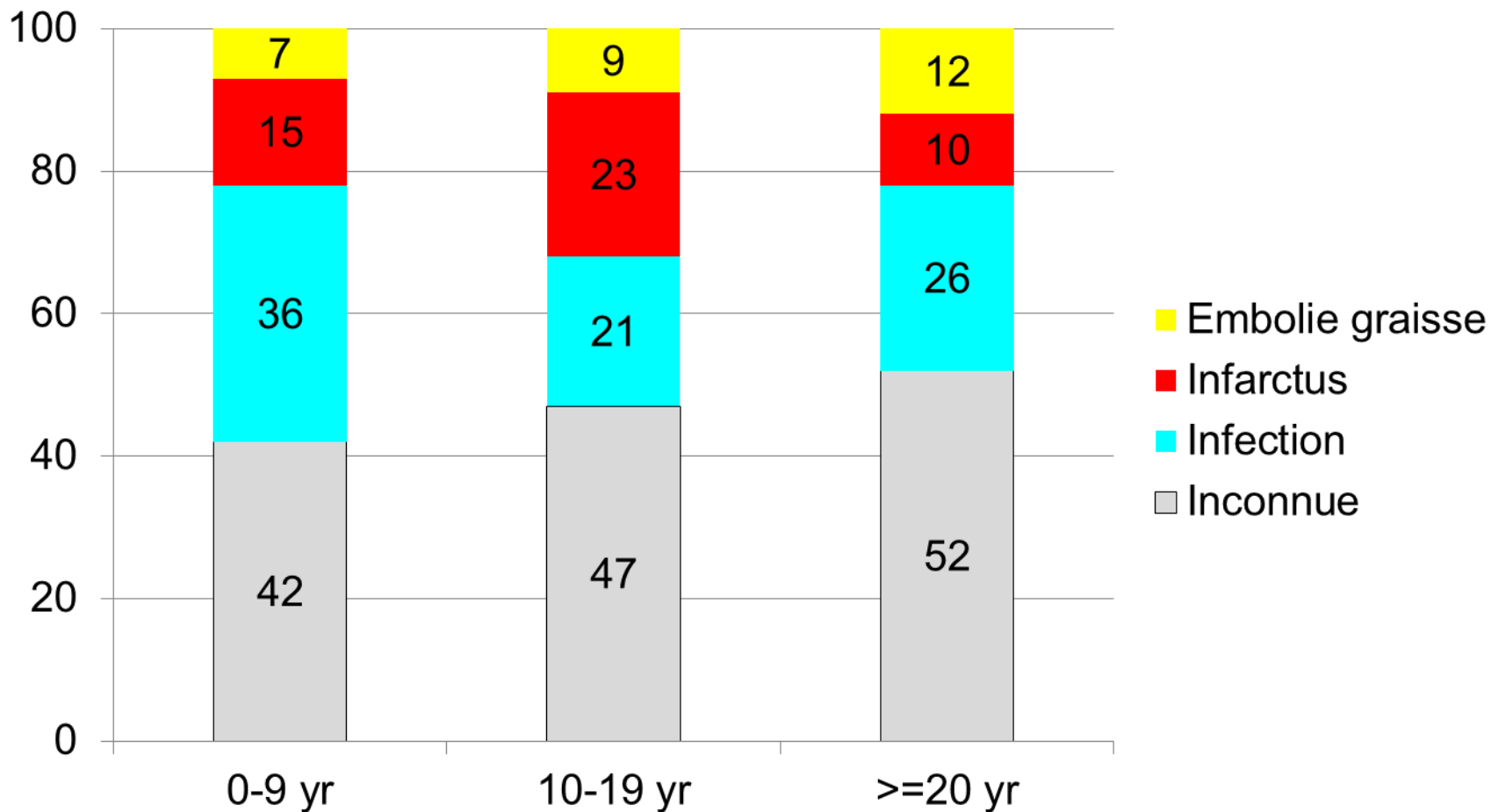
Infection et STA



Physiopathologie STA

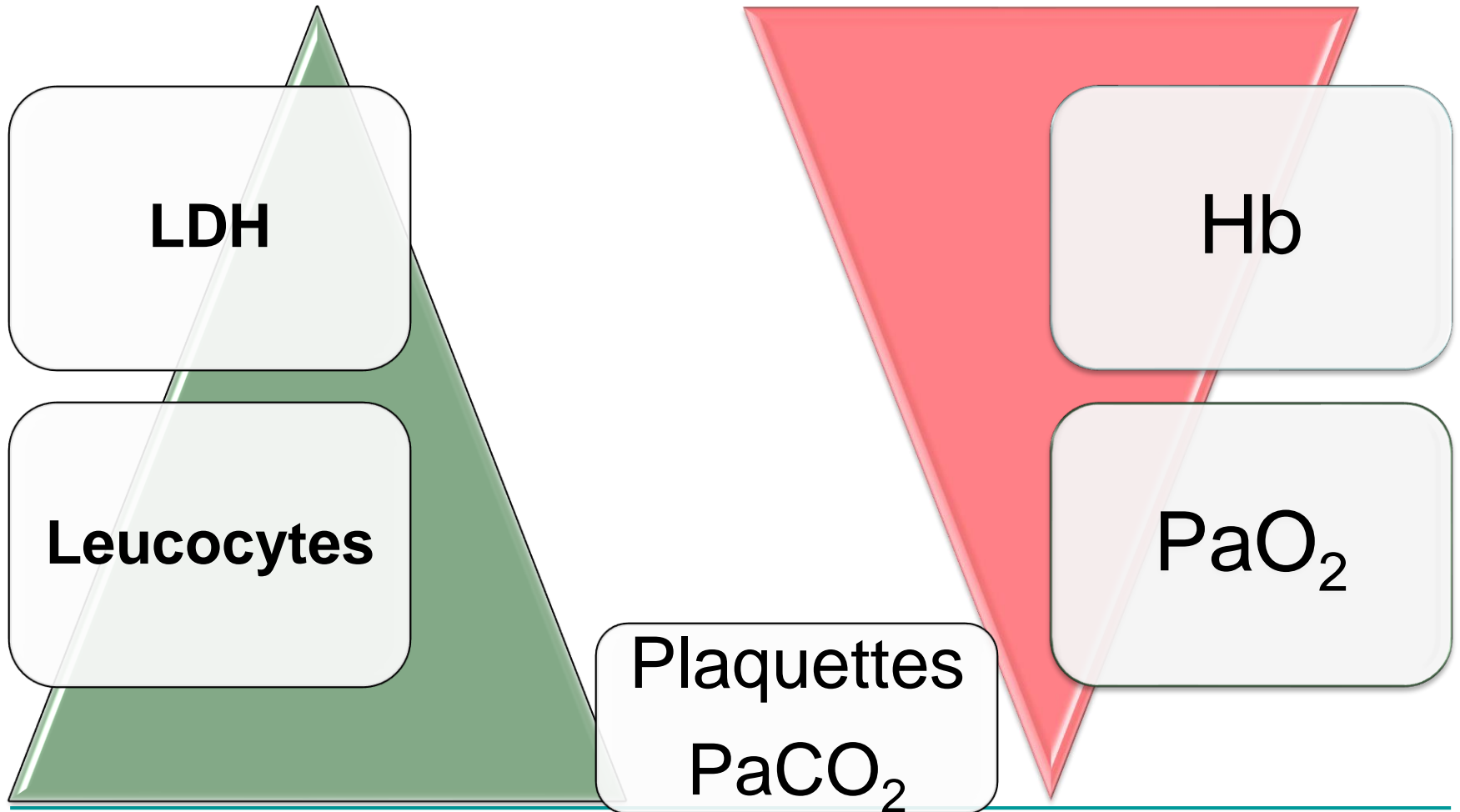


Mécanismes du STA

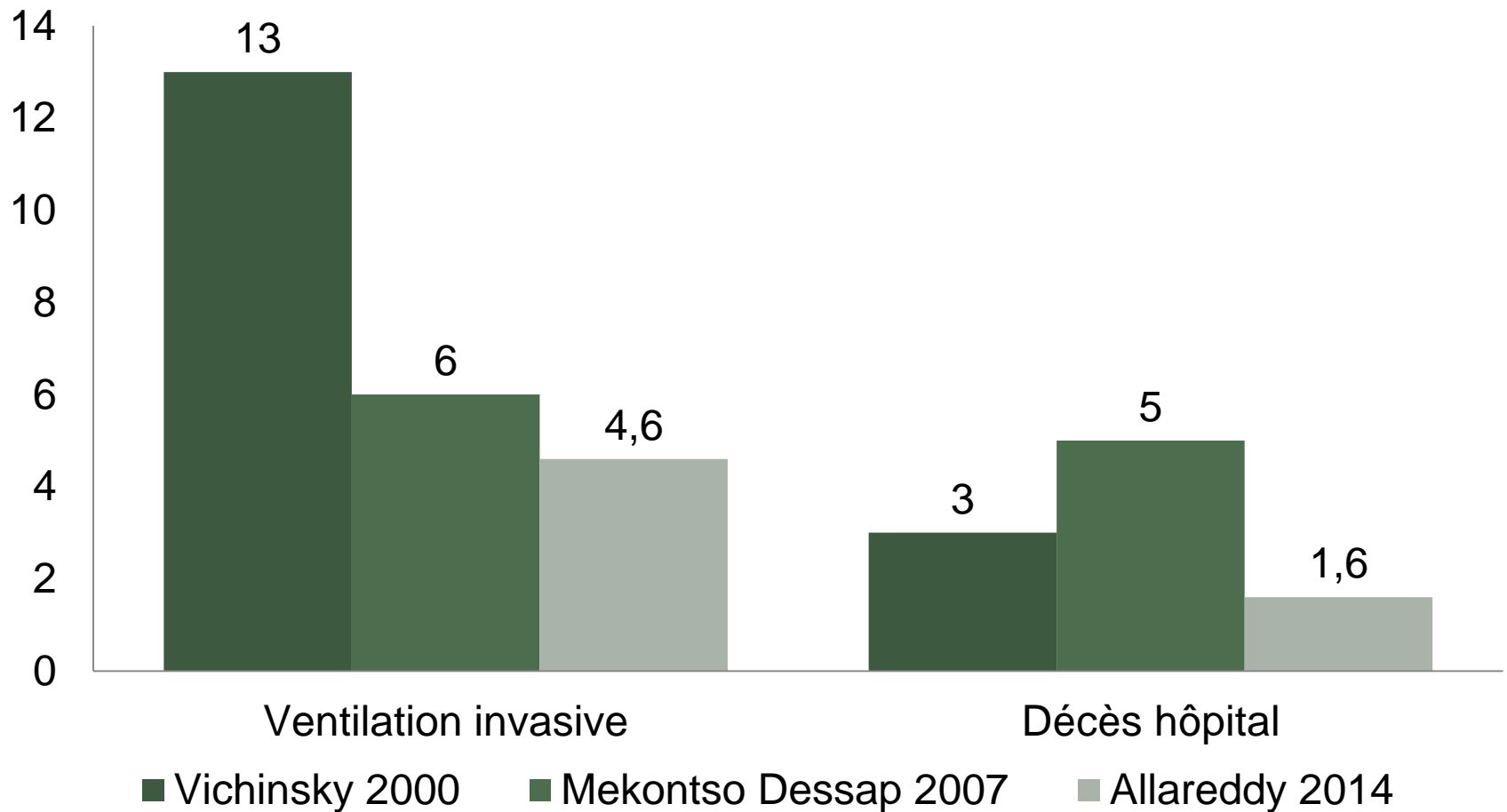


*Ni graisse ni infection
Vichinsky, NEJM 2000

STA: Biologie

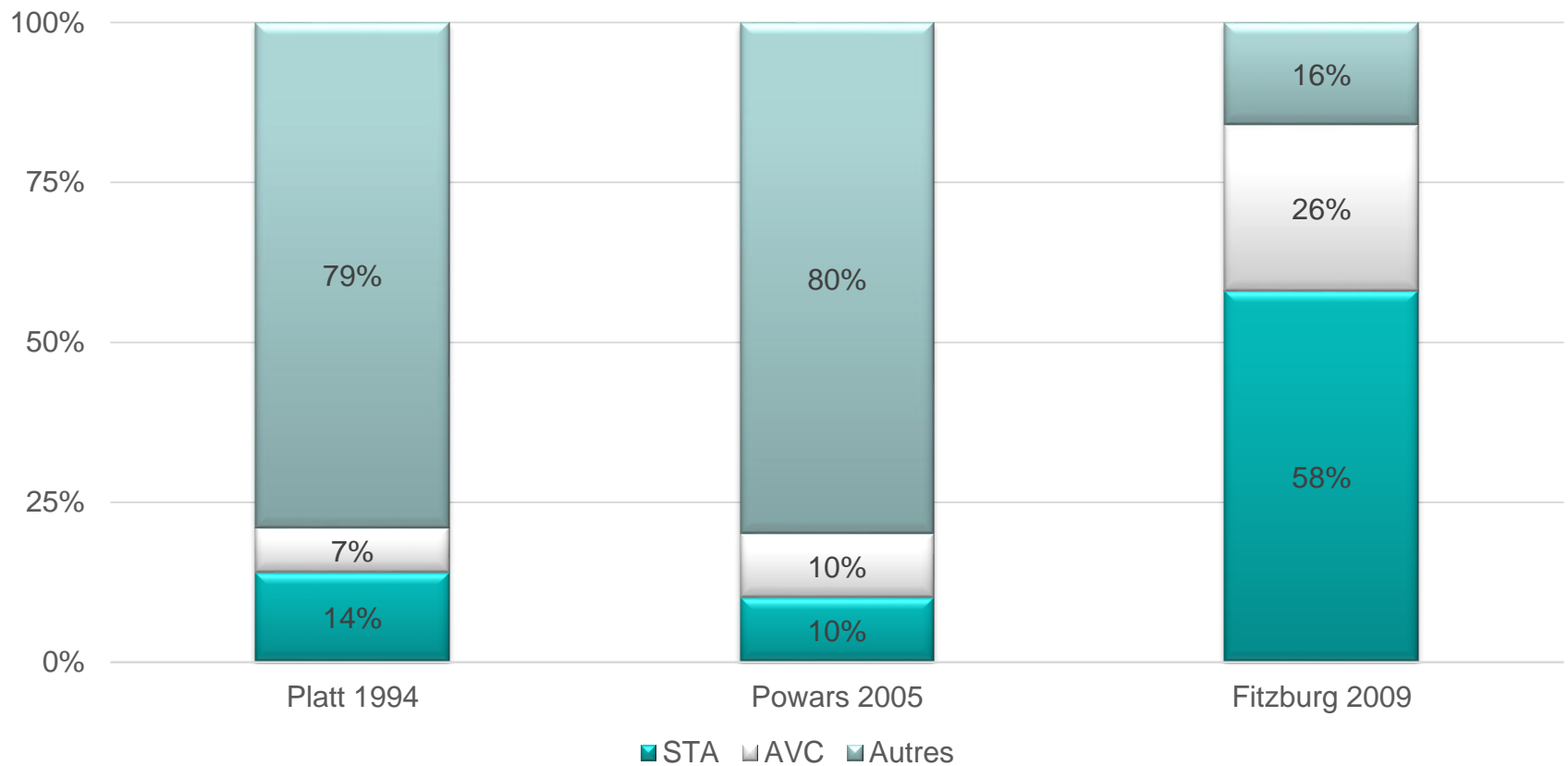


Pronostic STA



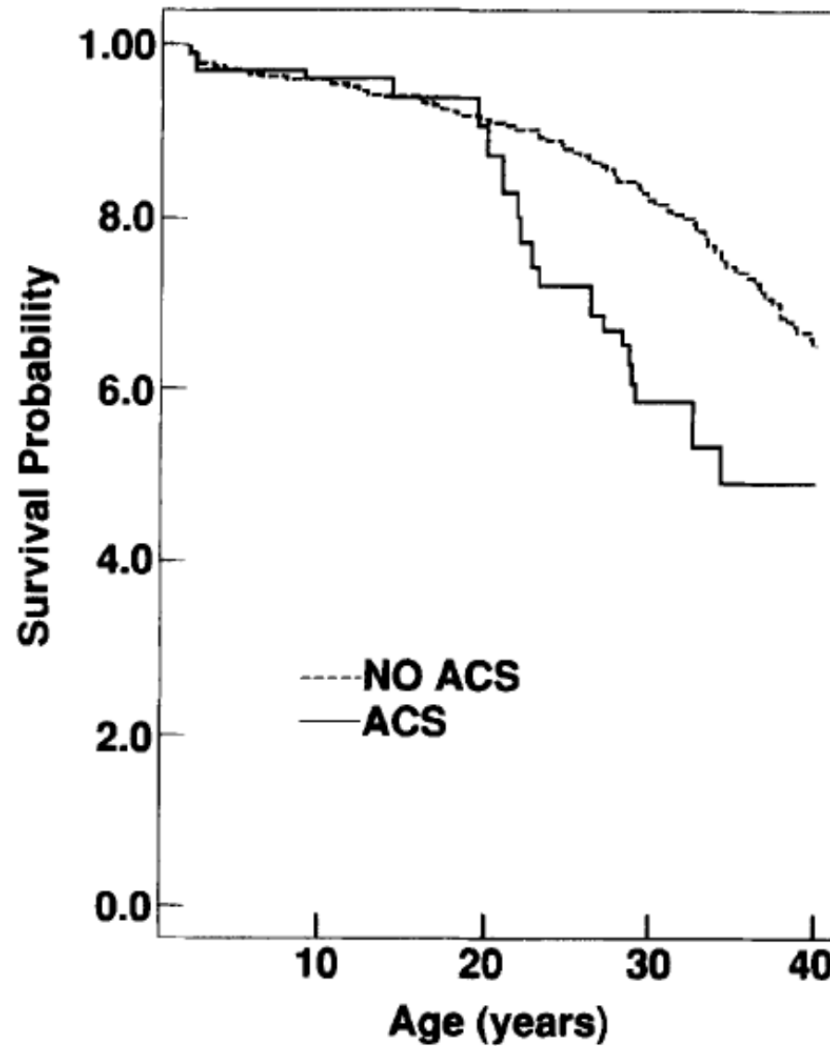
Pronostic STA

Décès hôpital

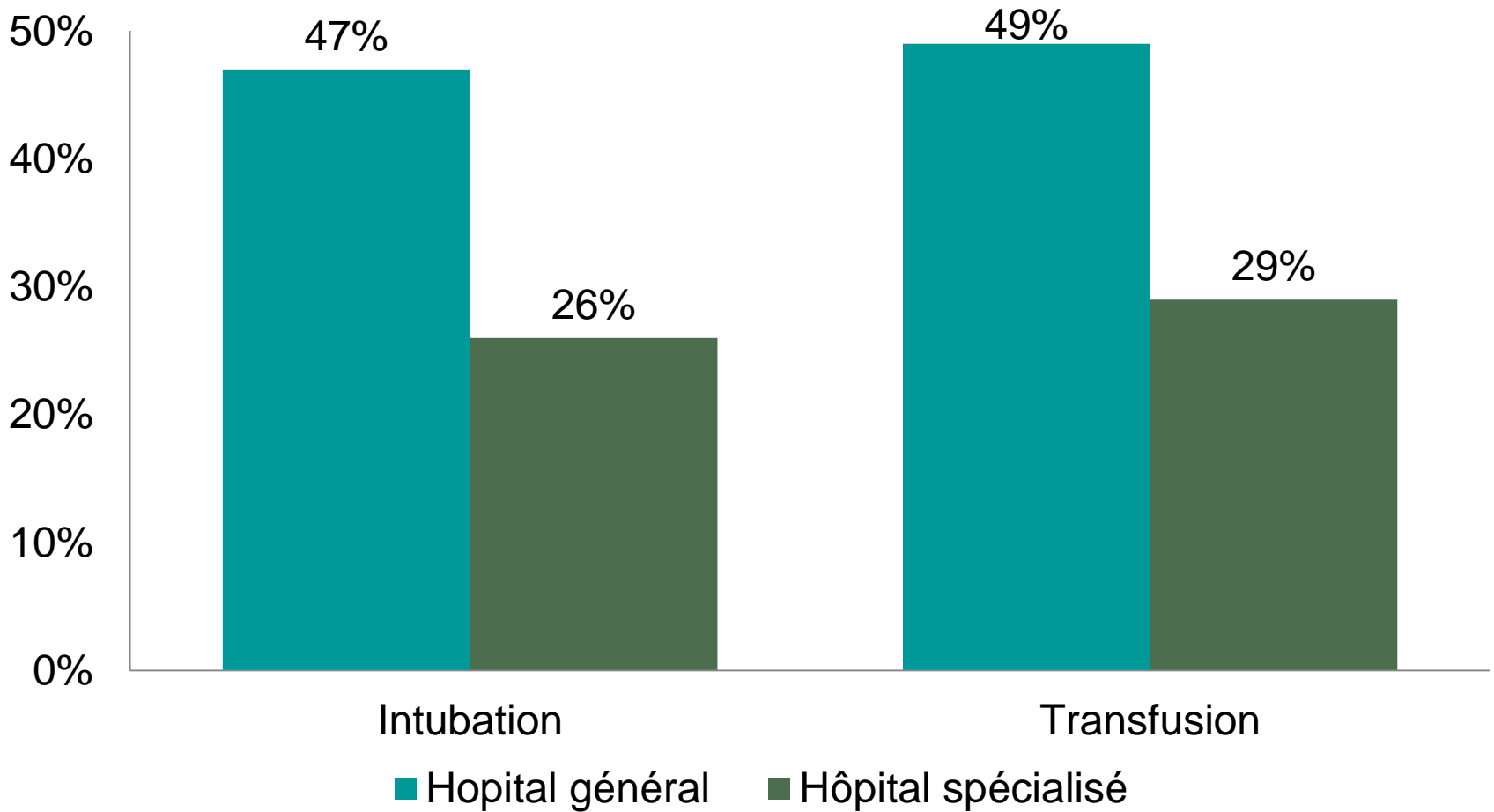


Castro, Blood 1994

Pronostic STA



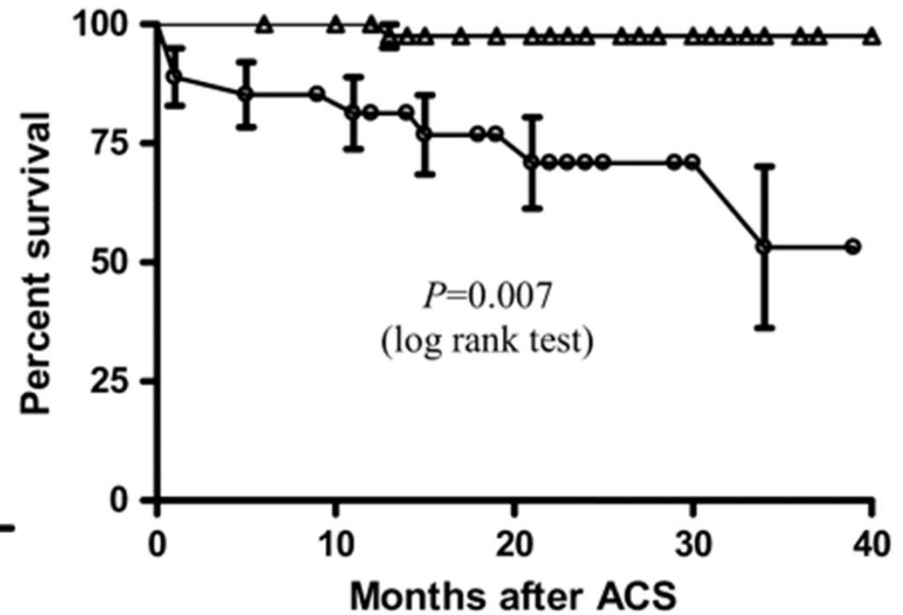
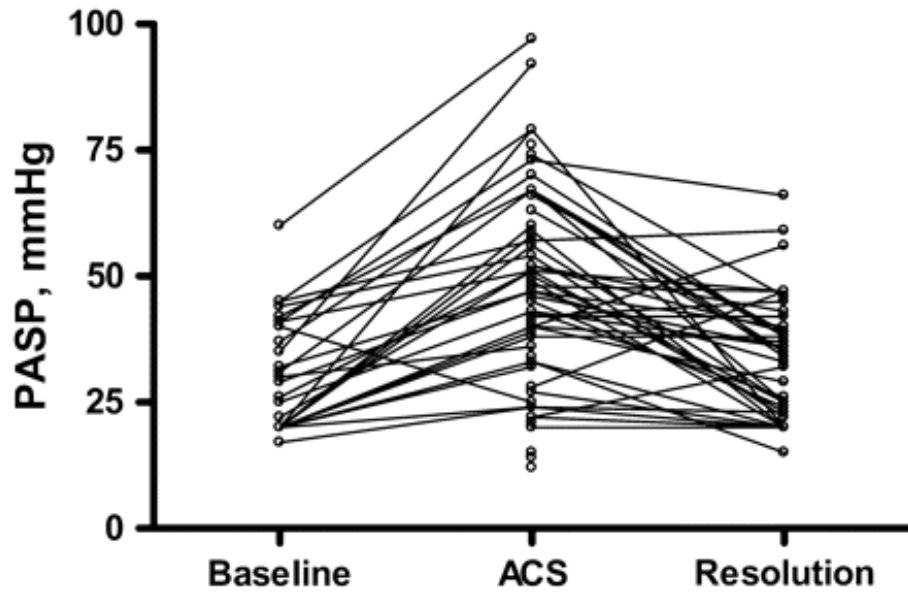
Effet centre



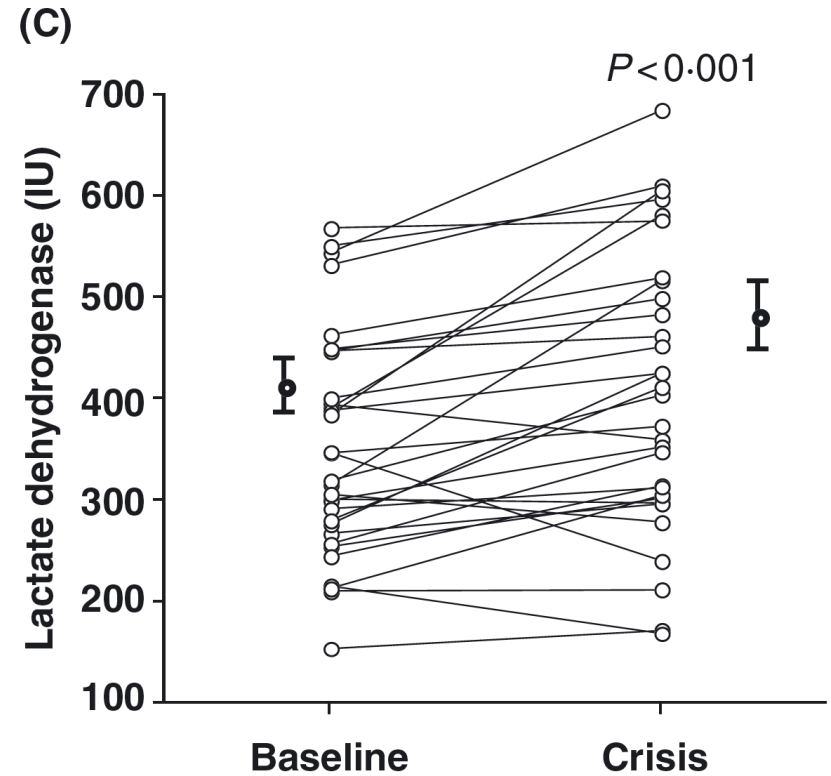
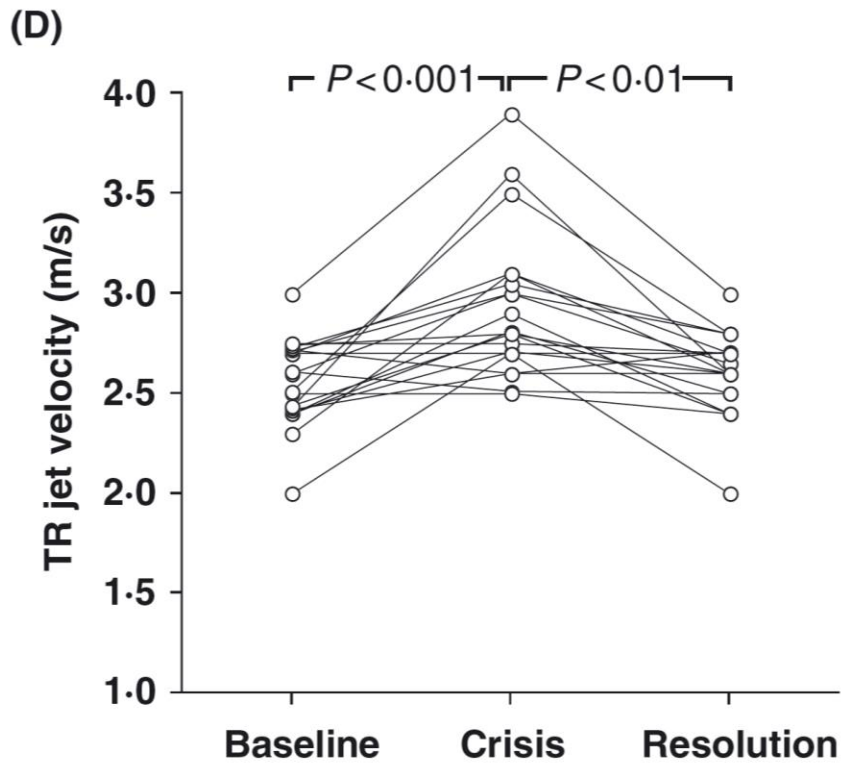
Facteurs de mauvais pronostic

	PERCENT REQUIRING MECHANICAL VENTILATION	ODDS RATIO (95% CI)§	P VALUE
Respiratory failure‡			
History of cardiac disease			
No	12	1.0	
Yes	44	6.7 (2.1–22.3)	0.002
No. of lobes involved on radiographic examination			
0 to 1	3	1.0	
2 to 3	11	2.2 (1.0–4.6)	0.04
≥4	54	9.0 (2.5–32.7)	<0.001
Platelet count at diagnosis			
0 to 199,000/mm ³	23	1.0	
200,000 to 399,000/mm ³	11	0.9 (0.37–2.1)	0.75
≥400,000/mm ³	8	0.3 (0.10–0.96)	0.04

HTP aigue du STA



HTP aigue de la CVO



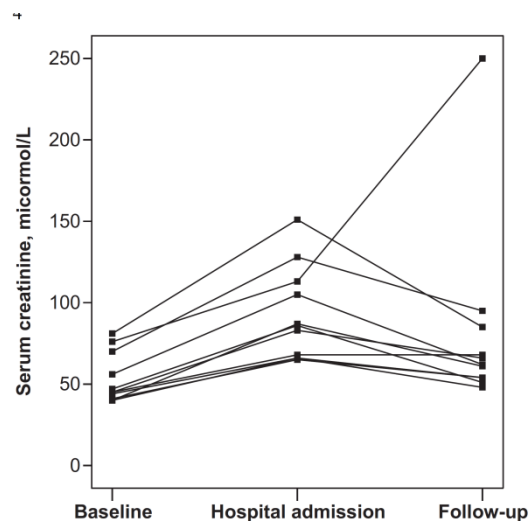


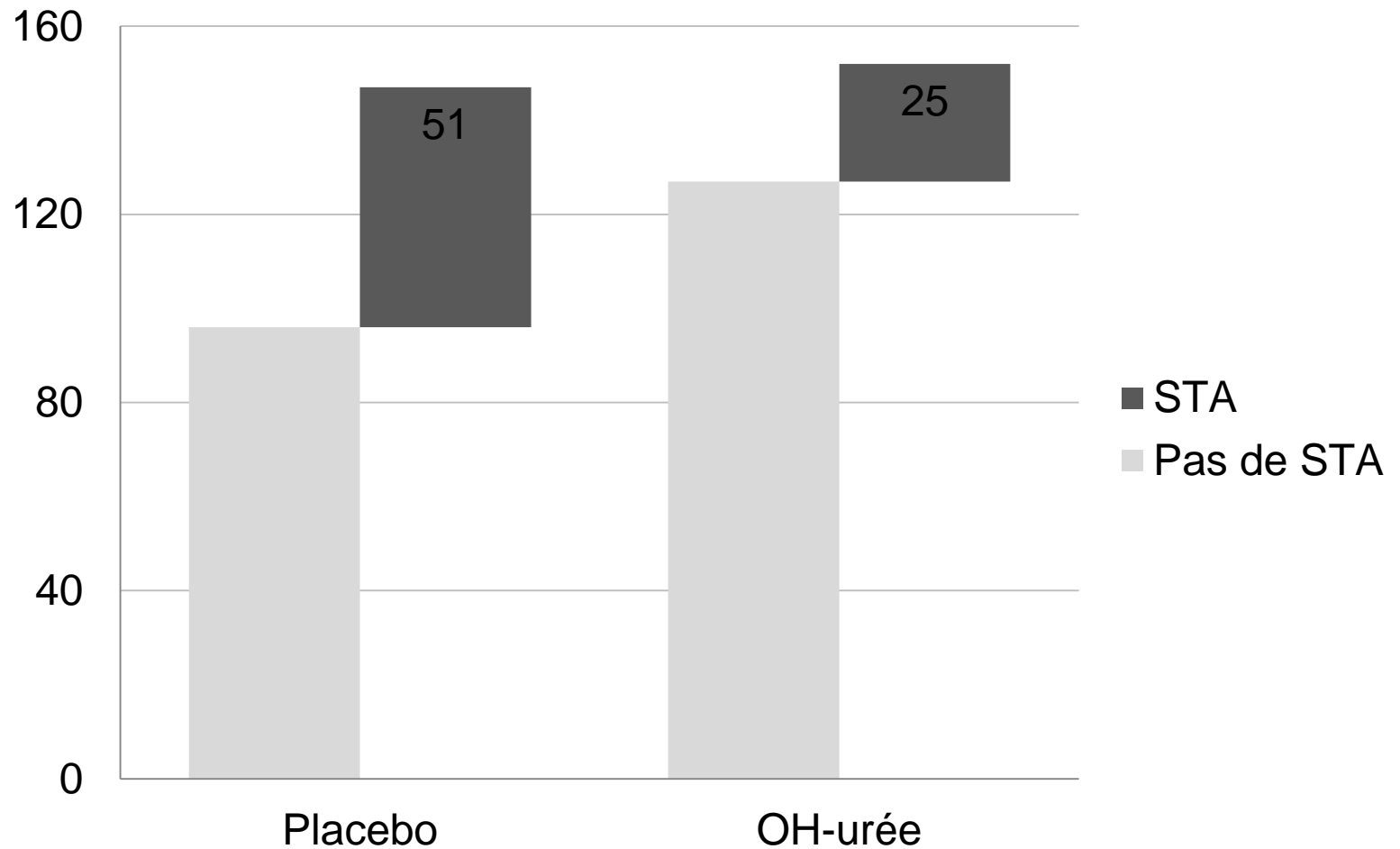
Fig. 1. Serum creatinine values at baseline, at hospital admission and at follow-up in patients with AKI during vaso-occlusive complications ($n = 11$ patients).

Table 5. Echocardiography data of patients with severe ACS at ICU admission in relation to whether they experienced AKI ($n = 65$ episodes)

Parameter	AKI during severe ACS		P-value
	No ($n = 59$)	Yes ($n = 6$)	
LVEF, %	55 (50–60)	55 (46–65)	0.96
E/A ratio	1.38 (1.10–1.74)	1.40 (0.85–2.49)	0.79
IVC collapse, %	16 (3–38)	0 (0–6)	0.02
Tricuspid regurgitant jet velocity, m/s	2.8 (1.8–3.2)	3.6 (3.1–3.9)	0.01
Systolic pulmonary artery pressure, mmHg	46 (28–54)	67 (54–74)	0.01
Cardiac index, L/min/m ²	3.5 (2.8–4.4)	3.5 (2.6–4.0)	0.73
Stroke index, mL/m ²	38 (33–43)	38 (23–45)	0.70
Cor pulmonale, ^a n (%)	5 (8.5%)	4 (66.7%)	<0.01

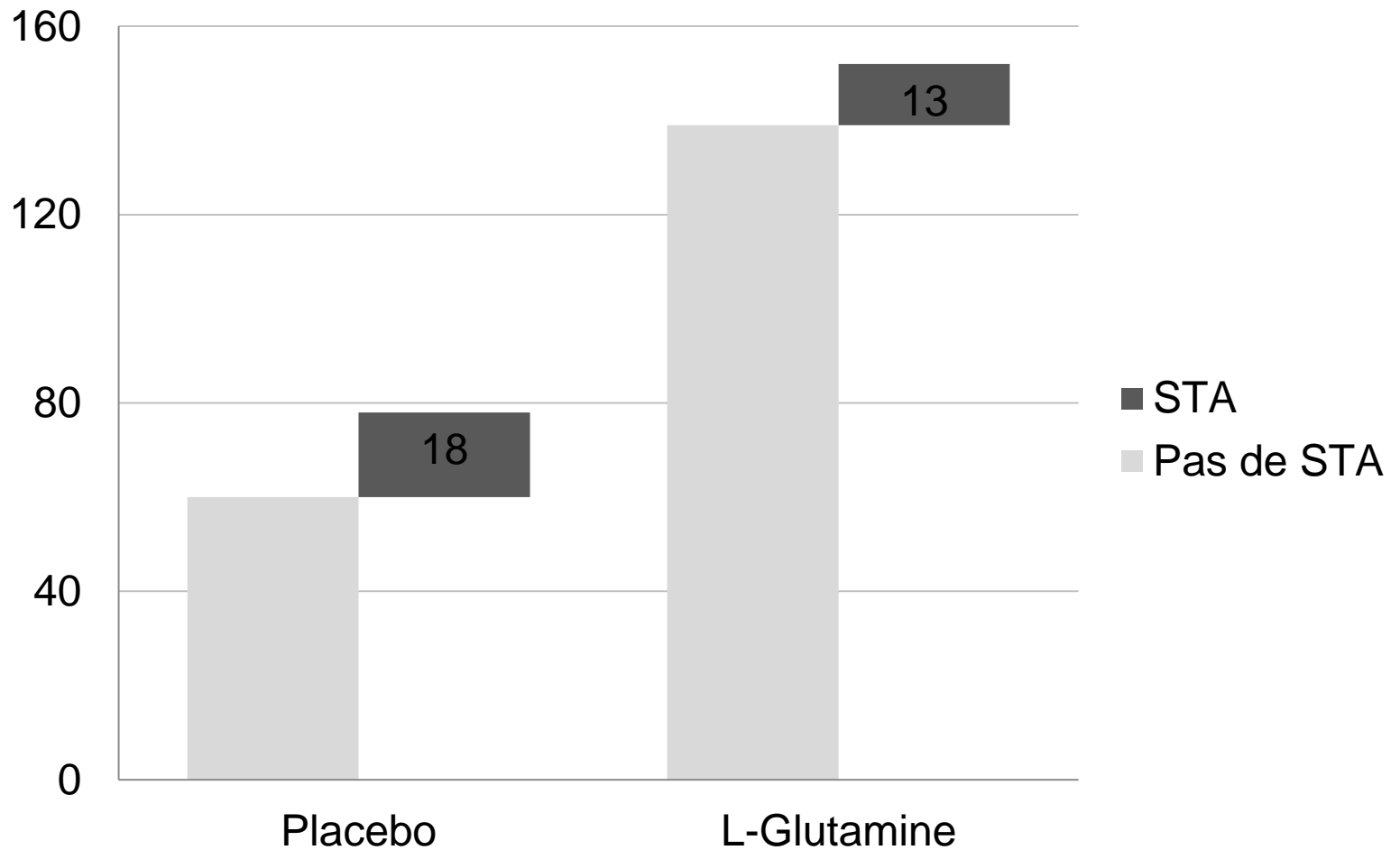
Prévention STA

OH-urée



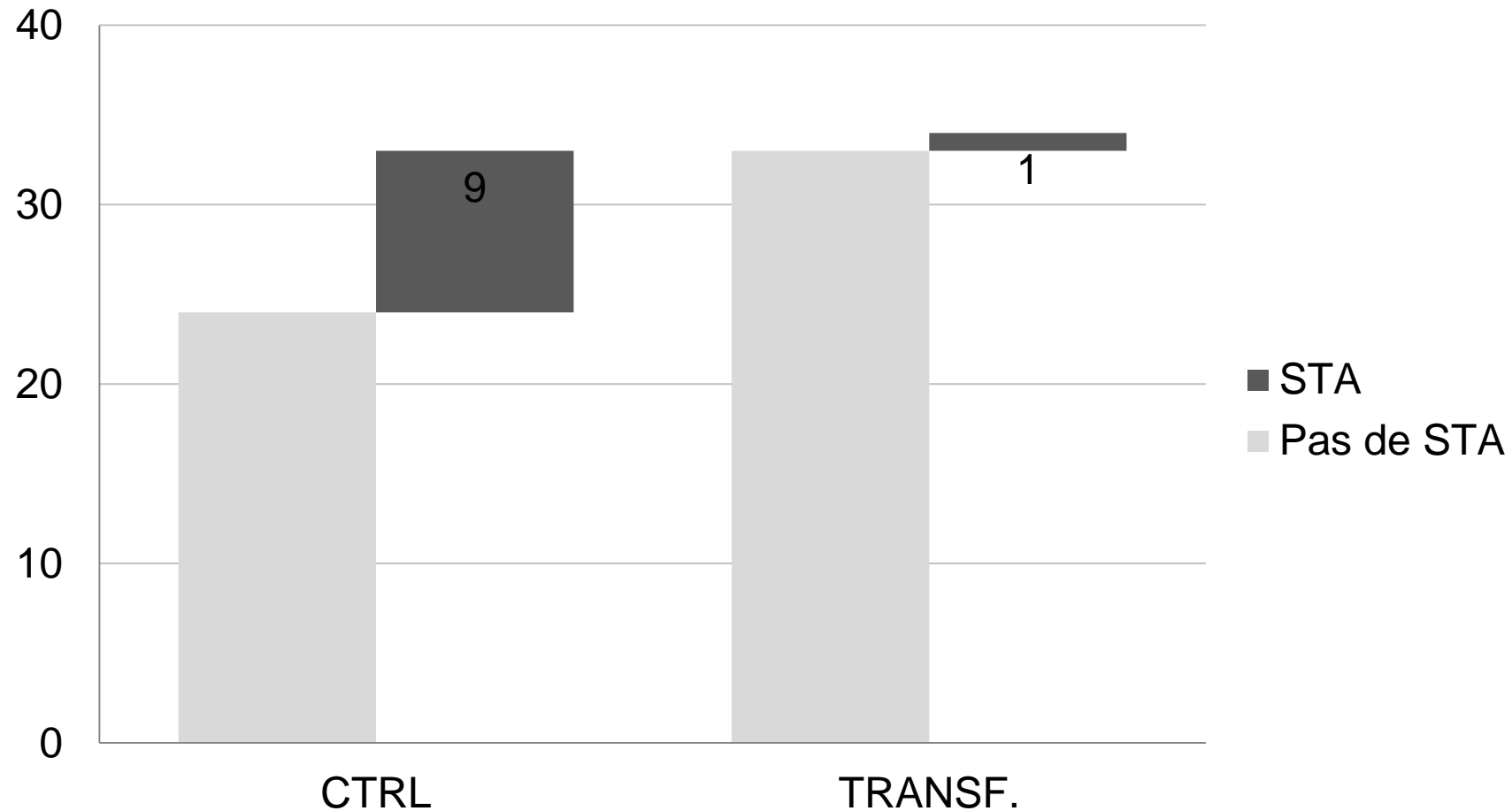
Prévention STA

L-Glutamine



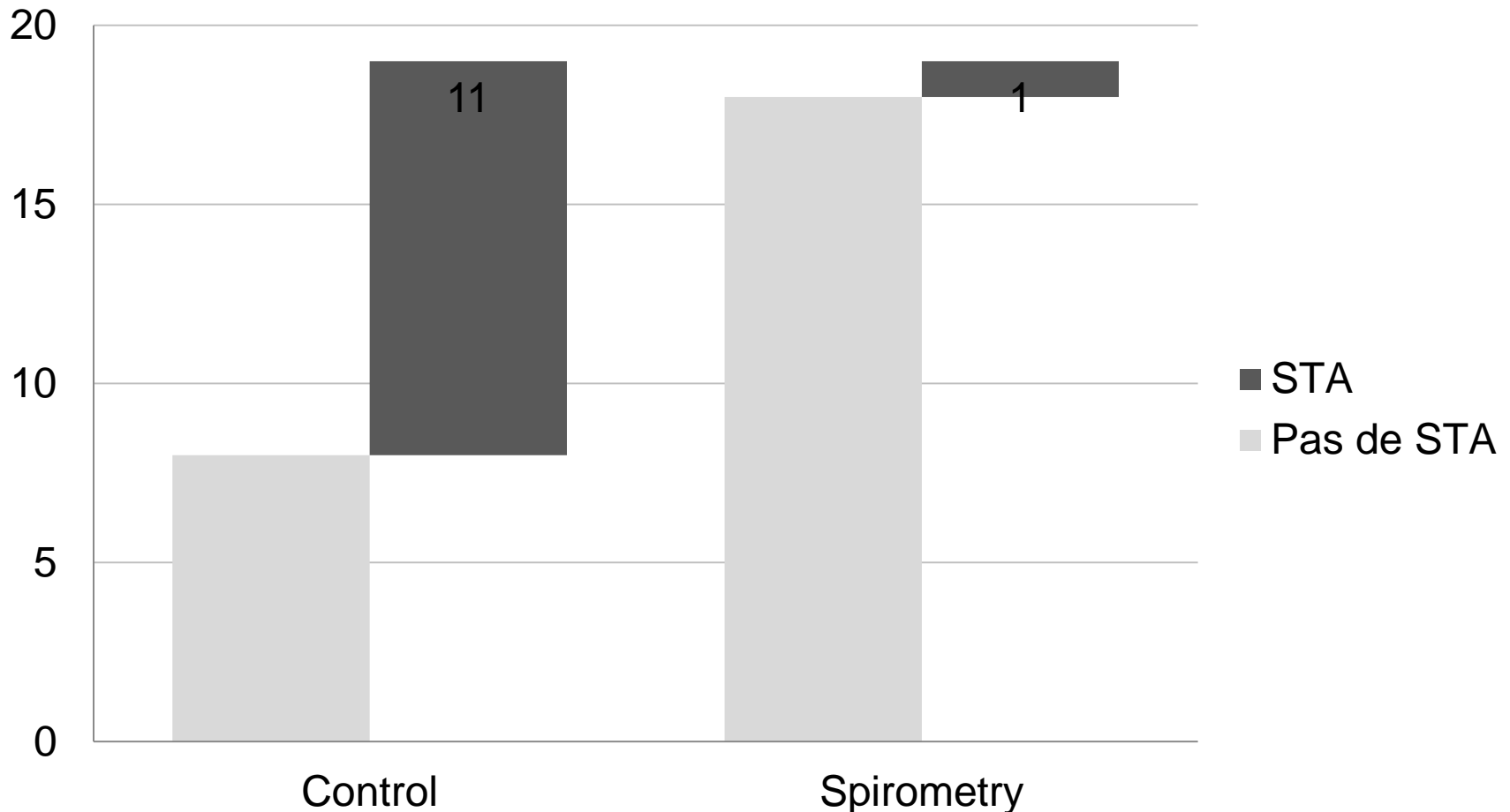
Prévention STA

Transfusion pré-opératoire



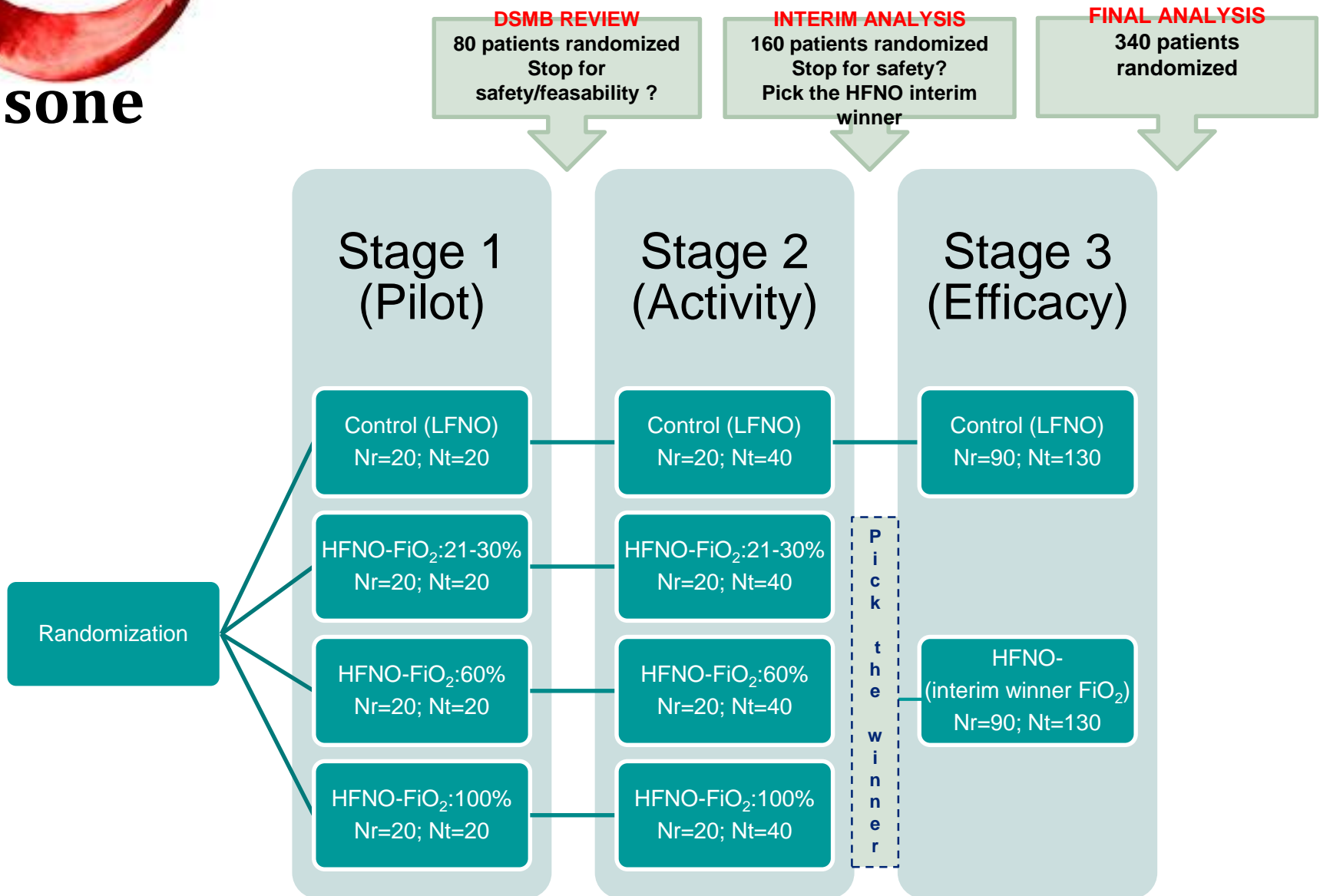
Prévention STA

Spirométrie incitative (CVO)





Ozone



Nr= number of patients to be recruited during the stage
 Nt= total number of patients in the arm at the end of the stage

Traitement STA

SYMPTOMATIQUE

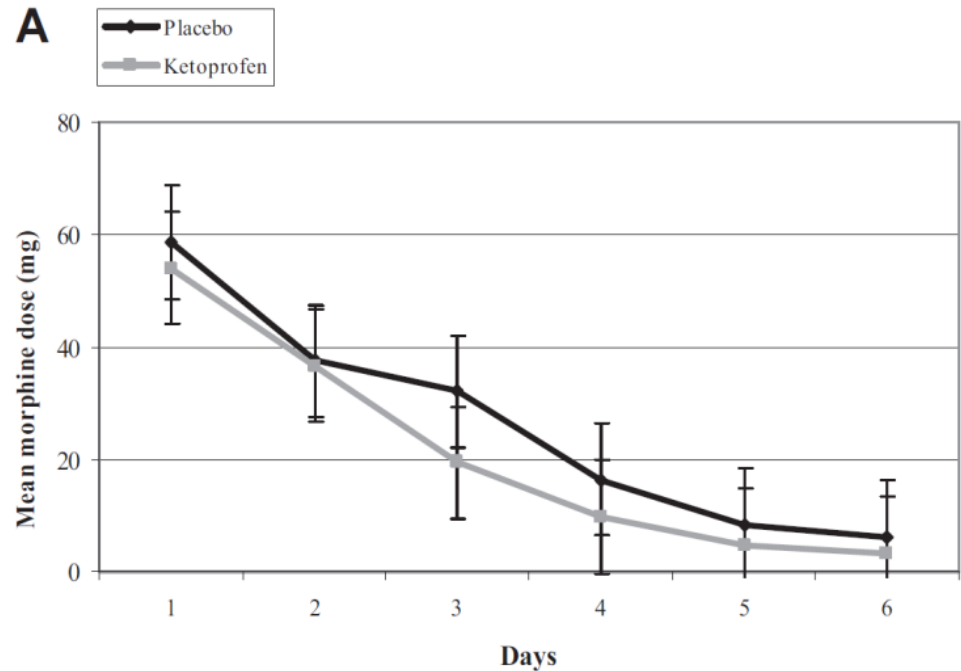
- Hydratation
- Analgésie
- Oxygène \pm VNI
- Transfusion
- Stéroïdes ?
- iNO ?

ETIOLOGIQUE

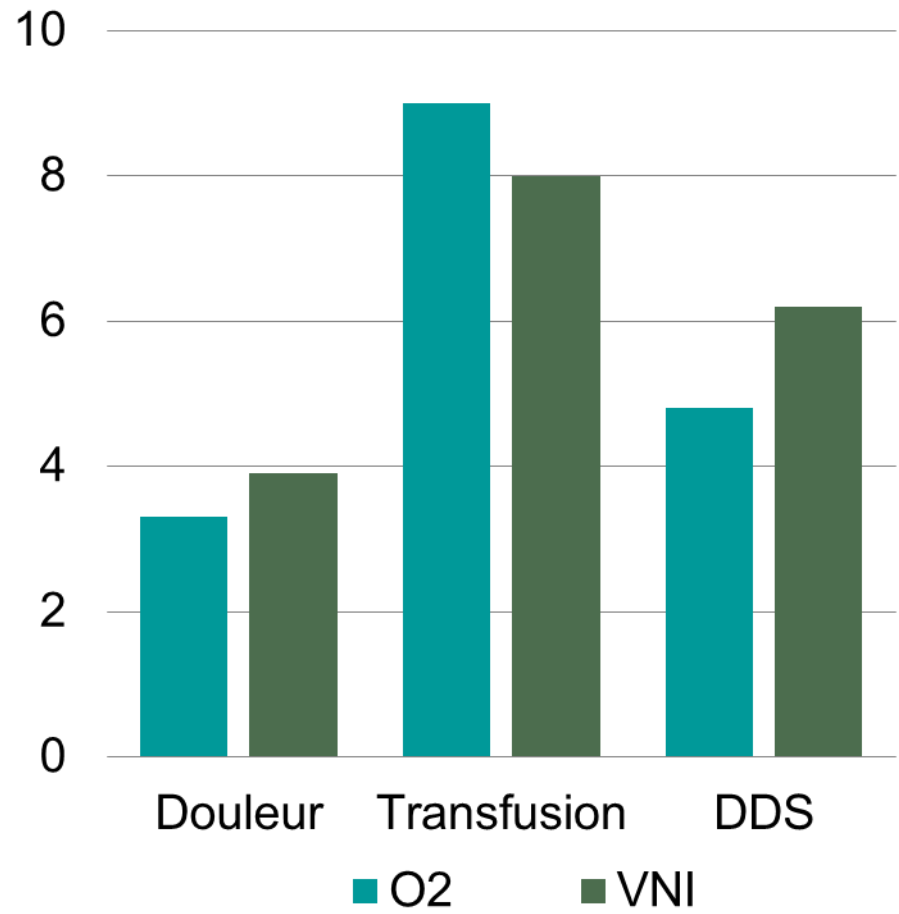
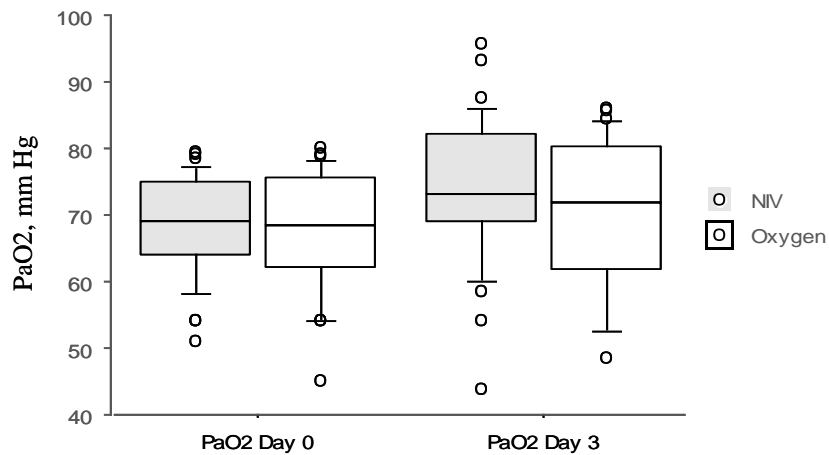
- Antibiotiques
- Anticoagulants
 - Thrombose pulmonaire

Analgesie multimodale

- Morphine
 - Titration
 - PCA
- Paracétamol
- Nefopam
- ± Kétamine
- ± Protoxyde d'azote



VNI et STA



Transfusion

- Rationnel:

- ↓ HbS, falciformation et vaso-occlusion
- ↑ TaO₂ et oxygénation tissulaire

- Risques

- Hyperviscosité
 - Objectif: Hb de base (<10 g/dL); HbS < 30% dans cas sévères
 - Allo-immunisation
 - Iso-groupe, iso Rhesus, phenotypé
 - Hémolyse
-

Modalités transfusion

<i>Taux d'Hb</i>	<i>Volume de la 1^{ère} saignée</i>	<i>volume du 2^{ème} saignée</i>	<i>Transfusion</i>
< 7 g/dl	0	0	2 à 3 CG
7.5	0	150 ml	3 CG
8	0	200 ml	2 CG
8.5	0	250 ml	2 CG
9	200 ml	200 ml	2 CG
9.5	200 ml	250 ml	2 CG
10	250 ml	300 ml	2 CG
10.5	300 ml	300 ml	2 CG
11	300 ml	350 ml	2 CG
11.5	350 ml	350 ml	2 CG
12	350 ml	400 ml+/- 1 saignée le lendemain	2 CG

Sang phénotypé, Rh, Kell, compatibilisé
Attention Historique RAI et ATCD DHTR

Transfusion

■ Indications principales

□ Terrain:

- Programme transfusionnel chronique
- Grossesse, post-partum,
- Post-opératoire

□ Sévérité clinique

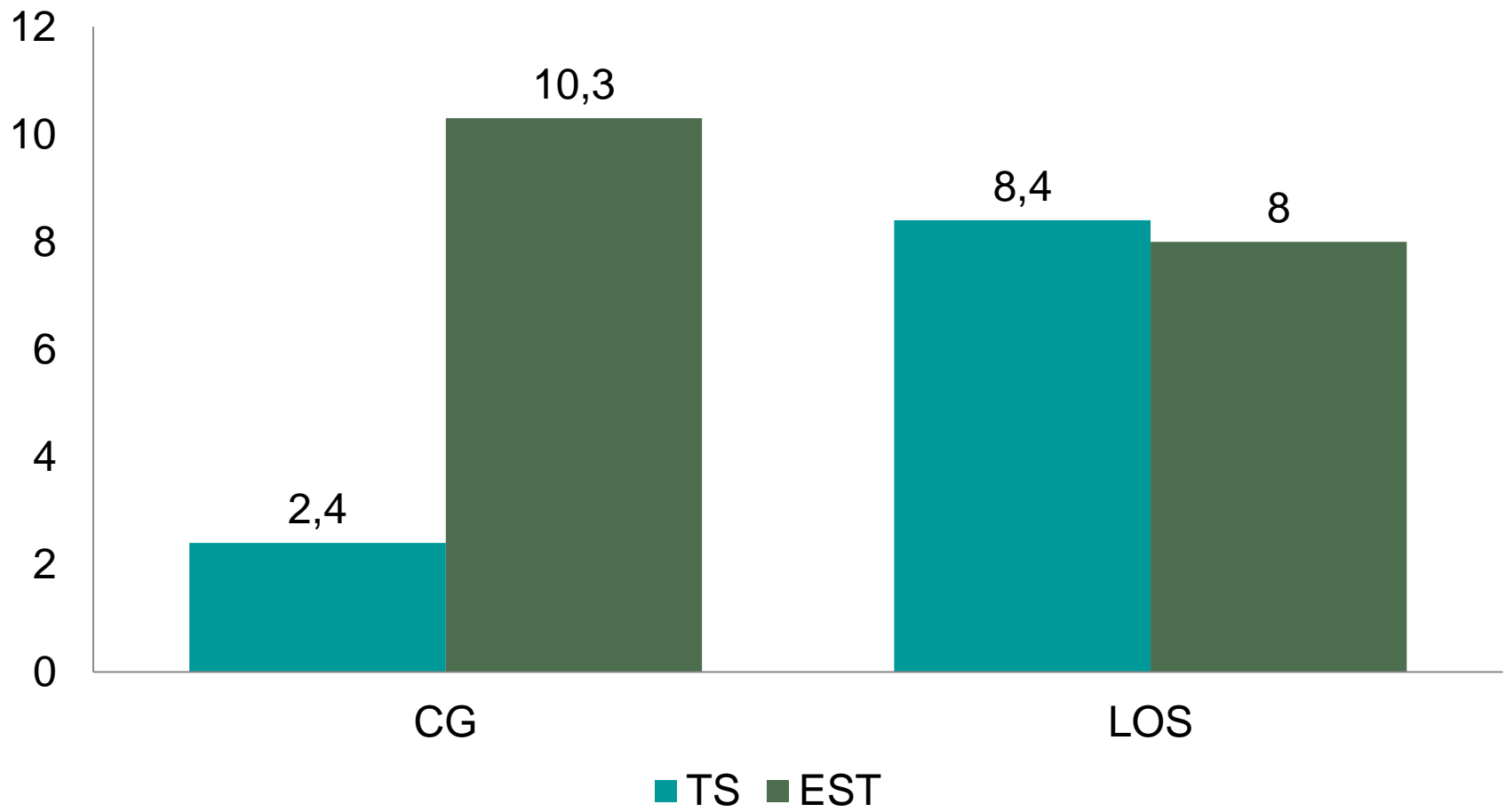
- Détresse respiratoire
- Troubles de la conscience
- IVD
- Sepsis sévère

□ Sévérité paraclinique

- Hb < 6g/dl, atteinte Rx étendue

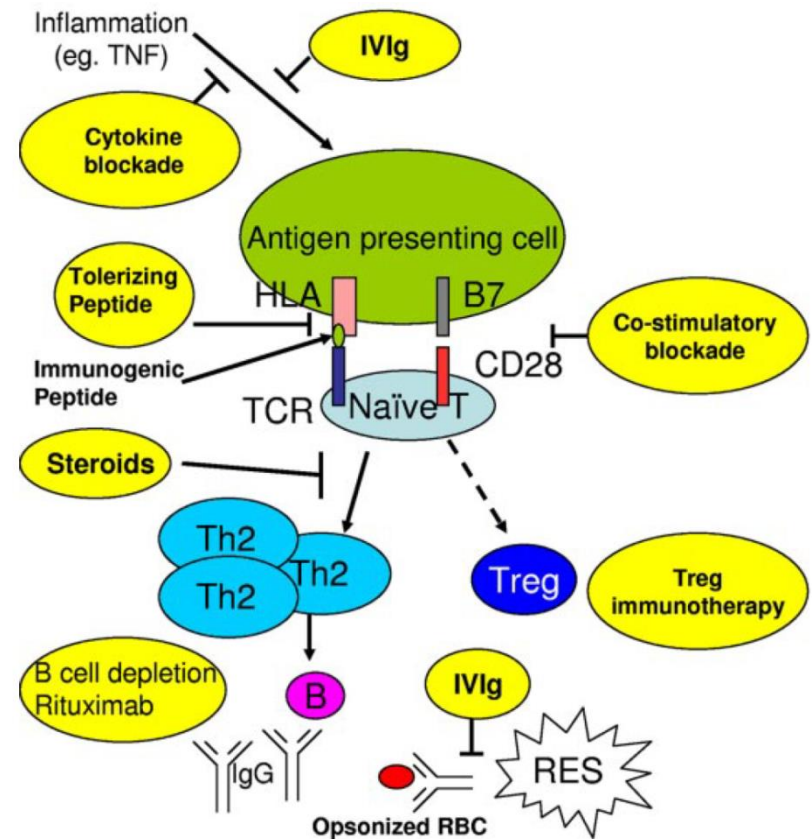
□ Absence amélioration après 72h

Transfusion simple ou EST ?



Allo-immunisation

- Fréquente:
 - 20-50% des patients
- Différences antigéniques raciales entre donneurs et receveurs:
 - Rhésus: C, E
 - Kell: K
 - Duffy: Fya
 - Kidd: Jkb (JK)
 - MNS: S



Hémolyse retardée post transfusionnelle

PRESENTATION

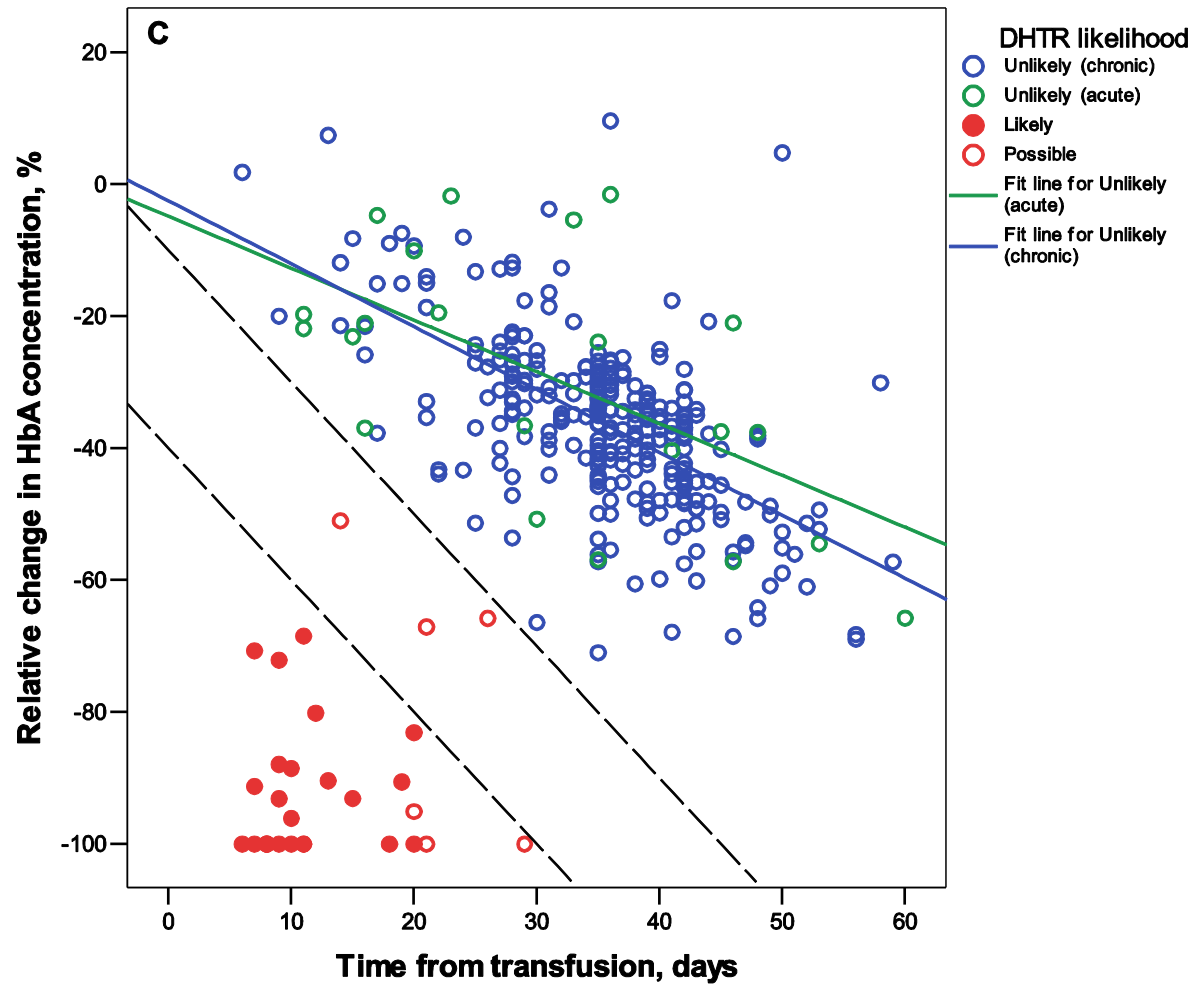
- >J3 transfusion
- CVO±STA



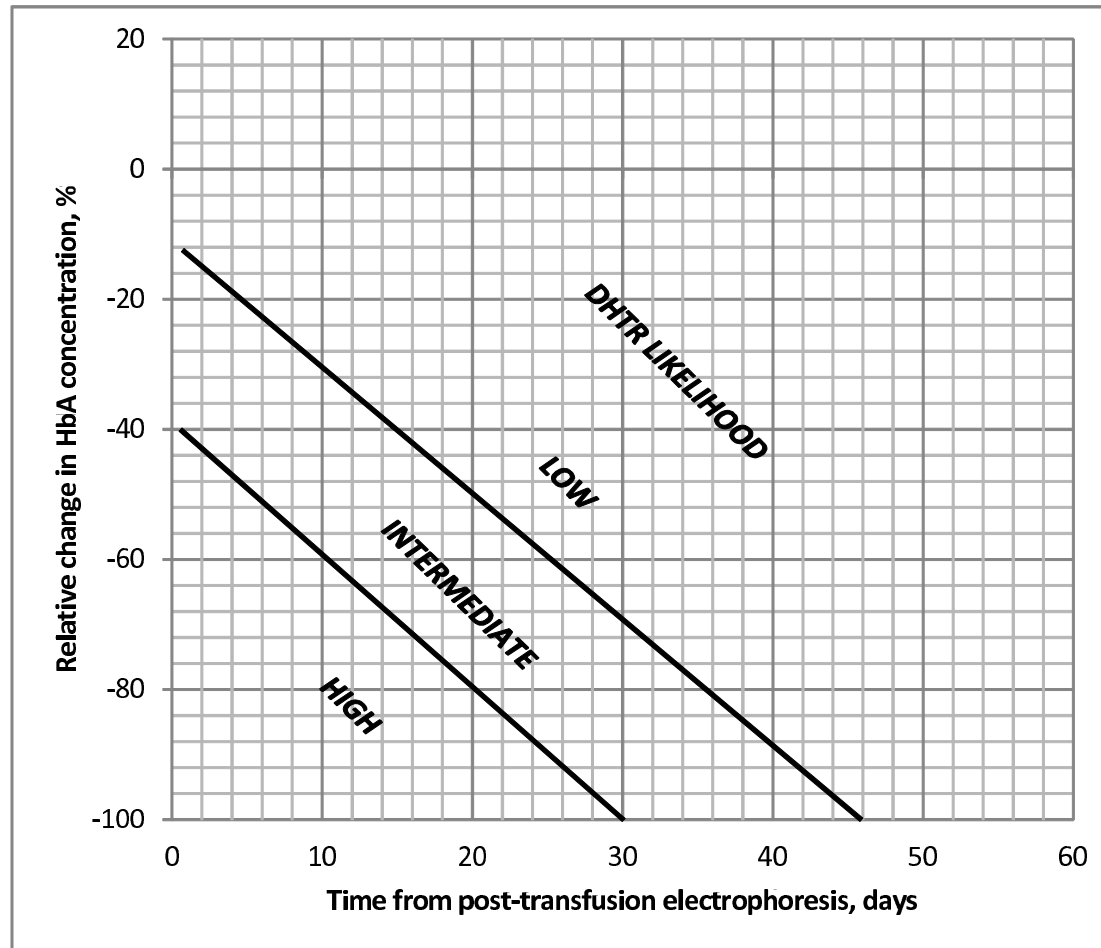
TRAITEMENT

- **Eviter nouvelle transfusion**
- EPO si reticulocytopenie
- Immunomodulation?
 - Ig
 - Rituximab (anti CD20)
 - Eculizimab (anti C5b-9)

DHTR nomogramme



DHTR nomogramme



<http://www.reamondor.aphp.fr/nomogram.php>

Risque de DHTR

Figure 2

PRESCRIPTION OF AN OCCASIONAL TRANSFUSION

Predictive score

- Historical significant Abs 6
- Historical non significant Abs and/or Rh/K 5
- Previous transfused units <12 8
- History of DHTR 5

Immunization status of the patient	Score < 8	Score ≥ 8 : transfusion maintained
No previous immunization or only RH/K Abs	Rh/K matched RBCs	Rh/K and extended matched RBCs (Fy, Jk, MNS)
Significant Abs	Rh/K and matched to Ab specificity + if possible extended matched (Fy, Jk, MNS)	Rh/K and extended match (Fy, Jk, MNS) + Rituximab treatment

Anémie selon réticulocytes

ELEVES

- Hémolyse
 - CVO
 - Post transfusionnelle
 - Paludisme
 - AHAI
- Séquestration
 - splénique
 - hépatique
- Hémorragie

BAS

- Carences (fer, folates)
- Inflammation
- Insuffisance rénale
- Toxicité OH-urée
- Nécrose médullaire
- Crise aplastique

NECROSE MEDULLAIRE

- CVO médullaire extensive
- Fièvre, embolies graisseuse pulmonaire (STA) et systémique, SDM
- ↑ LDH
- Erythromyélocytose puis pancytémie
- Scinti os (hyper) + moelle (hypo)
- Myélo: nécrose
- Transfusion ± EPO

CRISE APLASTIQUE

- Parvo B19
- Fièvre, rash, arthrite, STA, myocardite, glomérulonephrite
- Sérologie, PCR
- Myélo: érythroblastopénie ± nécrose
- Transfusion ± EPO, Ig

Antibiotiques et STA

■ Rationnel

- ↑ risque infectieux (asplénie)
- STA non discernable de la pneumonie
- Causes infectieuses rapportées, même si rares en routine clinique
 - Kirkpatrick Am J Med 1991

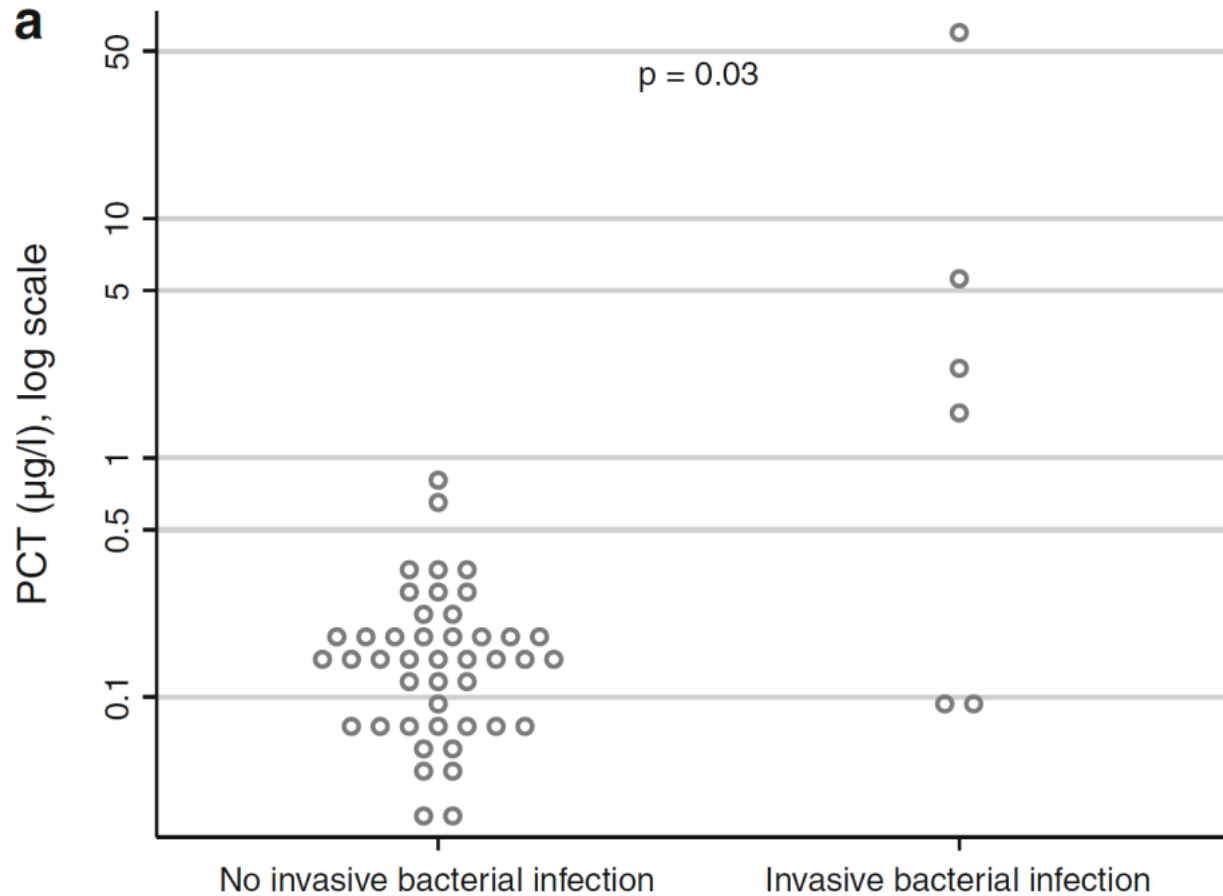
■ Indication

- Quasi-systématique, notamment si fièvre
- *S. pneumoniae* et intracellulaires
- Exemple: amoxicilline+macrolide; telithromycine

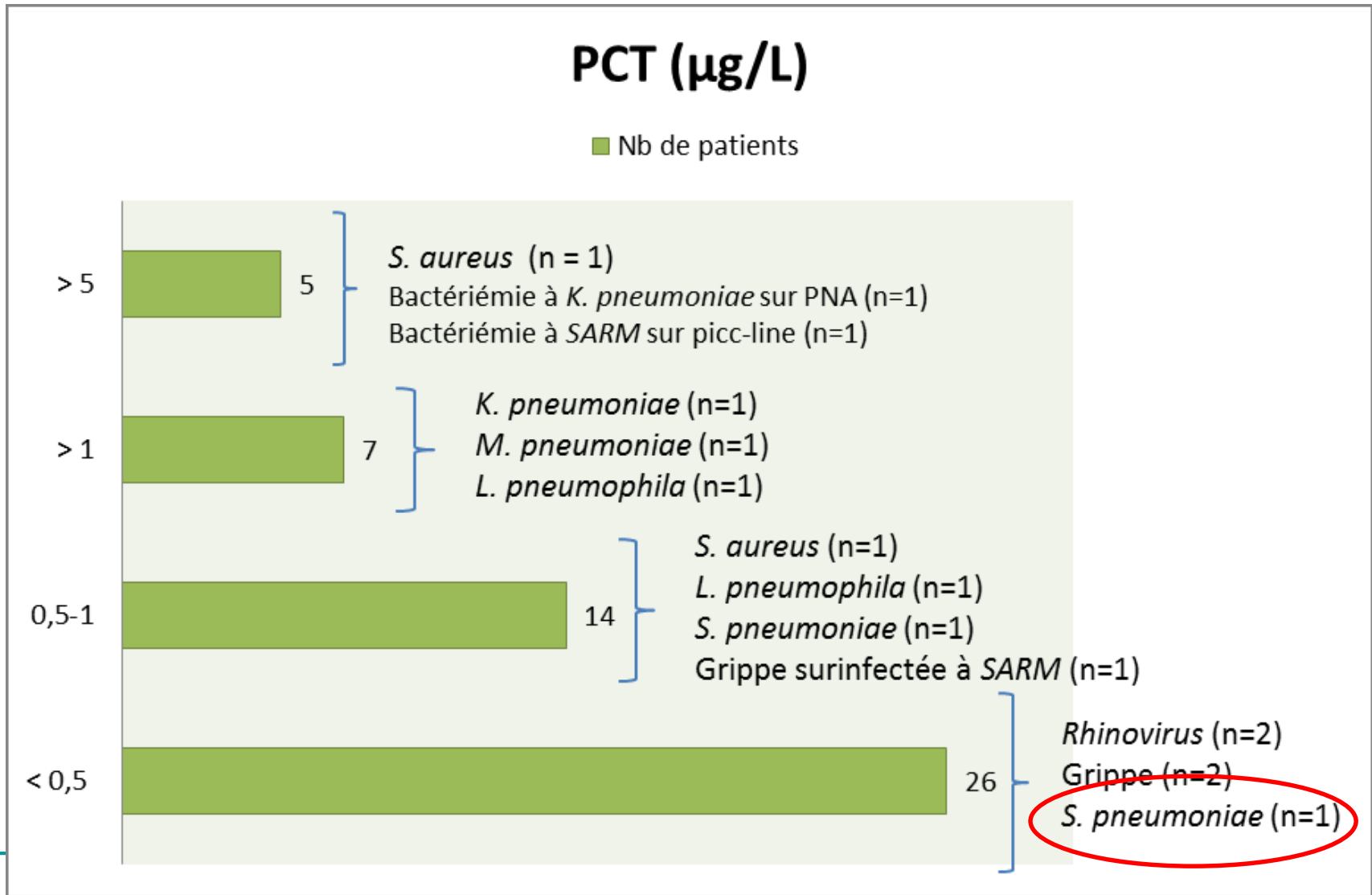
■ Documentation

- ECBC, antigénuries, sérologies atypiques
-

PCT et infection drépanocytaire



Procalcitonine et STA



Raffetin en préparation

PROSTA

Phase 2 « interventionnelle »

J1: prélèvements bactériologiques
et dosage de la procalcitonine
Antibiothérapie empirique

absence de
documentation

documentation
bactériologique

PCT < 0,5ng/ml
à J1 et PCT
< 0,25ng/ml à J2

PCT < 0,5ng/ml à
J1, J2 et J3

PCT > 0,5ng/ml à
J1, J2 et J3

durée habituelle de
l'antibiothérapie
Dosage de la PCT à J7

arrêt de
l'antiothérapie

arrêt de
l'antibiothérapie

durée habituelle de
l'antibiothérapie
Dosage de la PCT à J7

Arrêt si
PCT < 0,5ng/ml ou
baisse de 80% du
pic

Hyperfiltration glomérulaire

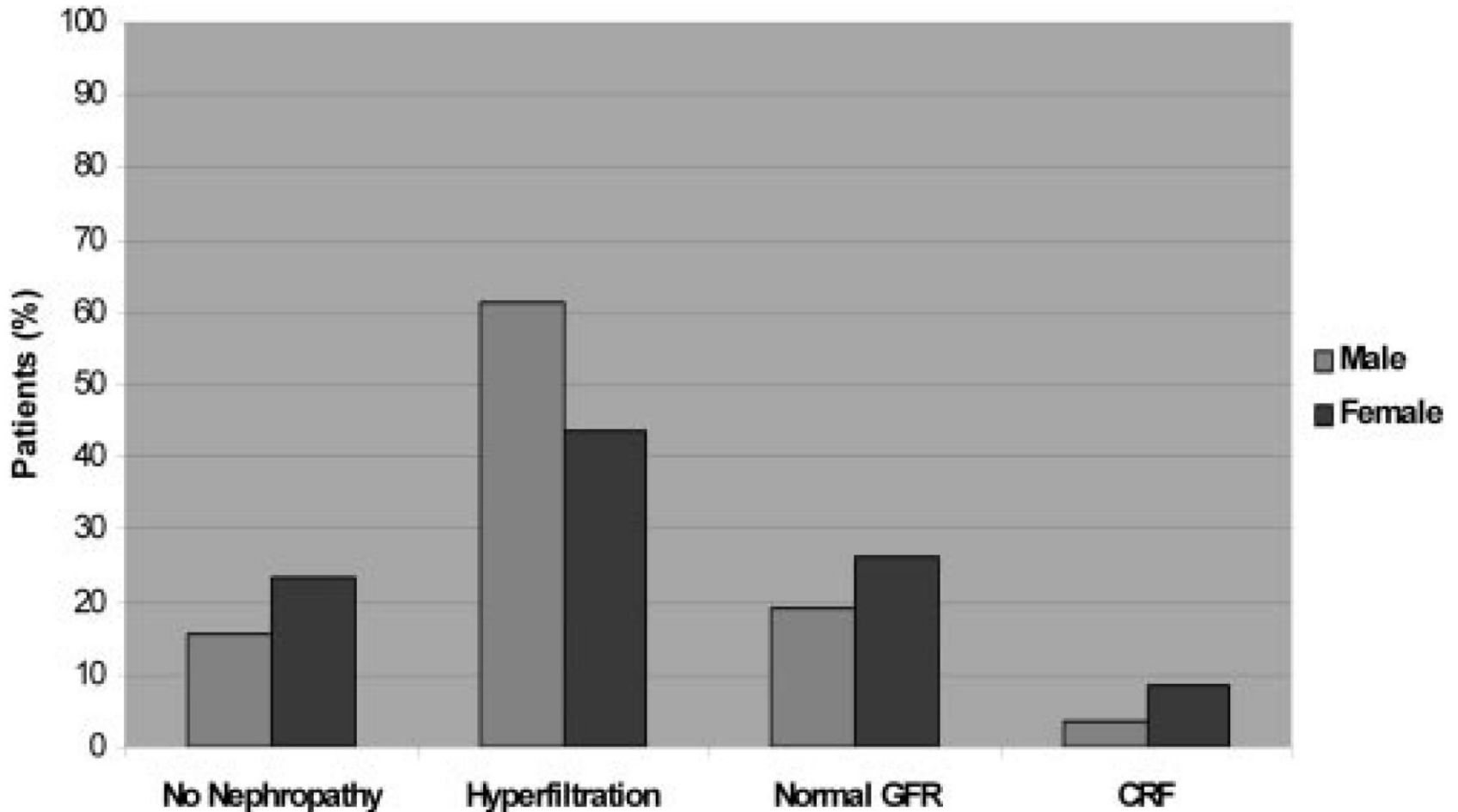
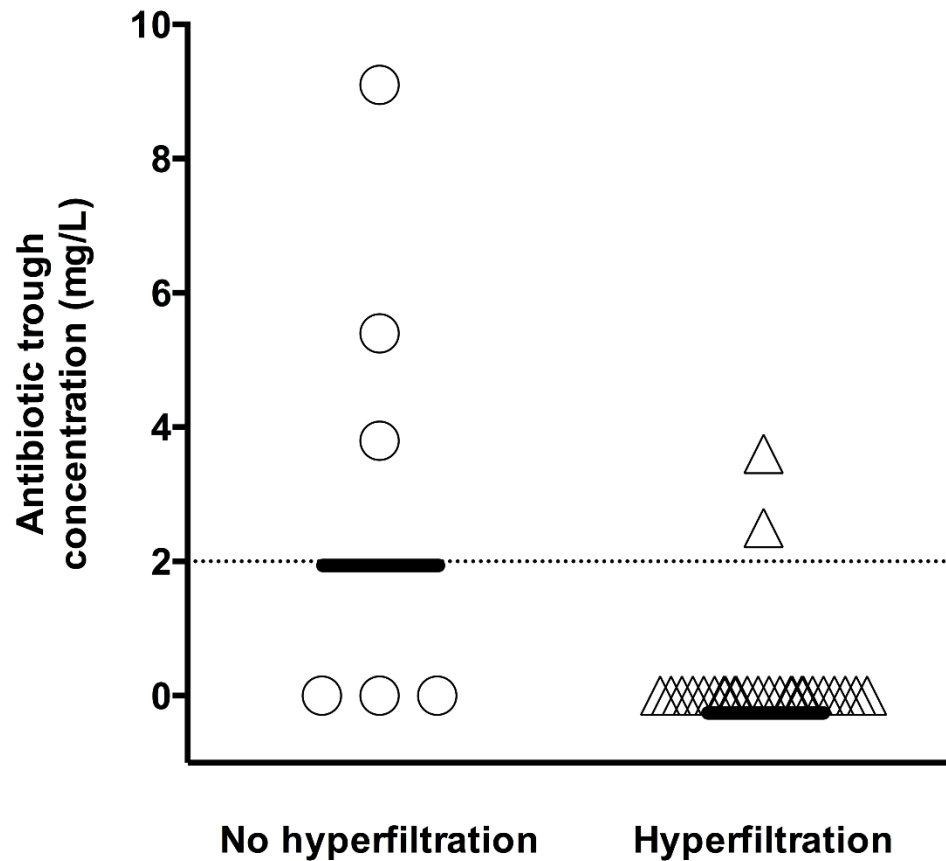
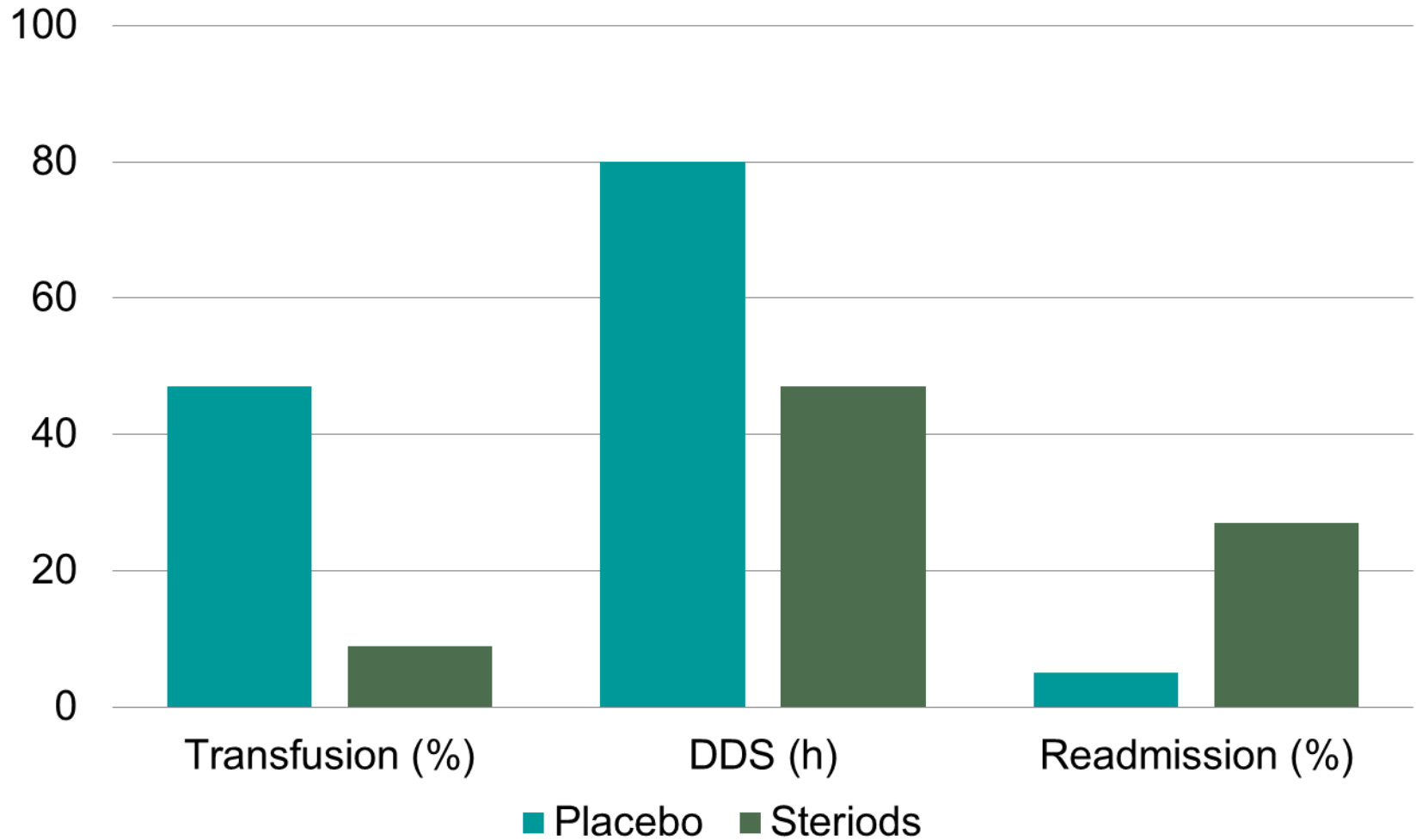


Figure 1. Distribution of patients with SS disease according to GFR.

Dosage antibiotiques



Corticoïdes



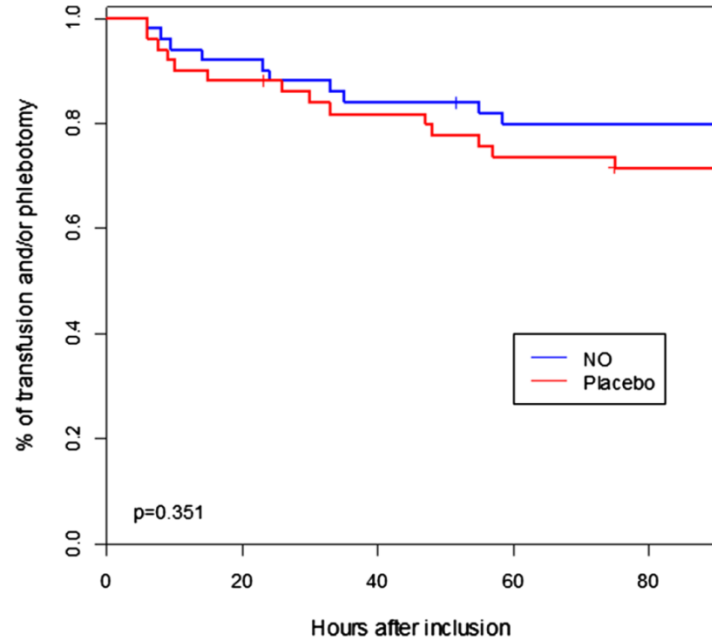
INOSTA

Intensive Care Med
DOI 10.1007/s00134-015-4060-2

B. Maitre
M. Djibre
S. Katsahian
A. Habibi
K. Stankovic Stojanovic
M. Khellaf
I. Bourgeon
F. Lionnet
A. Charles-Nelson
L. Brochard
F. Lemaire
F. Galacteros
C. Brun-Buisson
M. Fartoukh
A. Mekontso Dessap

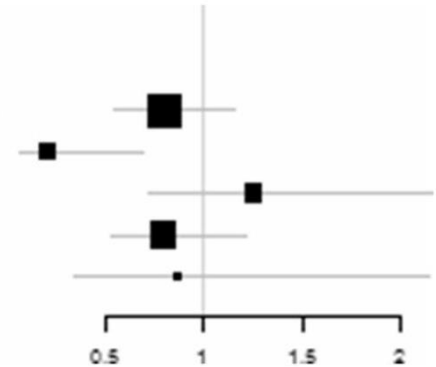


NO 80 ppm

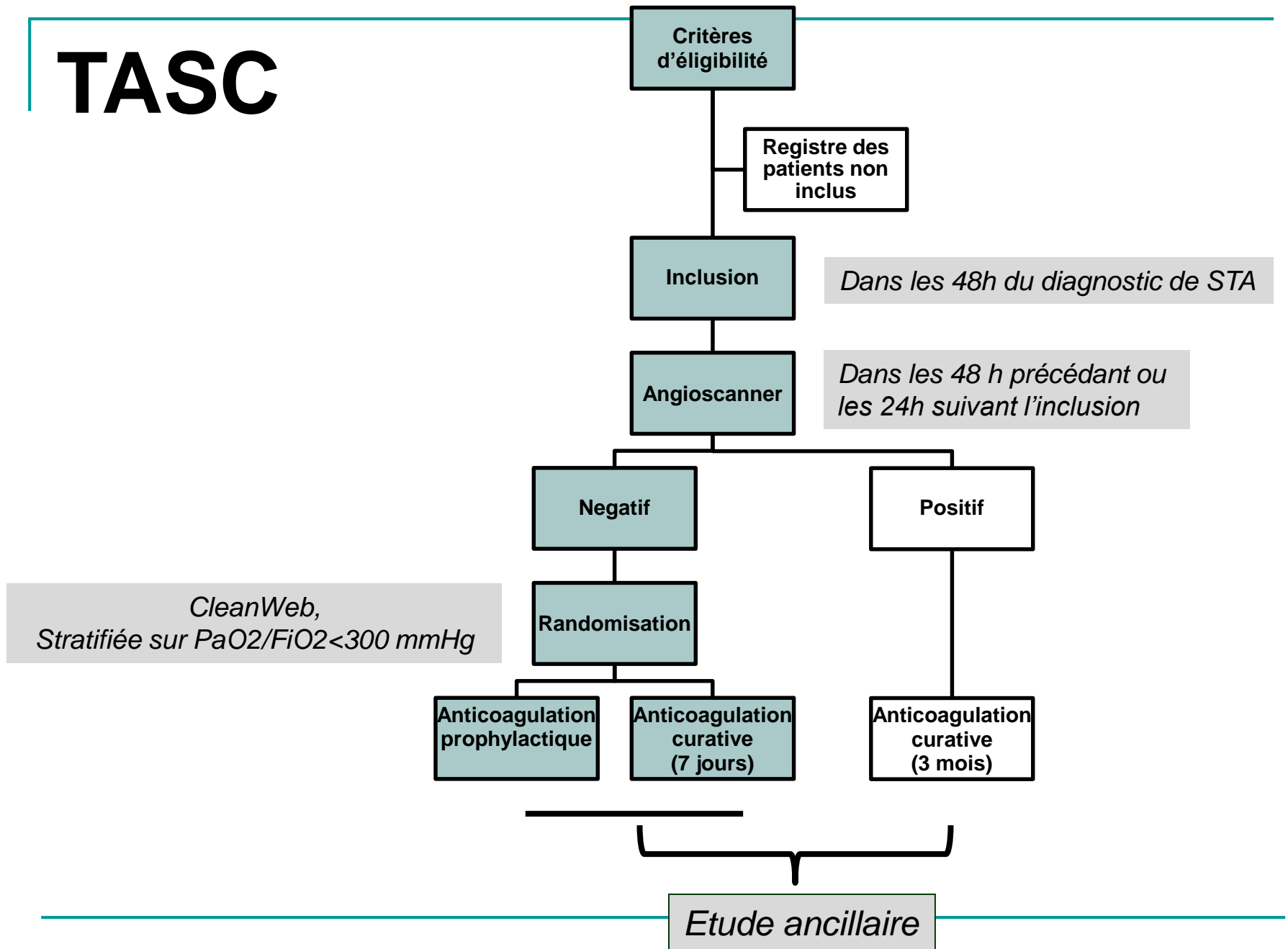


# at risk	0	20	40	60	80
NO	50	46	42	39	39
Placebo	50	44	40	36	34

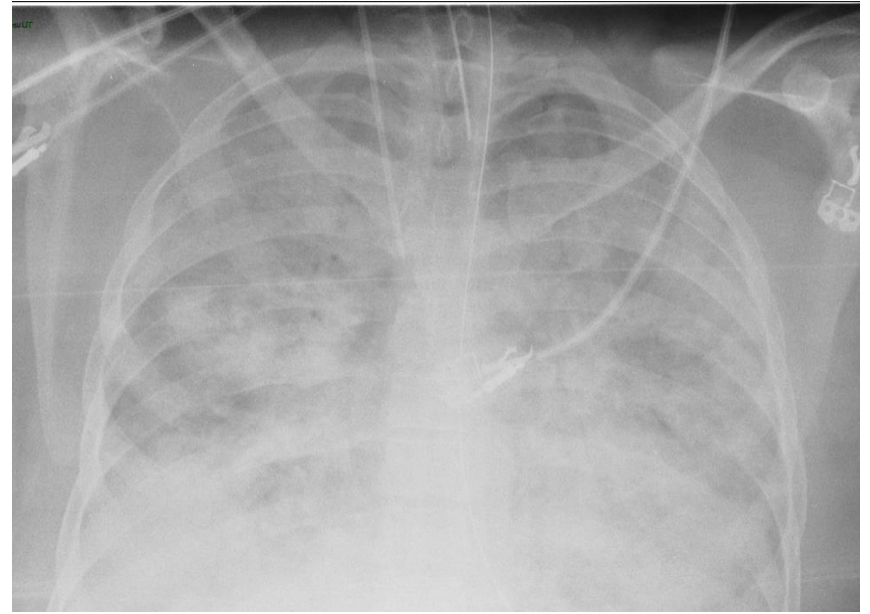
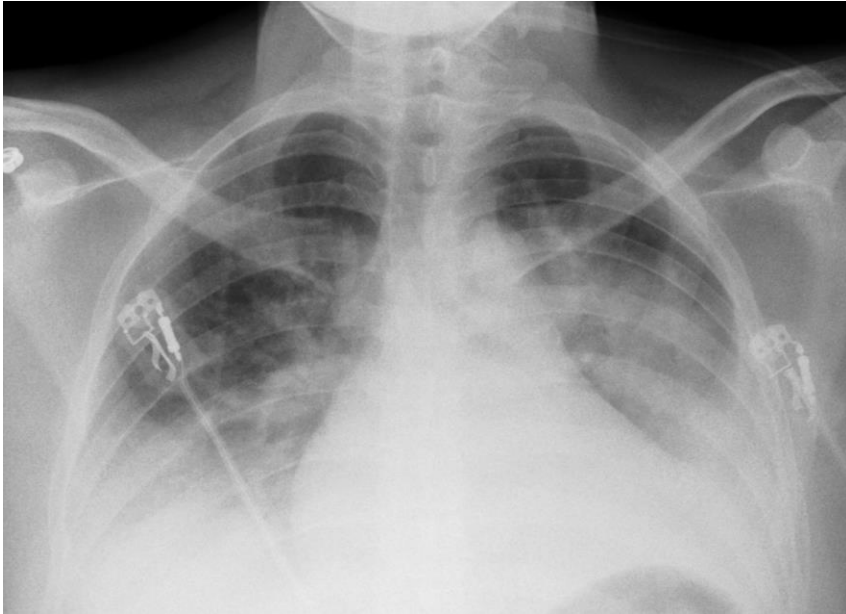
	iNO (N)	Placebo (N)	Risk Ratio (95% CI)	P-value
All patients	23/50 (46%)	29/50 (58%)	0.8 (0.54-1.16)	0.23
Hypoxemia	7/21 (33.3%)	18/25 (72%)	0.19 (0.06-0.68)	0.009
No hypoxemia	15/25 (60%)	11/25 (44%)	1.25 (0.72-2.17)	0.41
SS genotype	17/36 (47.2%)	25/42 (59.5%)	0.79 (0.52-1.21)	0.28
SC/SB genotype	6/14 (42.8%)	4/8 (50%)	0.86 (0.34-2.15)	1



TASC

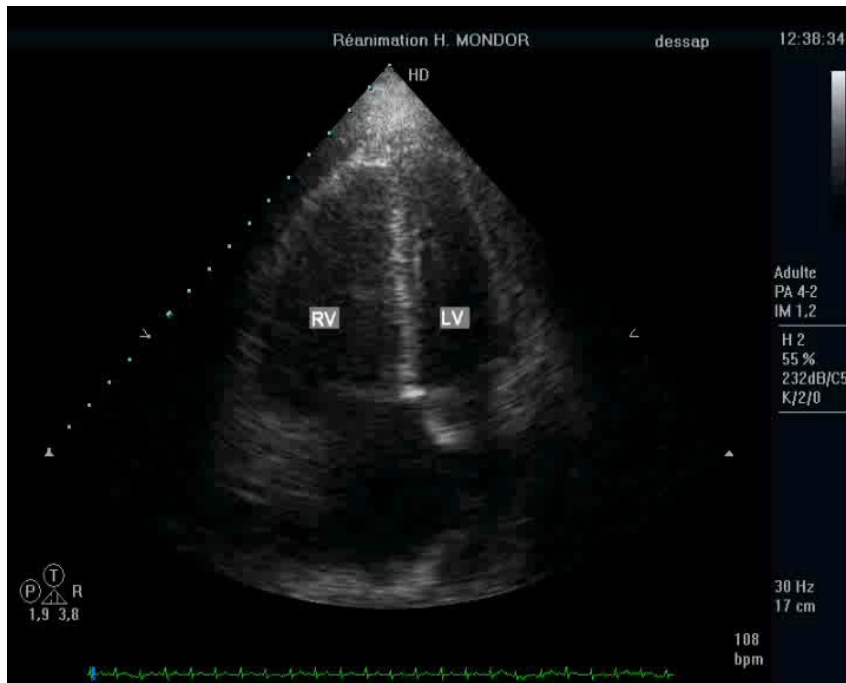


SDRA drépanocytaire

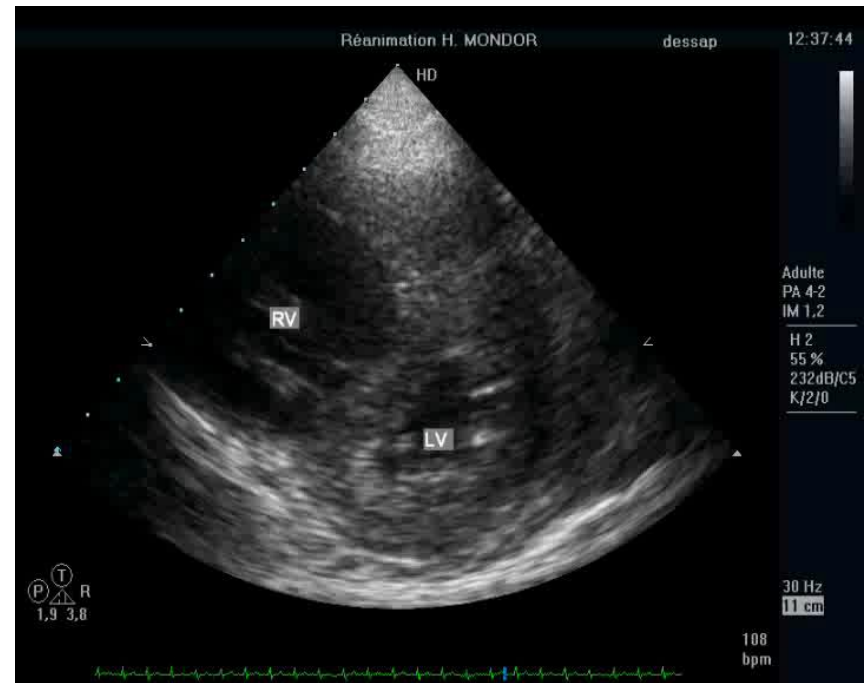


Coeur pulmonaire aigu

Dilatation VD



Septum paradoxal



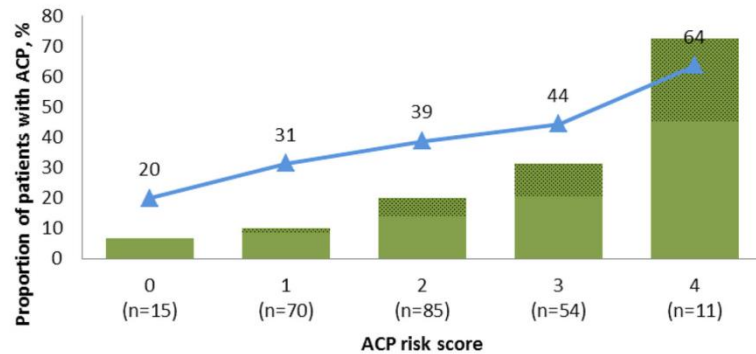
Facteurs prédisposant au CPA

Table 3 The acute cor pulmonale risk score

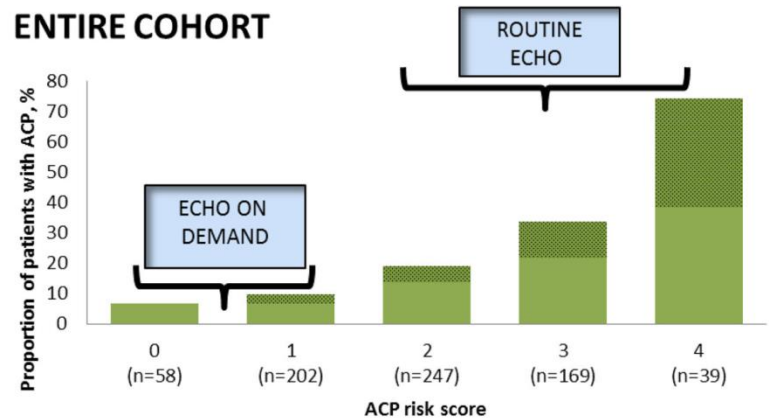
Parameter	Score
Pneumonia as cause of ARDS	1
Driving pressure ≥ 18 cmH ₂ O ^a	1
PaO ₂ /FiO ₂ ratio <150 mmHg	1
PaCO ₂ ≥ 48 mmHg	1
Total score	0–4

Pronostic du CPA

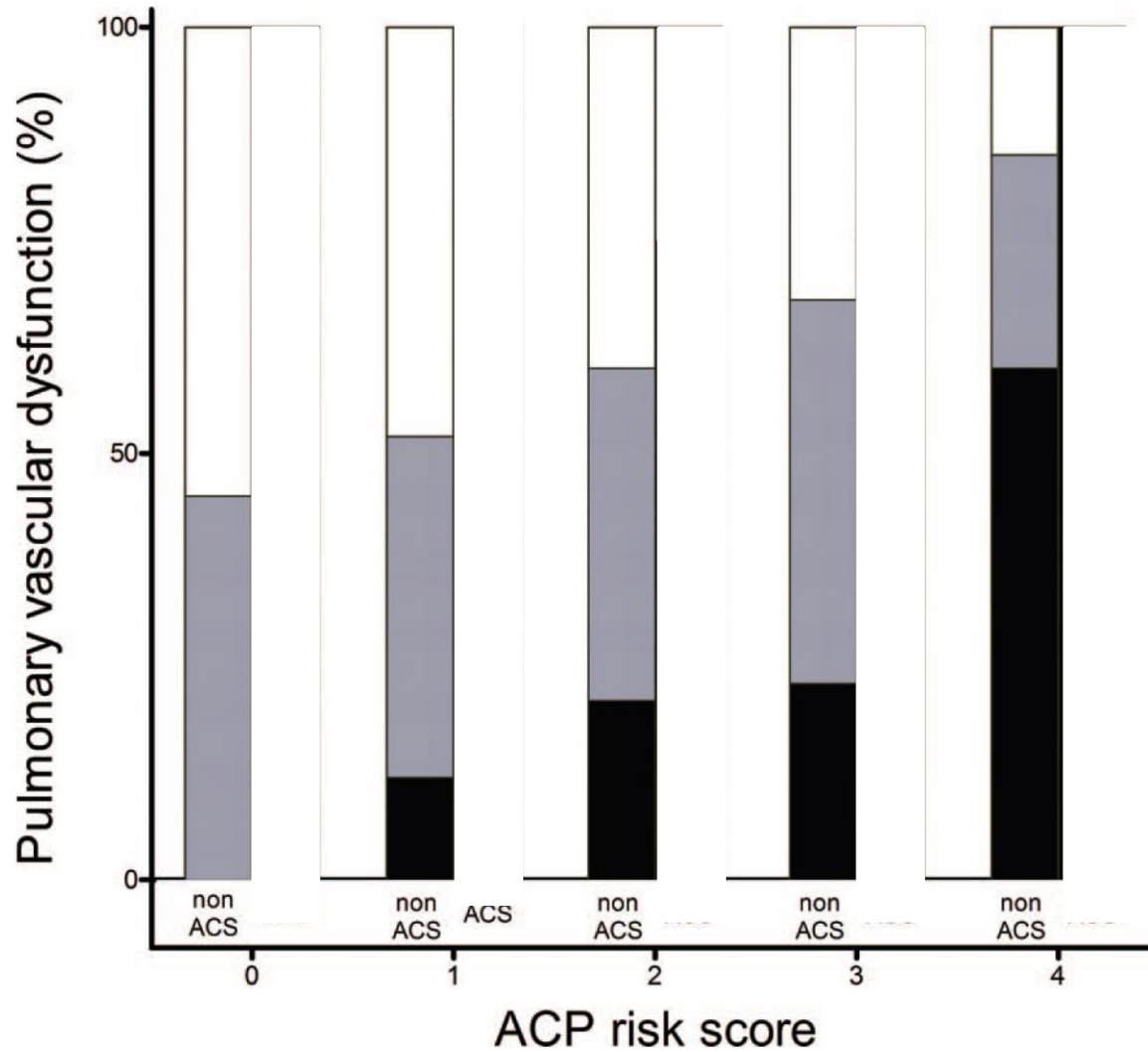
VALIDATION COHORT



ENTIRE COHORT



SDRA drépanocytaire



SDRA drépanocytaire

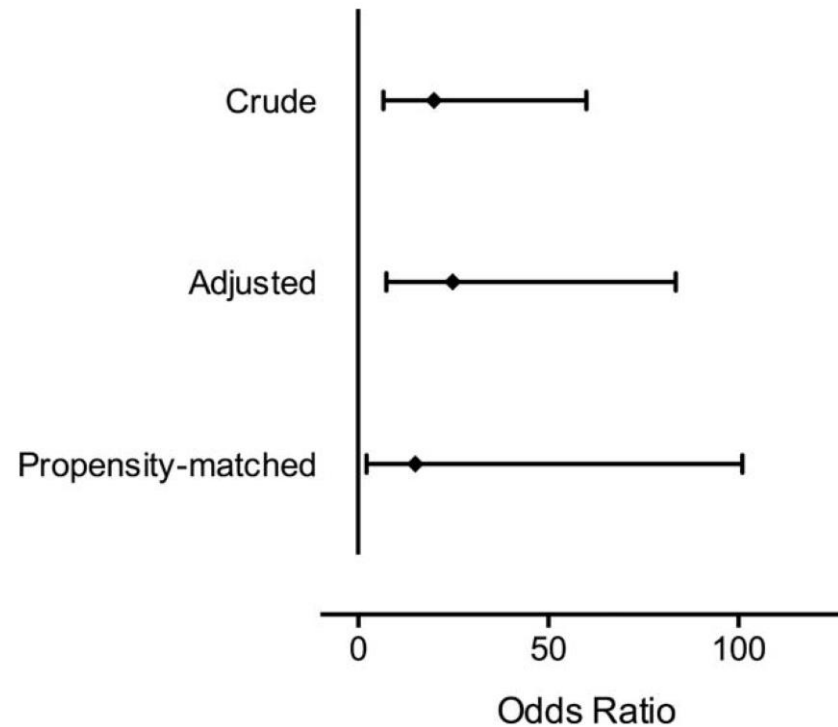
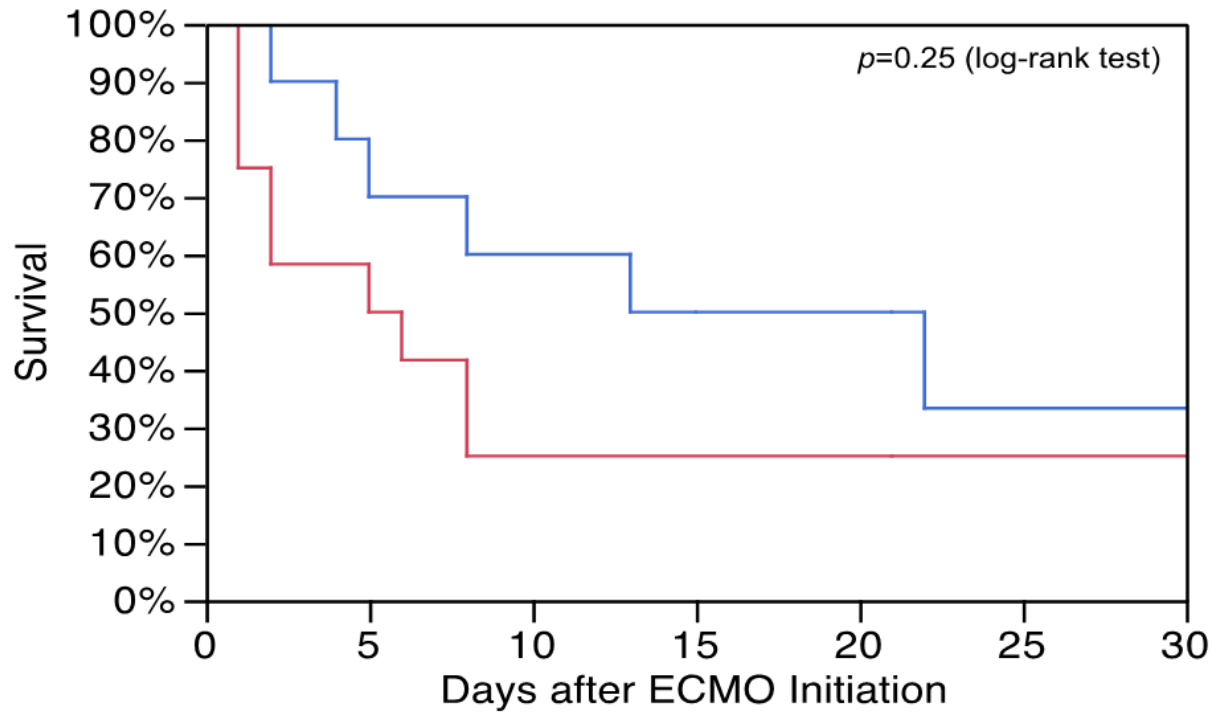


FIG. 2. Odds ratio with 95% confidence intervals for the association between acute respiratory distress syndrome secondary to acute chest syndrome and acute cor pulmonale in logistic regression models with crude analysis [19.9 (6.6–60), $P < 0.0001$], multivariable adjustment [27.4 (8.2–91.5), $P < 0.001$], and propensity matching [11.7 (1.2–110.8), $P = 0.03$].

SDRA drépanocytaire

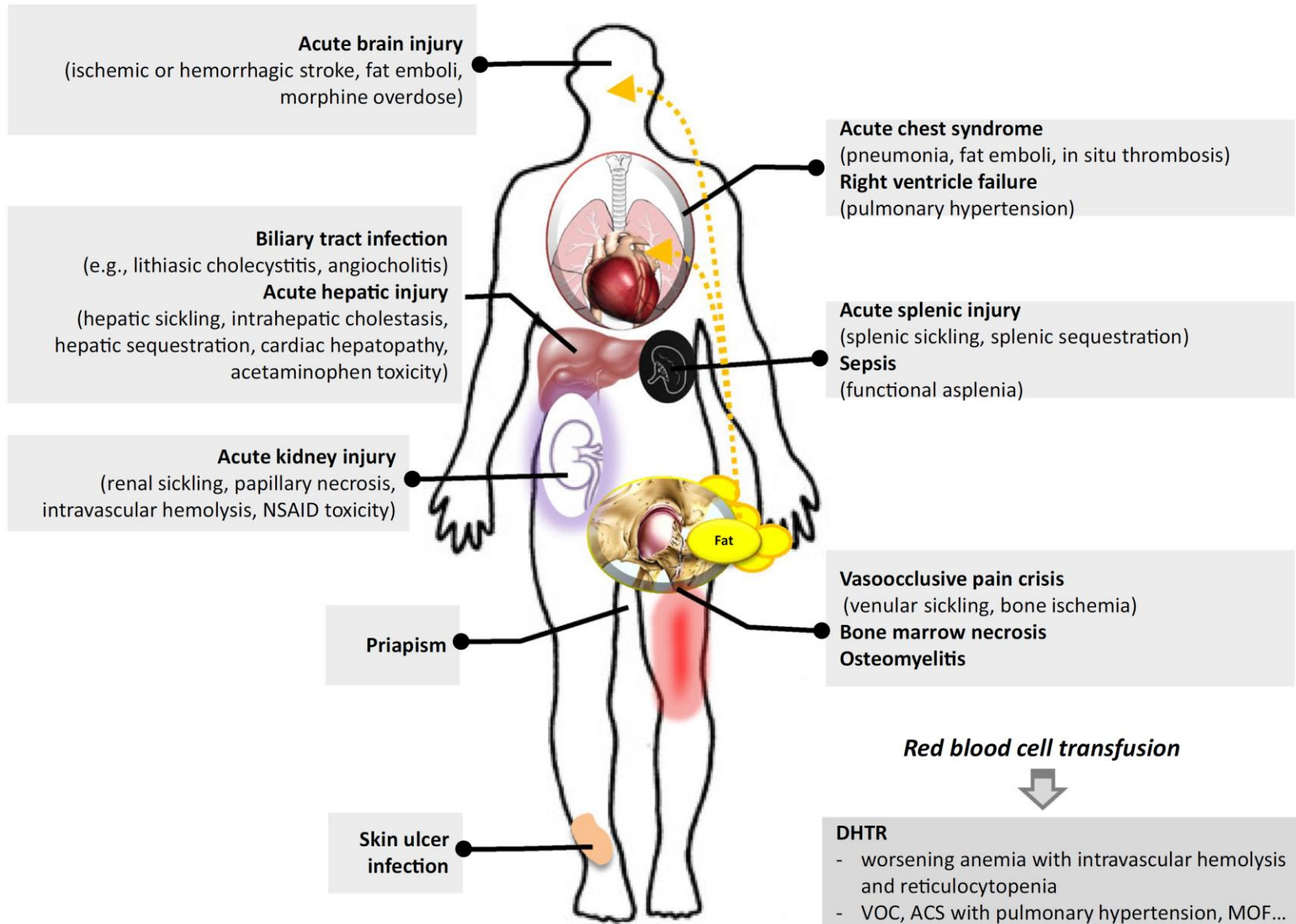
- Dysfonction vasculaire pulmonaire fréquente et majeure
 - Mesures de protection vasculaire pulmonaire
 - Limitation volumes et pressions
 - Limitation hypercapnie (espace mort instrumental)
 - Décubitus ventral ++
 - Vasodilatateurs pulmonaires ?
-

ECMO ?



Number at risk:
group VA: 12 7 5 5 5 3 3
group VV: 10 8 7 5 5 3 3

Maladie vasculaire systémique



Points clés

- Physiopathologie complexe
 - Evolution parfois rapide
 - ❑ SDMV avec SDRA et défaillance cardiaque droite
 - ❑ Surveillance clinique signes de sévérité
 - ❑ Echographie pulmonaire et cardiaque+++
-