Everything You Always Wanted to Know About SCD (But Were Afraid to Ask)

Sickle Cell Disease

H.U.B
HÔPITAL UNIVERSITAIRE DE BRUXELLES
ACADEMISCH ZIEKENHUIS BRUSSEL

INSTITUT JULES BORDET INSTITUUT
Hôpital Erasme | ULB
Hôpital Universitaire des Enfants Reine Fabiola
Universitair Kinderziekenhuis Koningin Fabiola

BHS Courses
Martin Colard MD-PhD
Red Blood Cells and Iron Disorders Unit
Hematology Department

Disclosures

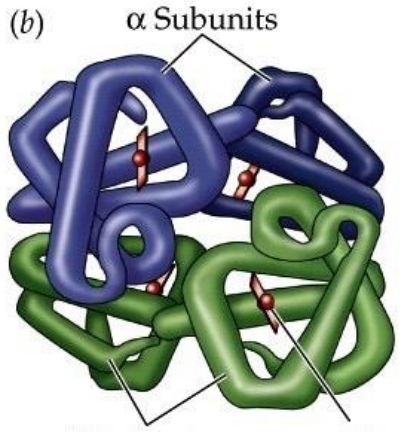
Advisory Board : Chiesi, Pharmanovia, Bristol Meyers Squibb

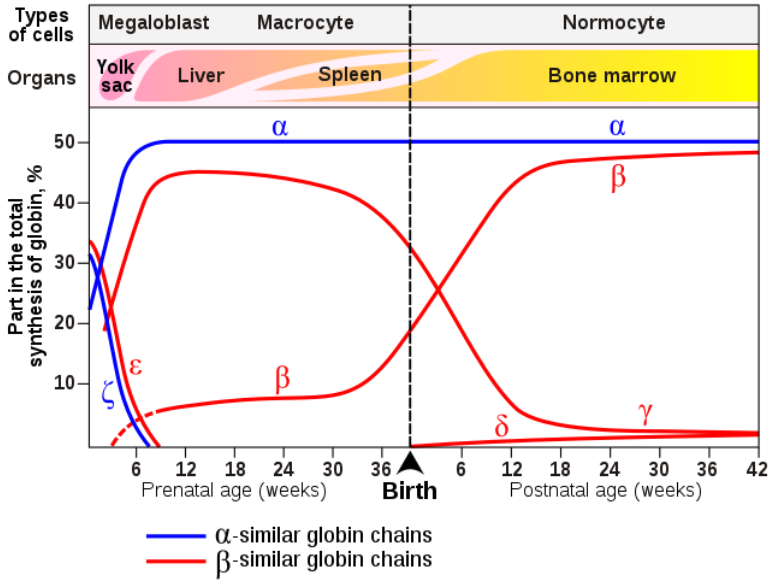
Consultancy : Bristol Meyers Squibb, Menarini

Congress attendance fees :
Novartis, Pharmanovia, Swedish Orphan Biovitrum

Sickle what ?

Hemoglobin





Hb F

2 α chains

2 γ chains

Hb A

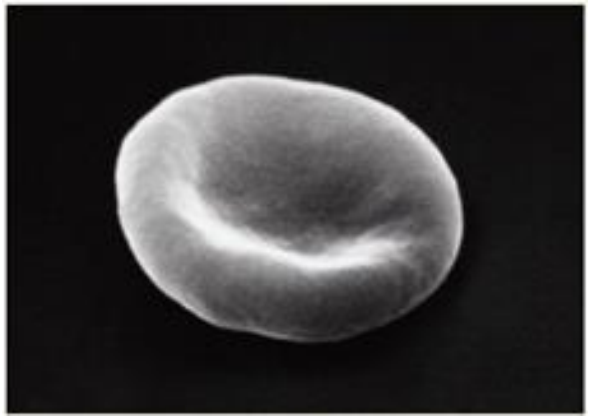
2 α chains

2 β chains

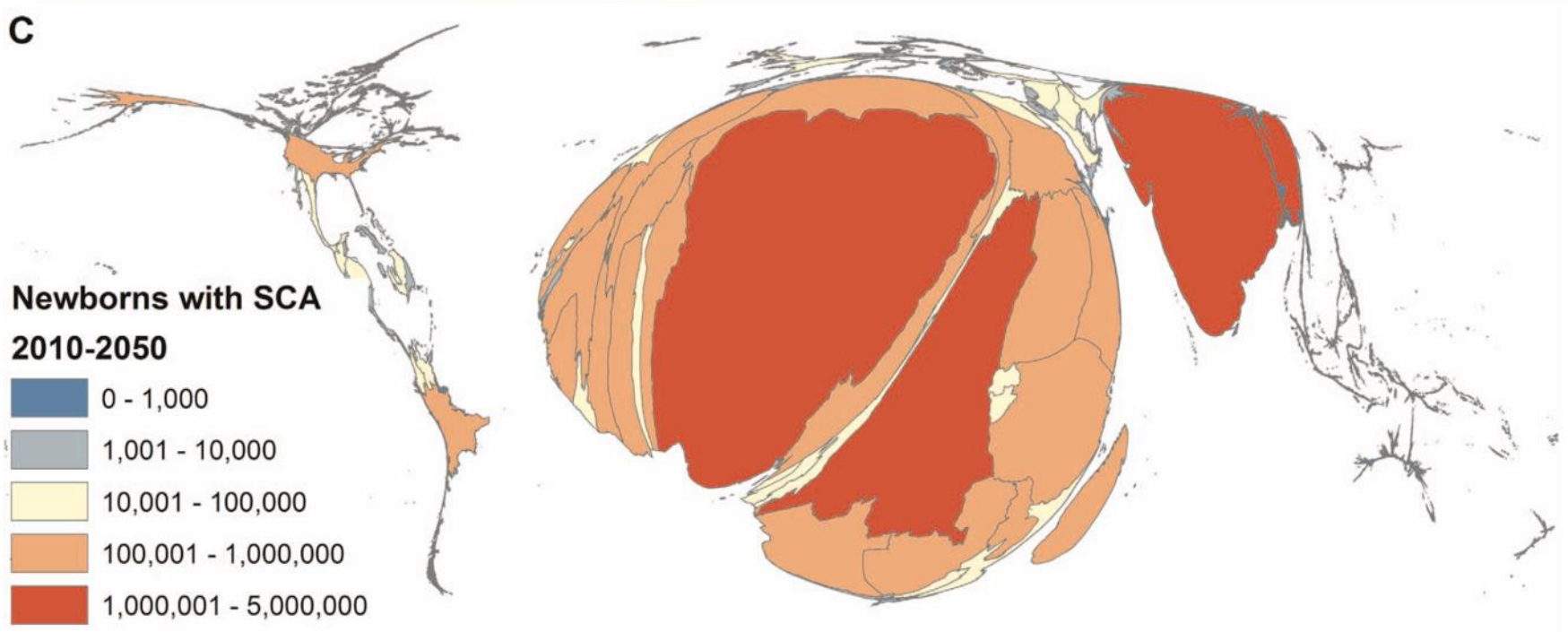
Hb S

2 α chains

2 mutated β^s chains



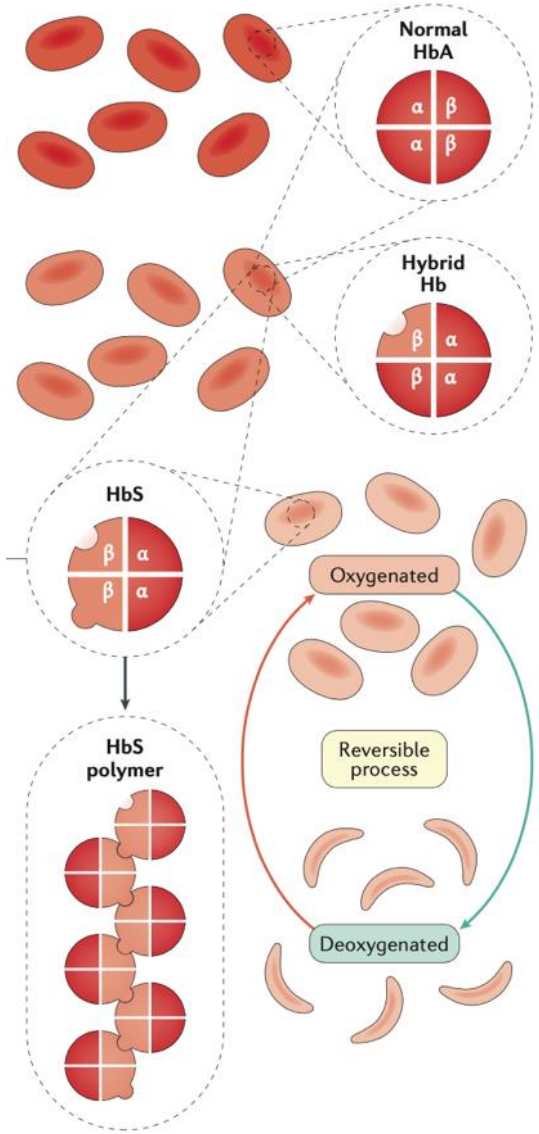
Sickle Cell Disease



Belgium

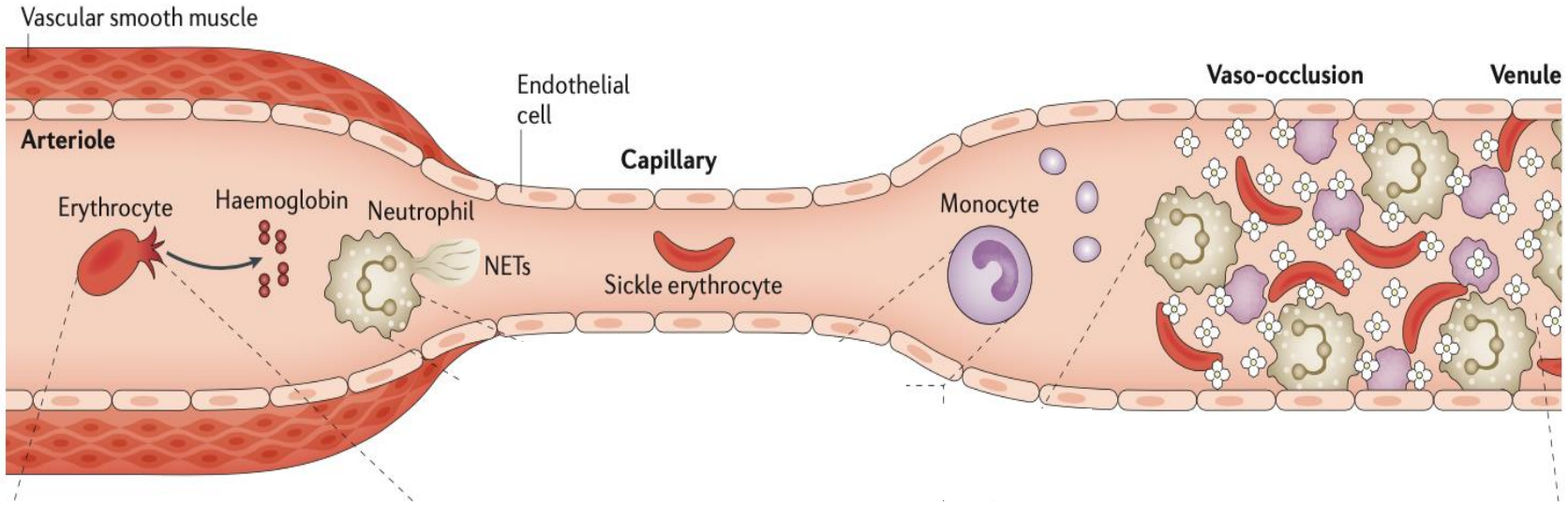
- 1% of newborns are carrier (« AS »)
- ≈1/2000 birth (SS, SC…)
- Nationanl Registry
  - 1203 patients (ped + ad) in Belgium 01/10/2023
- 230 patients in H.U.B. - Erasme

Physiopathology



Hemolyse

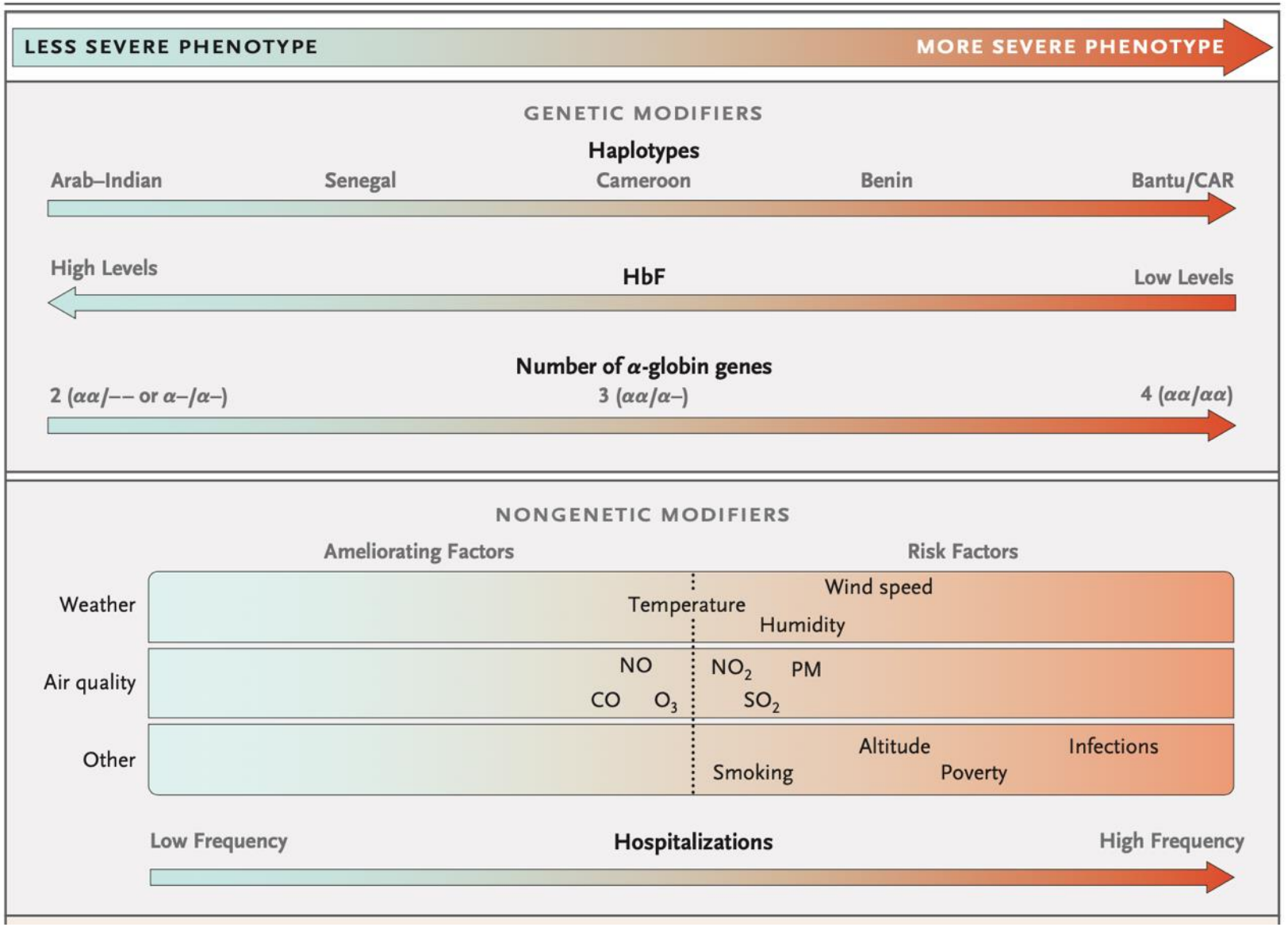
Vaso-Occlusion



Sickle Cell DiseaseS

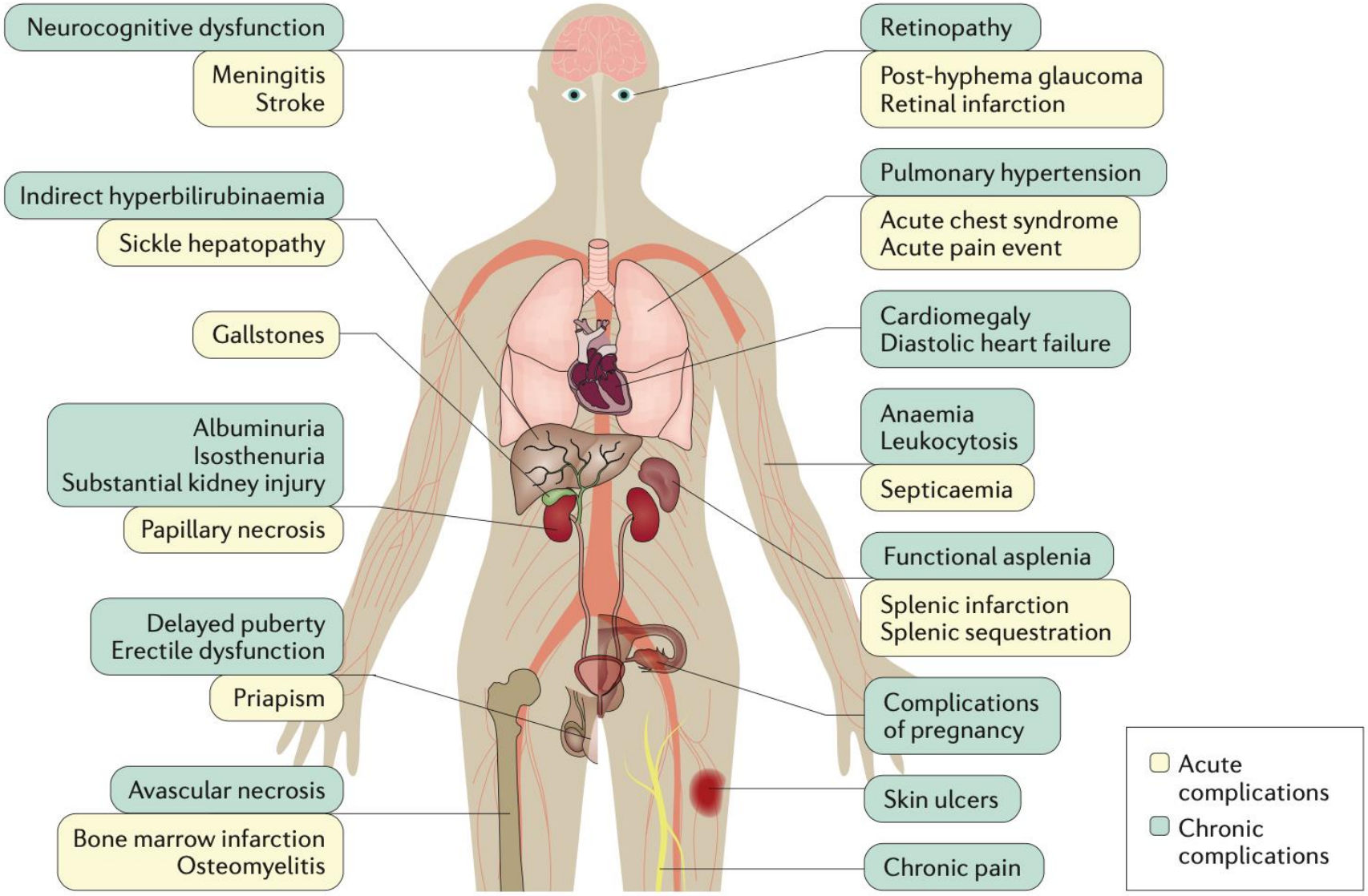
- Homozygoty SS
- Compound Heterozygoty S/C
- S / β^0- ou S/β^+- Thalassemia
- S / Other abnormal hemoglobin (S/E, S/D Punjab, …)

Physiopathology



Yeah, but…
That's just pain control right ?

Complications



Complications

Without screening :

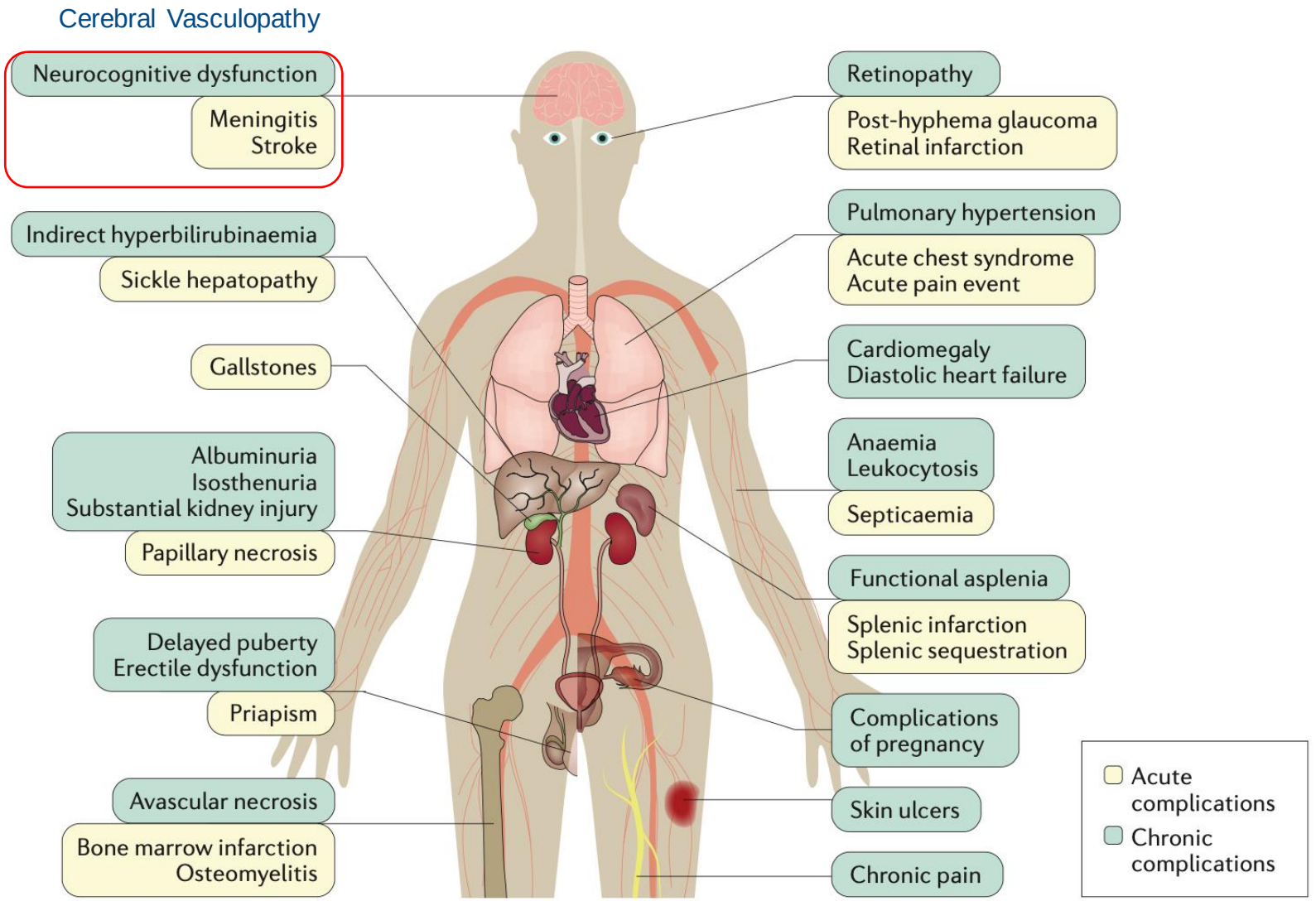
11% at 20year

25% at 45year

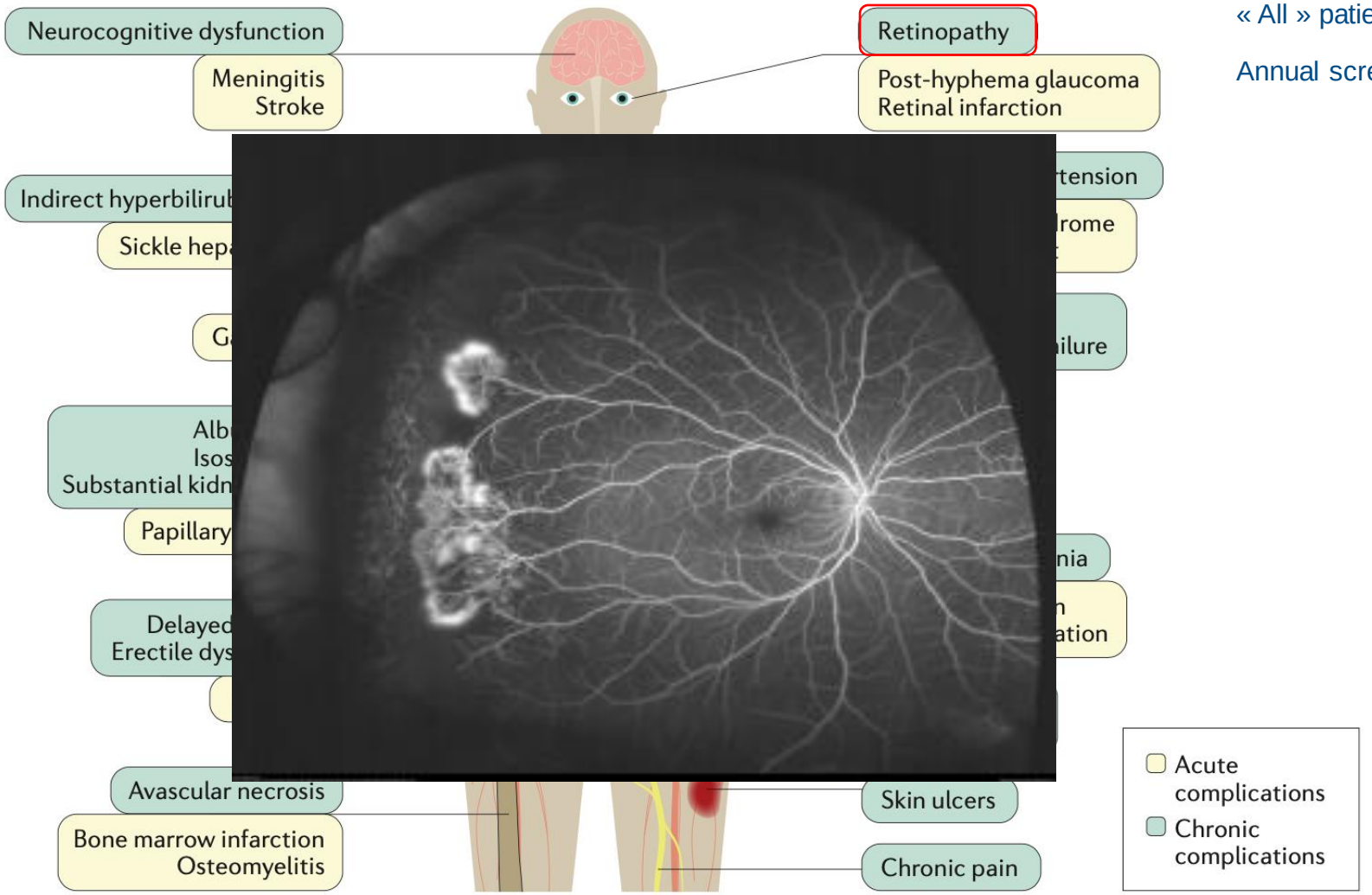
Screening :

* TCD US

* Angio-MRI (+Gado)



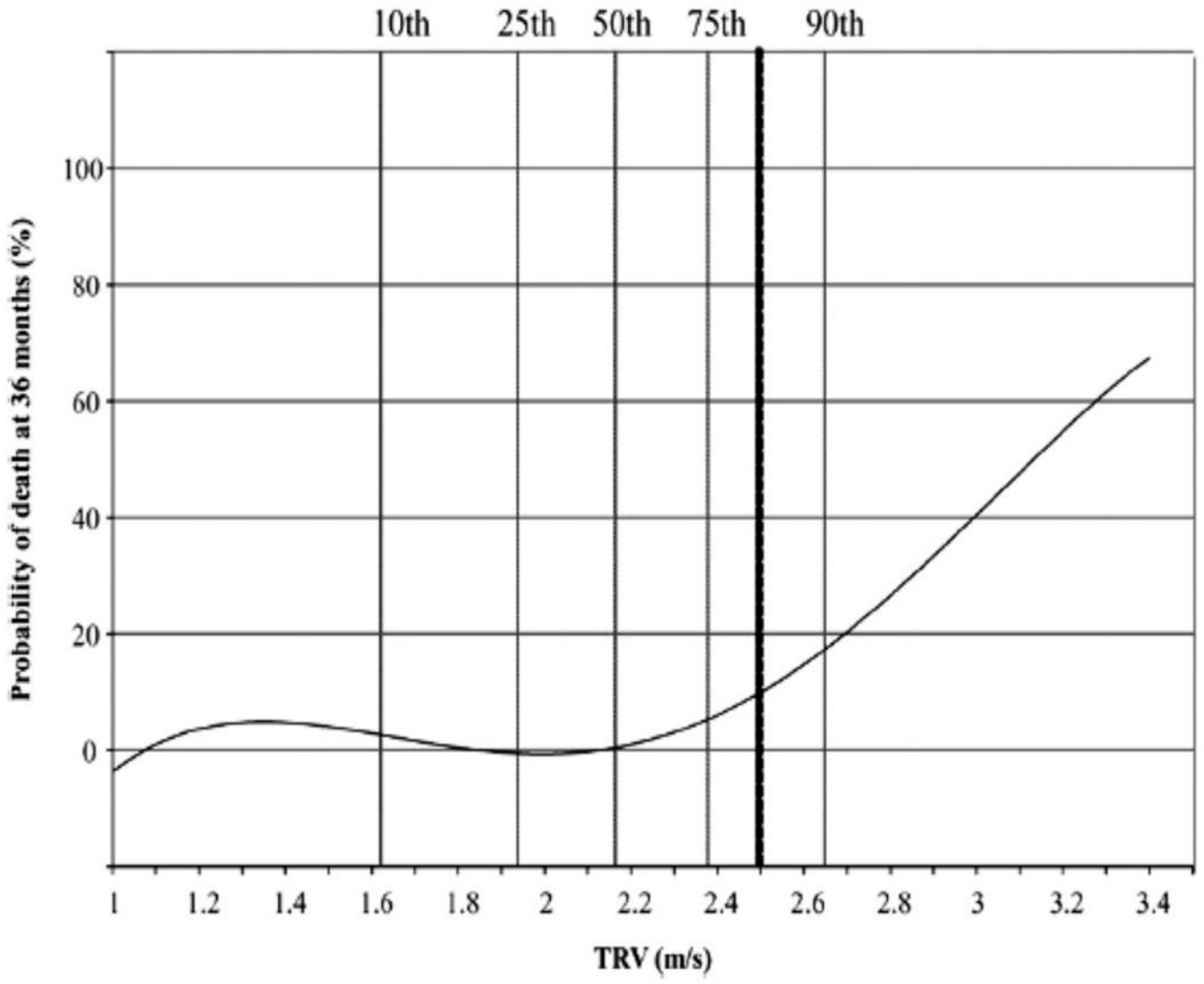
Complications



« All » patients

Annual screening starting at 10y

Complications



- Retinopathy
- Post-hyphema glaucoma
  Retinal infarction
- Pulmonary hypertension
- Acute chest syndrome
  Acute pain event
- Cardiomegaly
  Diastolic heart failure
- Anaemia
  Leukocytosis
- Septicaemia
- Functional asplenia
- Splenic infarction
  Splenic sequestration
- Complications of pregnancy
- Skin ulcers
- Chronic pain

Acute complications
Chronic complications

6-10% of adult patients

Screening :

* Heart US
* 6MWT

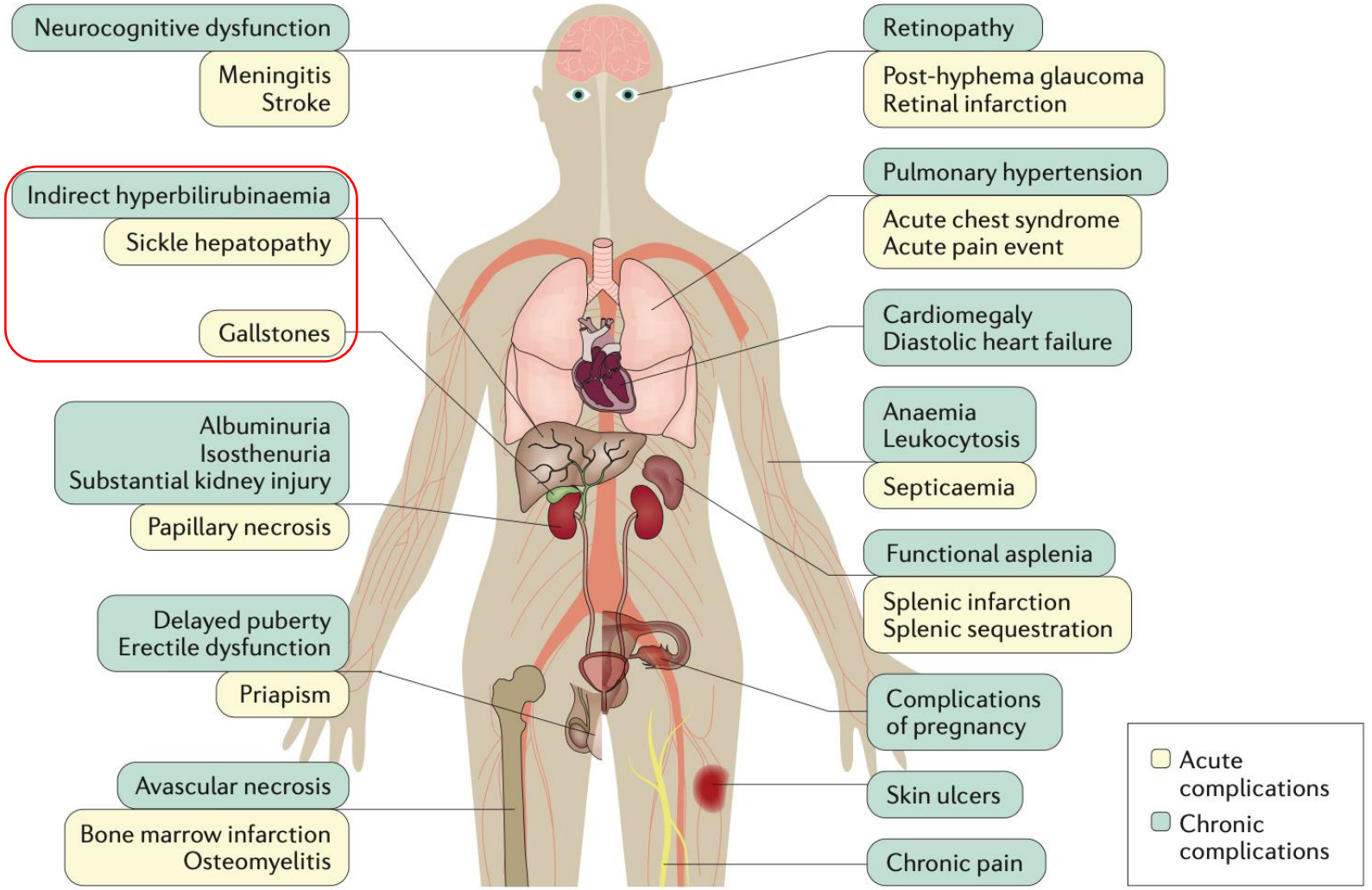
Gladwin *et al.* Hematology (2017).

Complications

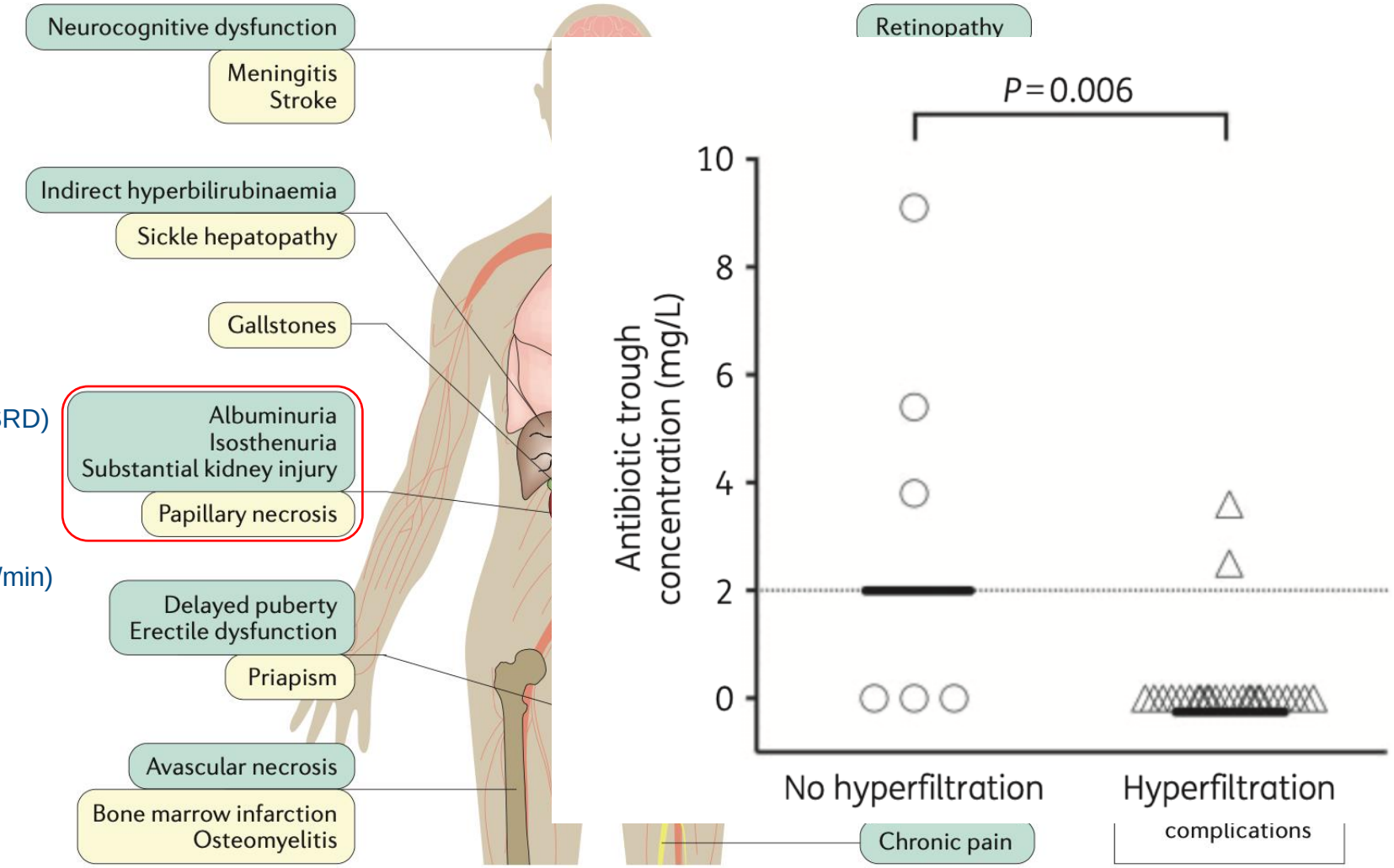
60% Stones

Chronic hepatitis (A-I, Ischemia, Virus, …)

Ischemic cholangitis



Complications

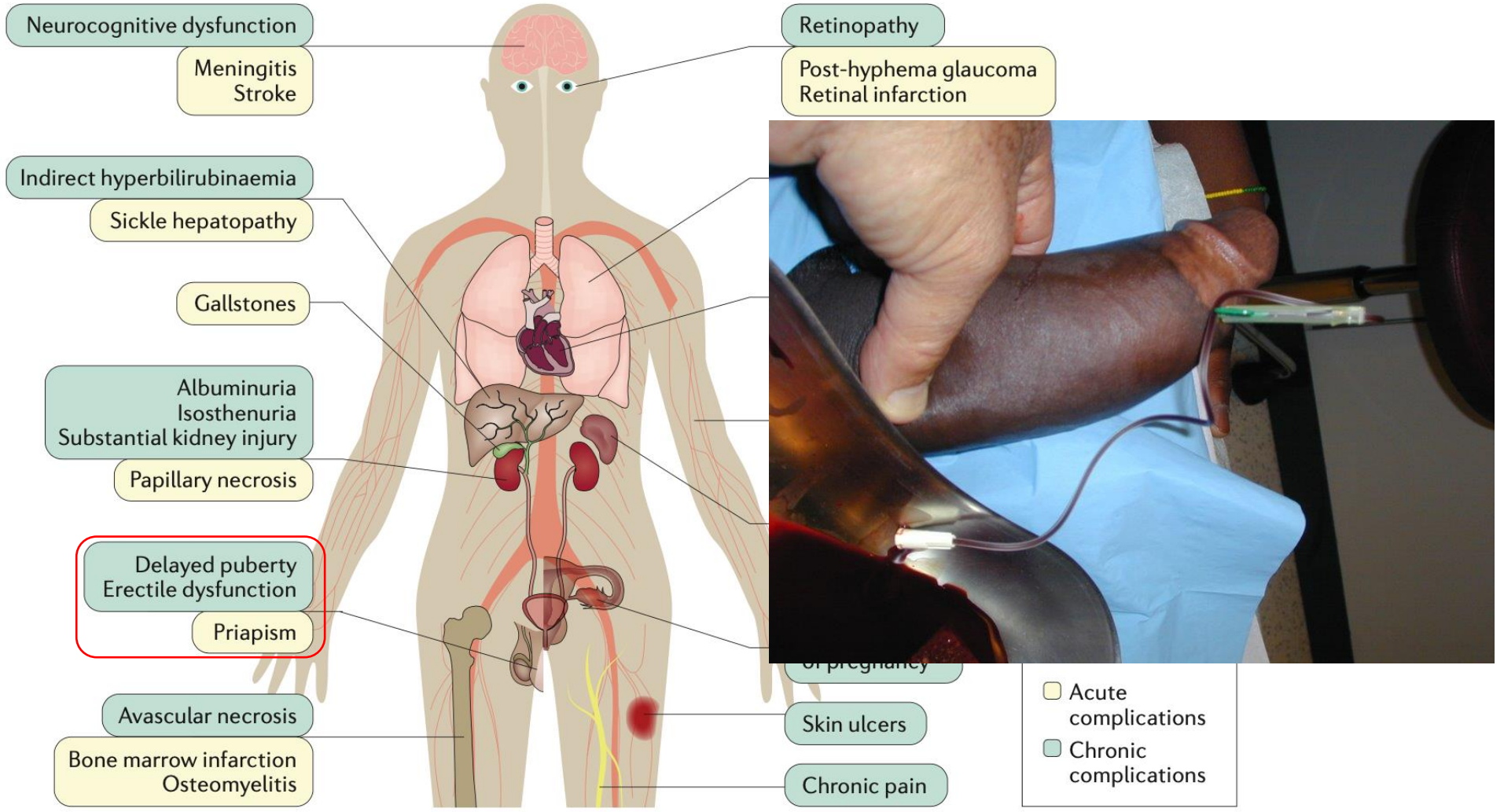


8-10% CKD 2 or more (4% ESRD)

CKD-EPI
NON corrected for ethnicity

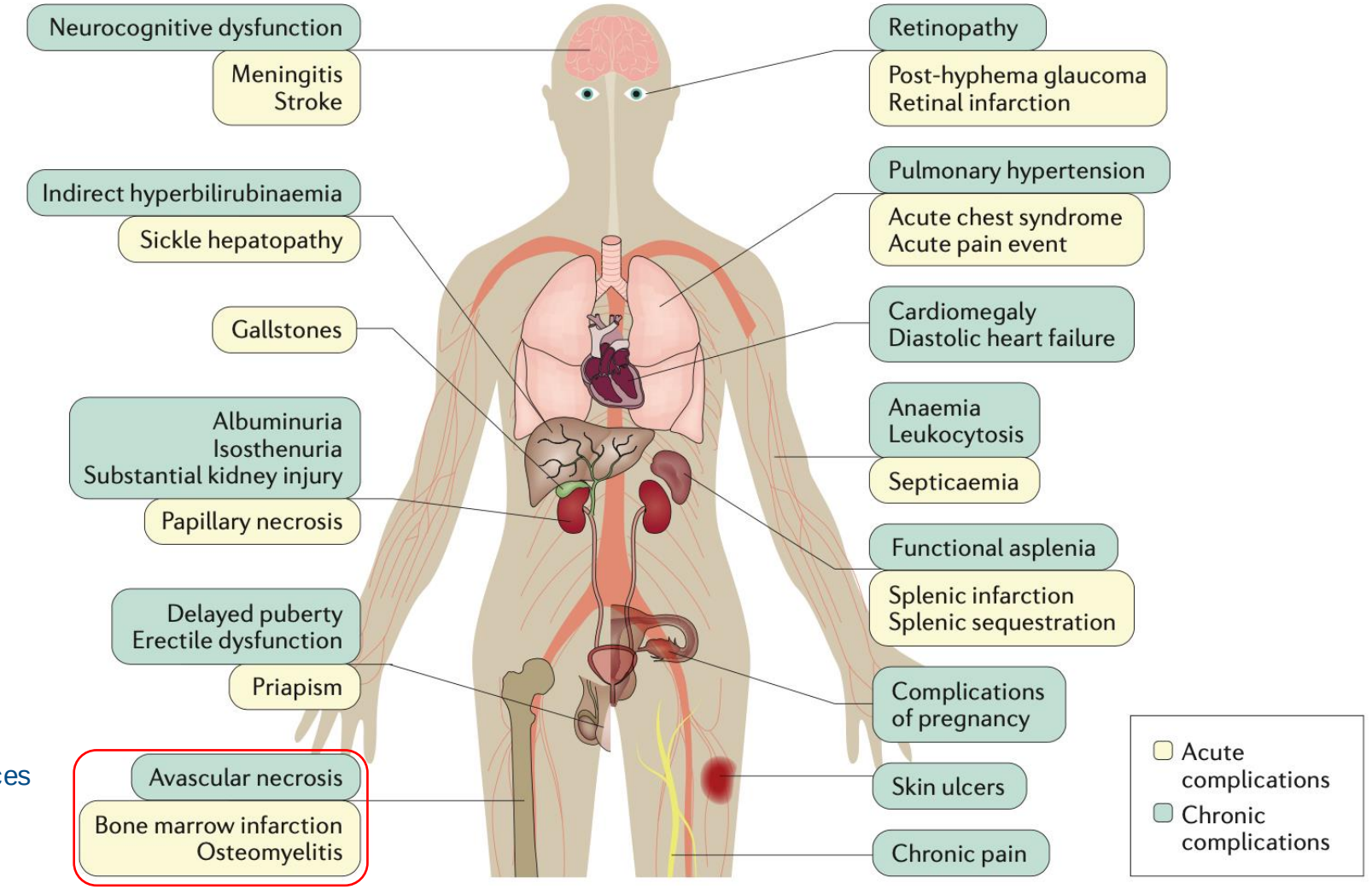
Hyperfiltration (eGFR >110mL/min)

Complications



Priapism : 2-95%

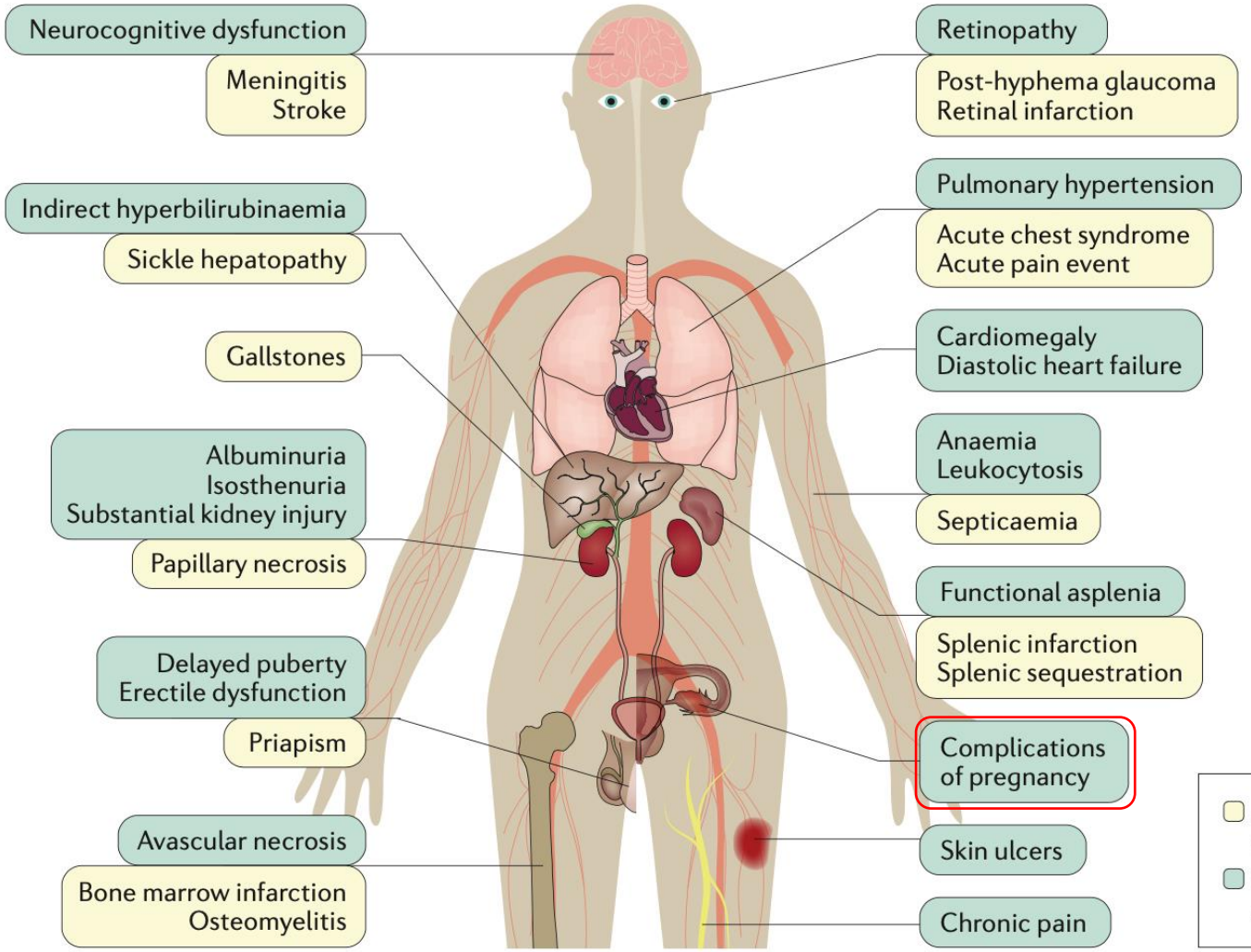
Complications



Functionnal consequences

Chronic pain

Complications



RR 3 for Pre-Eclampsia

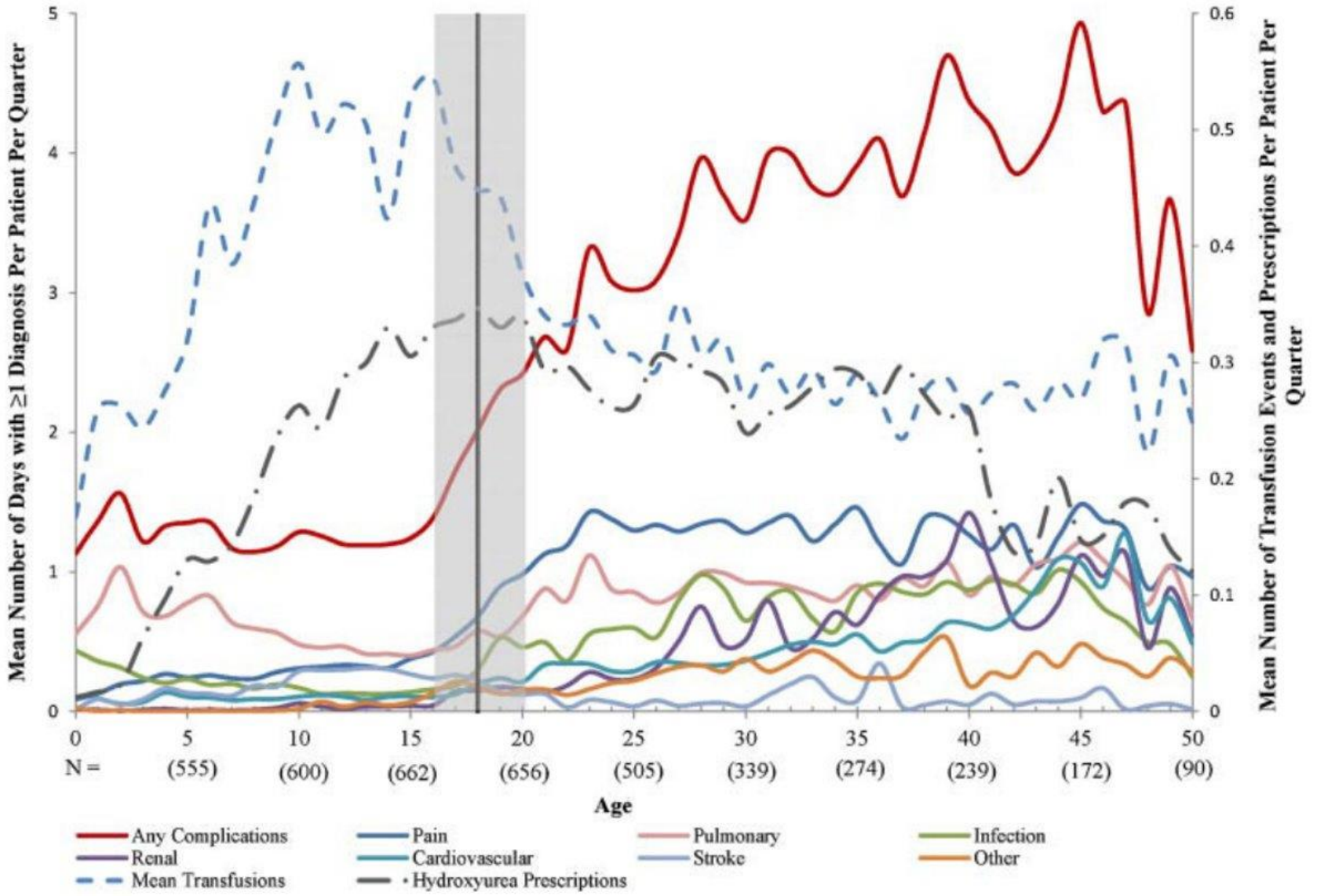
AAS prophylaxis

RR 7 for thrombosisHBPM
6 weeks post-partum

Complications

Complications

Median age of death :
31 – 45 years old

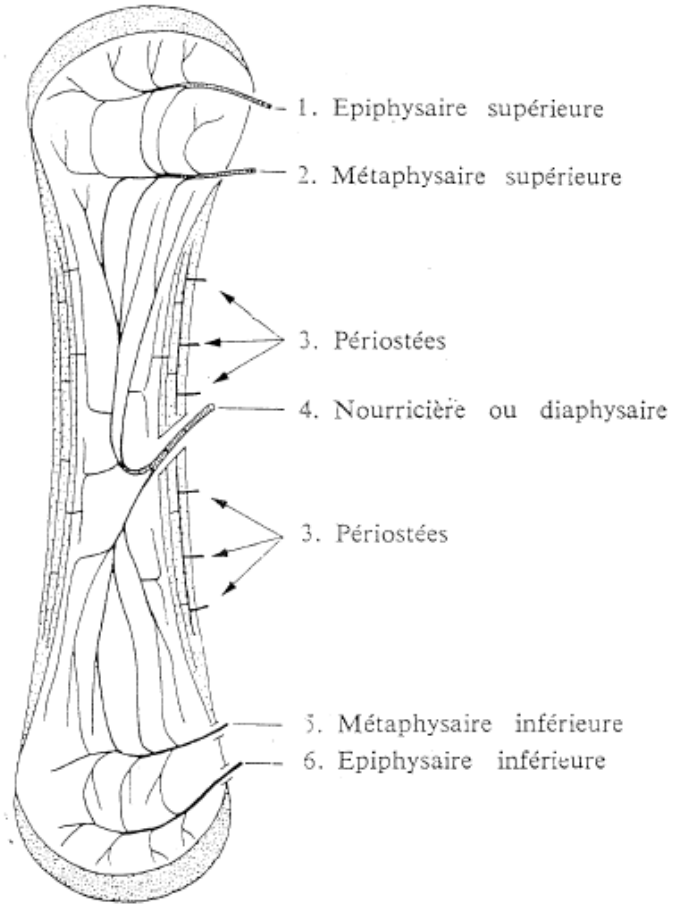


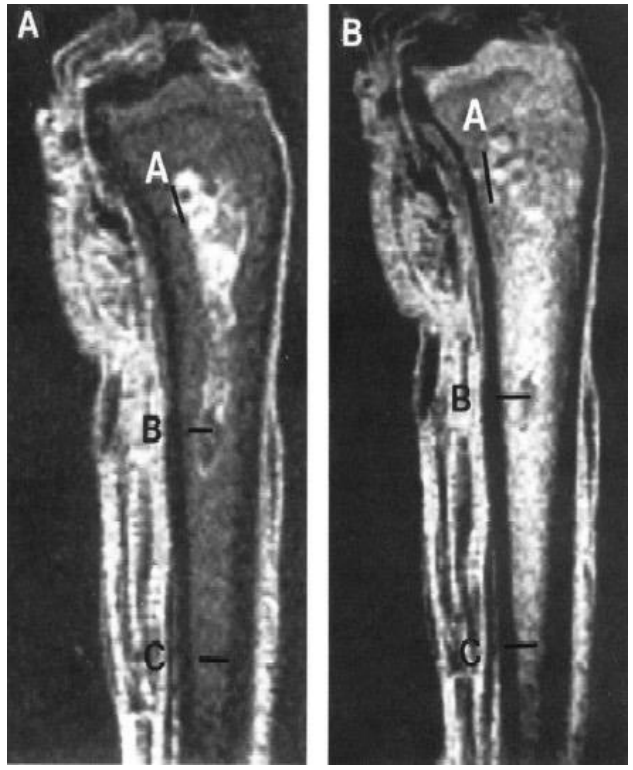
Then, chronic patients looking for more painkillers ?

Pain – Vaso-occlusive crisis (VOC)

- Causing 95% of hospitalisations
- Osteo-articular pain
  - Paroxytisc and intense
  - Localised / diffuse
  - Functionnal impotency

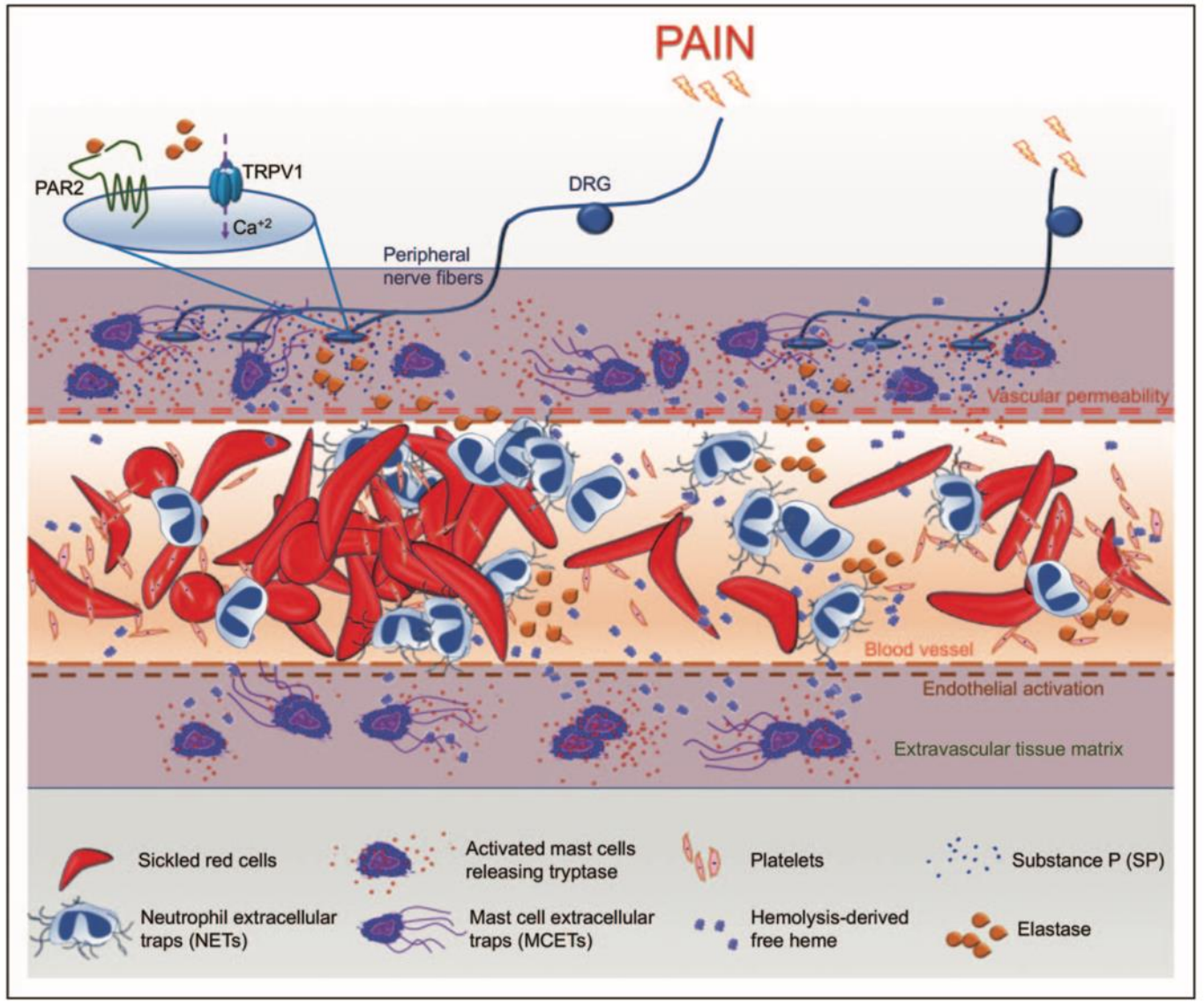
Pain – Vaso-occlusive crisis (VOC)





IRM T2

Pain – Vaso-occlusive crisis (VOC)



Aich *et al. Curr Opin Hematol* 2019

Pain – Vaso-occlusive crisis (VOC)

Table 2. Cox Model to Examine the Relationship between VOC and Complications

Outcomes among Sickle Cell patients (N=20,909)	Results from Cox Model for Follow-up VOC			
	HR	95% CI		p-value
Time-to-Death[a]	1.56	1.19	2.05	0.0014
Time-to-Acute Chest Syndrome[b]	58.67	50.21	68.55	<0.0001
Time-to-Splenic Sequestration[c]	43.99	30.65	63.13	<0.0001
Time-to-Pulmonary Embolism[d]	2.82	2.21	3.58	<0.0001
Time-to-Stroke[e]	2.26	1.94	2.63	<0.0001
Time-to-Pulmonary hypertension[f]	4.12	3.14	5.41	<0.0001

Pain – Vaso-occlusive crisis (VOC)

Pain = Emergency

TRIAGE :
VERY URGENT

First pain killers within 30 mn
PainScale < 4 within 60 mn

VOC – Red Flags

Unsual charecteristic or localisation of pain

Chest pain or respiratory symptoms

No trigger

Analsegia

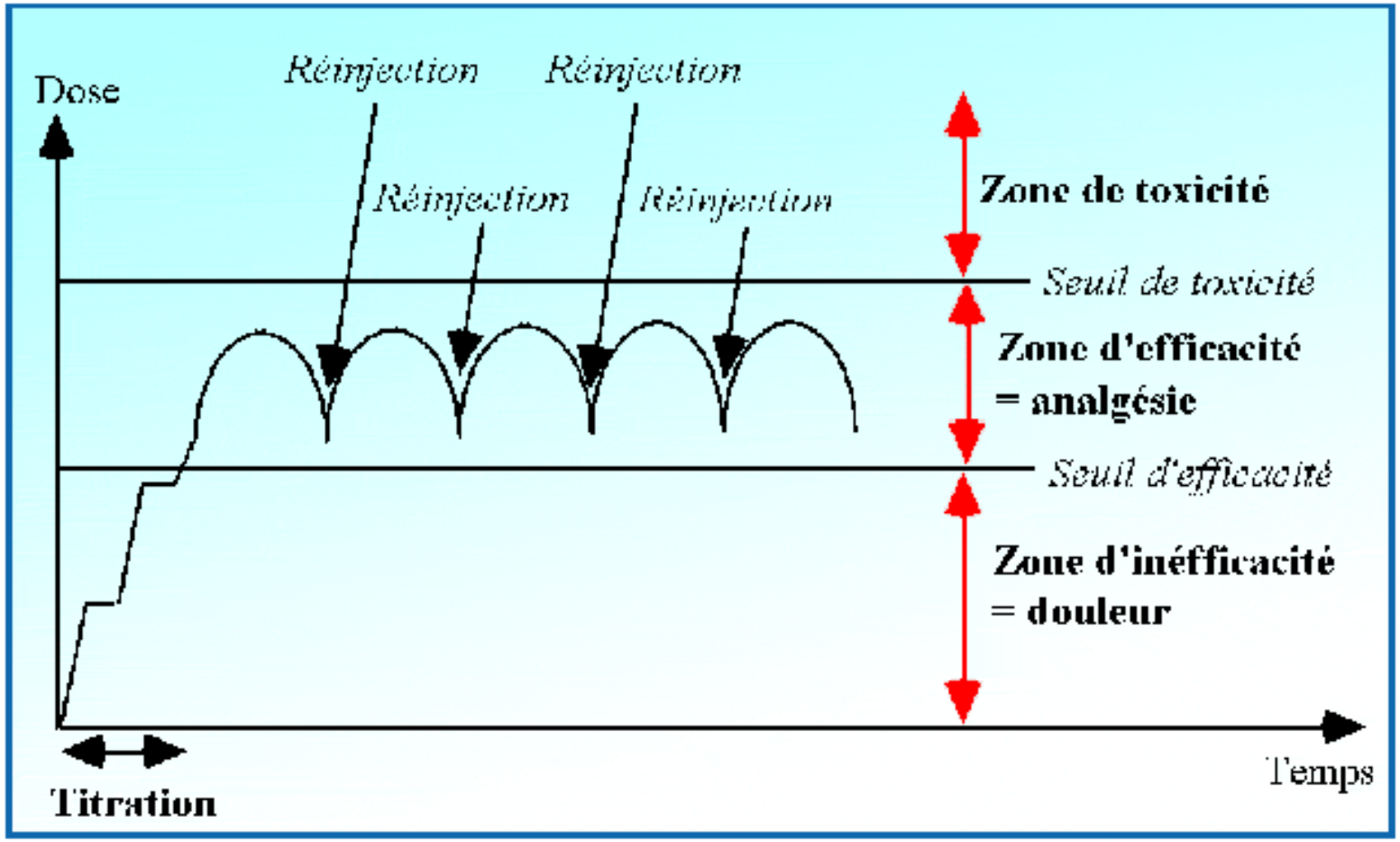
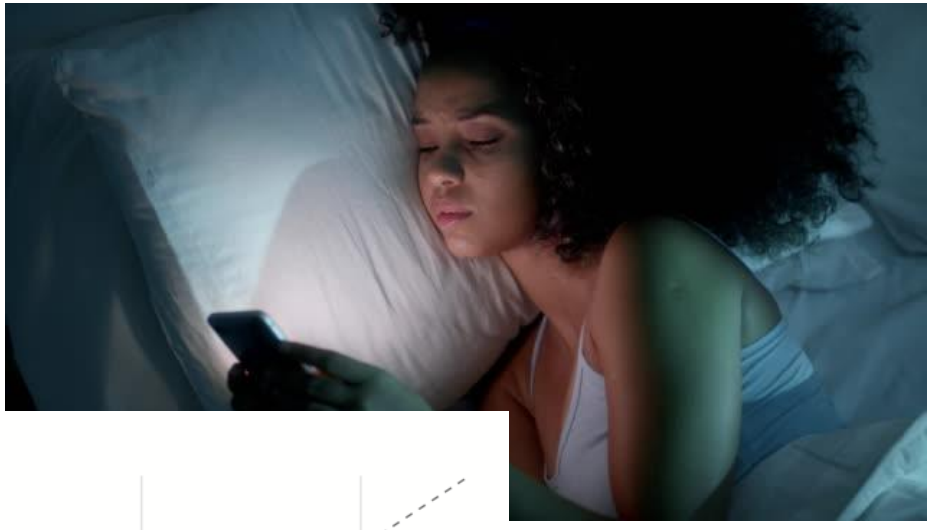


Figure 3 : Technique d'analgésie morphinique correcte associant une titration initiale et des réinjections à bonne posologie et à horaires fixes permettant de maintenir les seuils plasmatiques d'analgésique dans la zone d'efficacité. [7]

Pain perception *vs* Pain expression

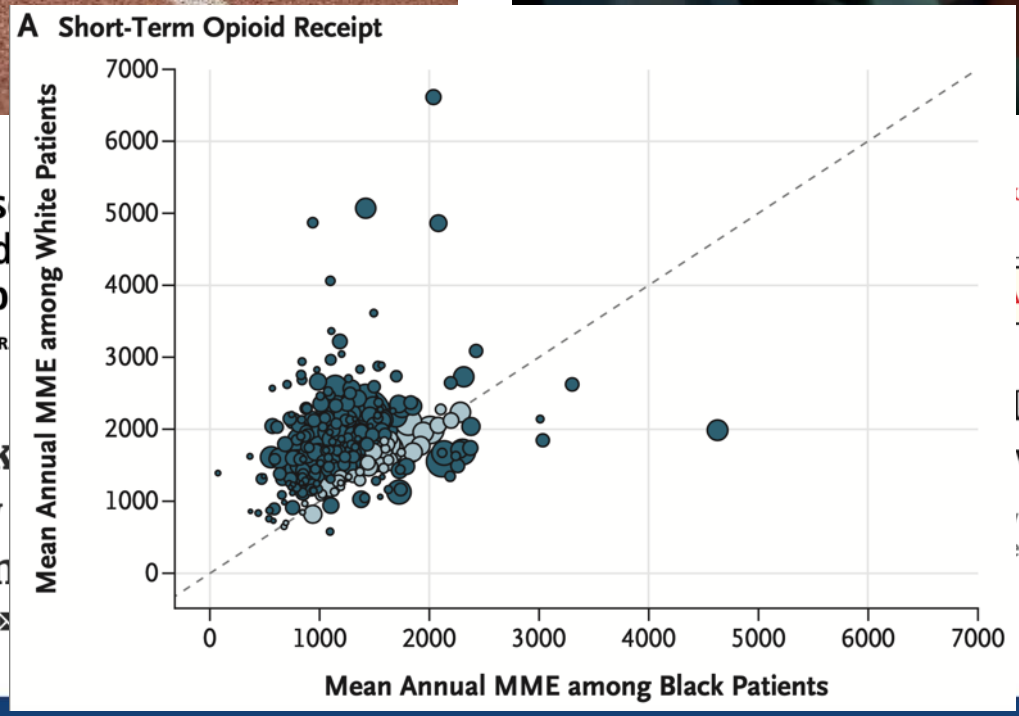


Racial bias in pain ass
recommendations, and
differences between b

Kelly M. Hoffman[a,1], Sophie Trawalter[a], Jordan R

Time to Take Stock
Systematic Review
Disparities for Pain

Salimah H. Meghani, PhD, MBE



URNAL of MEDICINE

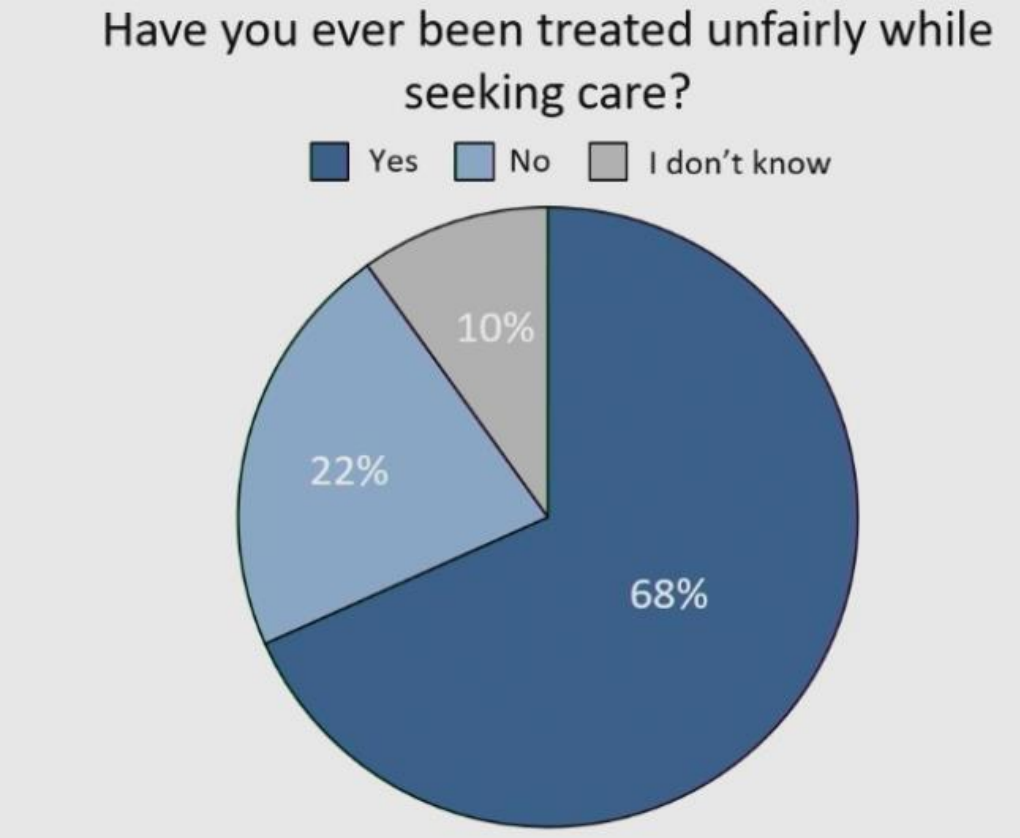
RTICLE

Prescription Opioid
vidual Health Systems

n, M.P.H., Andrew Wood, M.P.H.,
ara, Ph.D.

Pain perception *vs* Pain expression

Because of race (67%)



Because of requesting more pain medicine (65%)

Approximately 60% of participants felt that the **health care system treats people unfairly** based on **race or ethnic background** "quite a bit" or "very much"

Morphine

Titration of morphine (IV)

In case of AKI prefer Piritramide (Dipidolor®) (equianalgesia 1:1)

Loading dose : 0,1 mg/kg

Re-infusion every 5-10 minutes → ENS < 4

Monitoring of respiratory rate and sedation

STOP TITRATION : RR < 10 or sedation (EDS ≥ 2)

Échelle de Sédation (EDS)

S0 : Pas de sédation, patient bien éveillé

S1 : Patient somnolent, stimulable verbalement

S2 : Patient somnolent, stimulable tactilement

S3 : Patient non réveillable, comateux

Co-analgesic

- Paracetamol 1g / 6h
- Diclofenac : 75mg then 37,5mg/6h

- Clonidine (Catapressan®) : 75micrograms IV in 30 min (monitoring) then *per os*

- **Hot water bottles**

Adjuvants

- Hydratation IV :
  Ionolyte ® 84mL/h

- Prophylactic anticoagulation
  First dose in the ER

- Oxygenotherapy : 2L/min

How could we miss a severe complication ?

Clinical example

- Woman – 19 ans
- SS Homozygoty
  - No chronic organ damage
  - Hydrea 1000mg qd
  - 1 hospitalization a year for VOC
- D3 : Saturation 93%
  Abnormal pulmonary auscultation

Acute Chest Syndrome

Definition

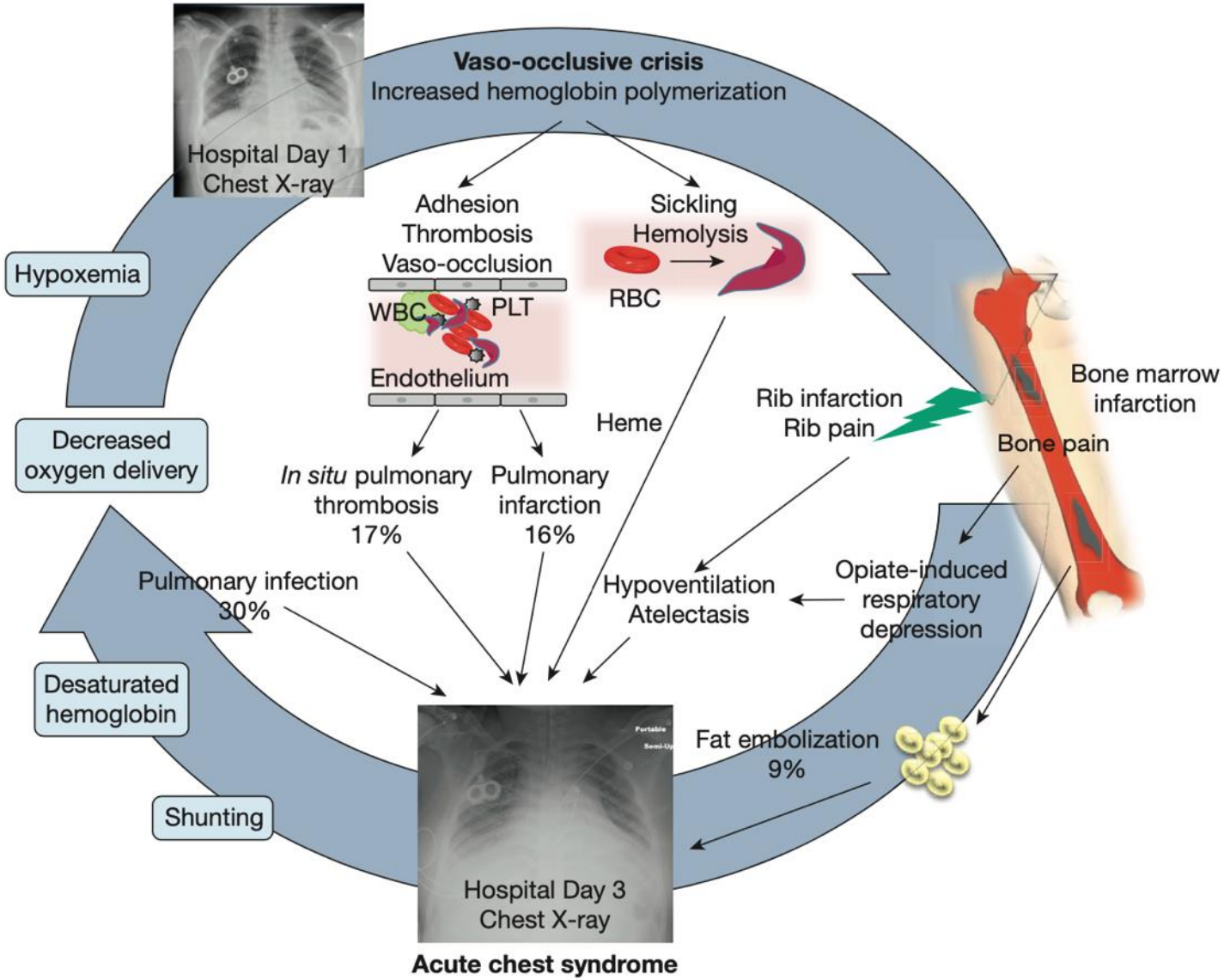
At least 2 of 3 critera among :

- Abnormal auscultation
- Radiographic abnormality
- Chest pain (55-95%), dyspnoea (50-60%) or fever (60-80%)

Epidemiology - Risk

- 2nd more frequent acute complication
- 50% are preceded by a VOC
- Onset on average within 2-3 days after a VOC
- **Mortality 10%** - 13% need invasive ventilation

Acute Chest Syndrome



ACS - Evaluation

Biological

– NO D-dimers dosage

Imaging

– Pleuro-pulmo US

Parameters	All Episodes (n = 44)	Lung Ultrasound Score: Lower Values (n = 25)	Lung Ultrasound Score: Higher Values (n = 19)	P
Treatment				
Oxygen flow, L/min	4 [3–8]	4 [3–6]	6 [4–12]	0.02
Antibiotics	43 (98)	24 (96)	19 (100)	>0.99
Antibiotics duration, d	7 [5–9]	7 [5–10]	7 [5–8]	0.76
Transfusion	36 (82)	18 (72)	18 (95)	0.11
Total number of transfused red blood cell units	4 [2–6]	2 [0–4]	6 [3–6]	<0.01
Total volume of exsanguinated blood, mL	450 [0–1488]	250 [0–700]	1150 [350–2050]	<0.01
Outcome				
Mechanical ventilation	11 (25)	3 (12)	8 (42)	0.04
Noninvasive	11 (25)	3 (12)	8 (42)	0.04
Invasive	3 (7)	0 (0)	3 (16)	0.07
ICU stay, d	5 [3–8]	4 [2–7]	7 [5–8]	0.02
ICU death	0 (0)	–	–	–

Razazi, K. *et al. Medicine* (2016)

LU Score : Bouhemad, B. *et al. Critical Care Medicine* (2010)

STA - Evaluation

Imaging

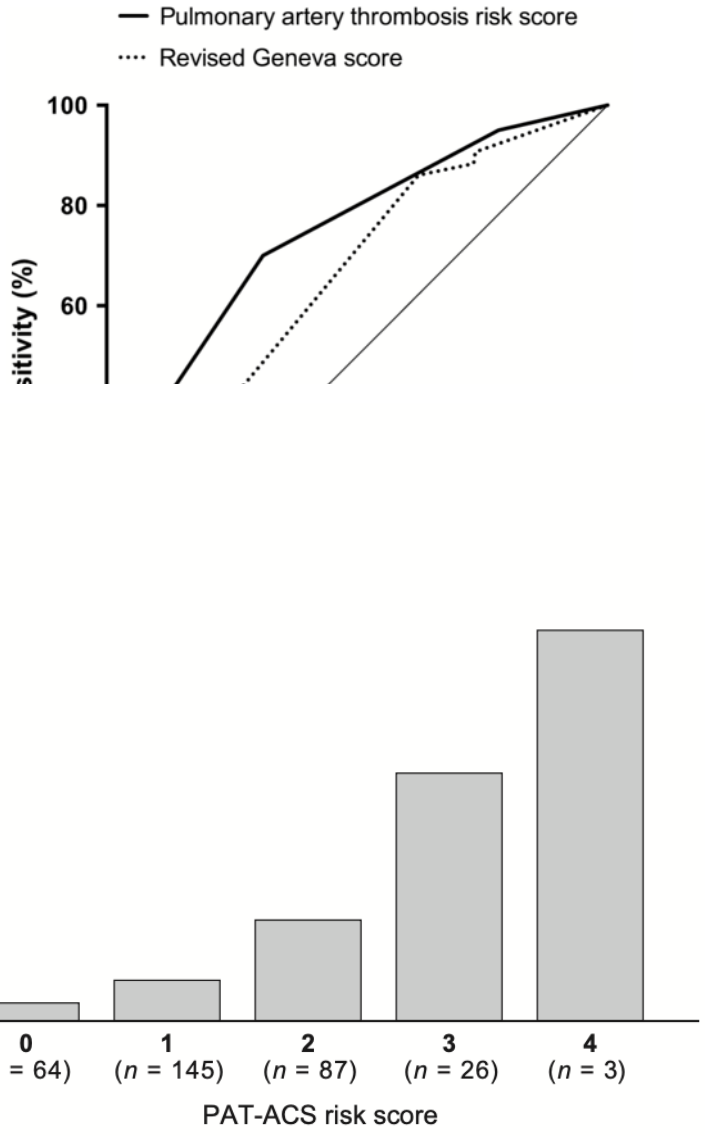
- Pleuro-pulmonar US
- Chest Xray
- Chest-CT ?

Pulmonary arterial thrombosis in ACS
PAT-ACS Risk Score

Variable	OR (95% CI), p value	Score weight
Baseline total hemoglobin > 8.2 g/dL		
No	1	0
Yes	3.32 (1.48-7.45), p=0.004	1
No triggering factor*		
No	1	0
Yes	2.00 (0.98-4.11), p=0.057	1
Platelet count >440.10^9/L*		
No	1	0
Yes	3.88 (1.88-8.00), p<0.001	1
$PaCO_2$ <38 mmHg*		
No	1	0
Yes	3.14 (1.37-7.18), p=0.007	1

Point cut-off*	NPV (95% CI)	PPV (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)
0	-	12.3% (8.9-16.4)	0.0% (0.0-1.3)	100.0% (91.2-100.0)
1	96.9% (89.2-99.6)	14.6% (10.5-19.4)	21.8% (17.1-27.0)	95.0% (83.1-99.4)
2	94.2% (90.1-97.0)	23.9% (16.5-32.7)	68.8% (63.0-74.1)	70.0% (53.5-83.4)
3	90.8% (87.0-93.9)	43.3% (25.2-62.9)	94.0% (90.6-96.5)	32.5% (18.6-49.1)
4	88.2% (84.2-91.0)	66.7% (9.4-99.2)	99.7% (98.1-100.0)	5.0% (0.6-16.9)

Cut-off 2



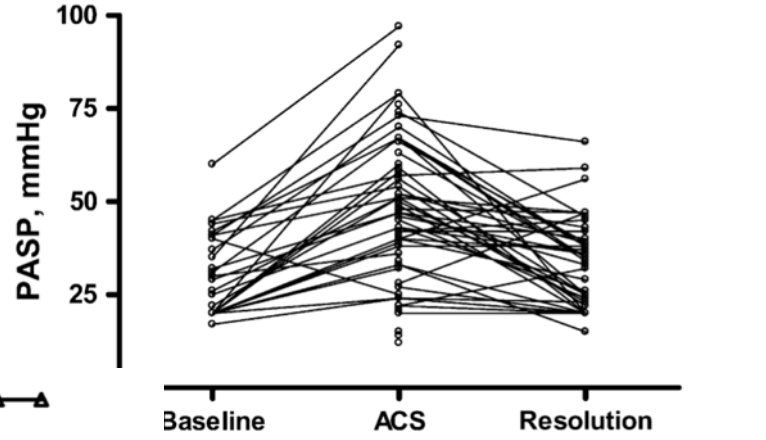
ACS - Severity

Severity criteria

- Hypoxemia with PaO2 < 70mmHg
- « classical » (hemodynamics, neuro, …)
- Acute pulmonary hypertension

In case of severe ACS :

- Chest-CT
- Cardiac US



ry artery systolic pressure (PASP) at baseline (n = 29),
e chest syndrome (ACS) (n = 84), and after its
. PASP was estimated from tricuspid regurgitant jet

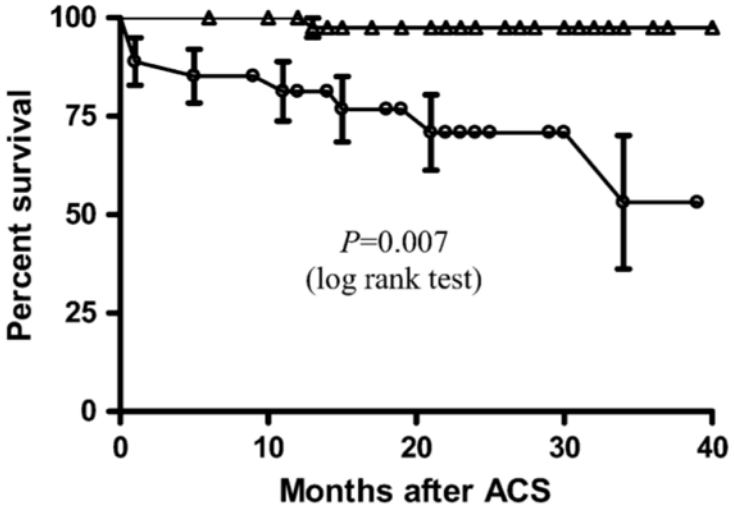


Figure 4. Kaplan-Meier long-term survival curves according to tricuspid regurgitant jet velocity (TRV) during severe acute chest syndrome (ACS). *Triangles*, TRV < 3 m/second during all episodes (n = 43, deaths = 1); *circles*, TRV ⩾ 3 m/second during at least one episode (n = 27, deaths = 8).

That's RBC disease…
Why not just give them blood ?

Indication for transusion in acute setting

- Acute anemia (> 2g below baseline), poorly tolerated and hypoproliferative
- Severe Acute Chest Syndrome
- Stroke
- Any acute organ damage due to SCD complication or not
- Prophylactic transfusion befor major surgery

NOT

- Chronic anemia even at a « very » low level
- Severe pain
- Non-severe ACS
- Recently (<30days) transfused patient
- Allo-immunized patient

Clinical example

- Woman – 19 ans
- SS Homozygoty
  - No chronic organ damage
  - Hydrea 1000mg qd
  - 1 hospitalization a year for VOC
- D3 : Saturation 93%
  Abnormal pulmonary auscultation
- D4 : OTI – Prone position
- Exchange transfusion with rapid improvement

Clinical example

Hémoglobine	↓ 10.5
Hématocrite	↓ 31.5
MCV	86.1
MCH	28.7
MCHC	33.3
RDW	↑ 19.5
Réticulocytes	↑ 5.79
Réticulocytes absolus	↑ 211.9
Plaquettes	284
MPV	↑ 11.1
Fraction reticulo.immature	↑ 30.1
ormule leucocytaire	
Polyneutrophiles	62.7
Polyneutrophiles absolus	↑ 7.21
Erythroblastes	↑ 16.5
Erythroblastes absolus	1.9
echerche/Suivi d'une moglobinopathie	
moglobine ormale/thalassémies	
Hb A	75
Hb A2 (par élec. capillaire)	↑ 3.4
Séparation des Hbs à pH 9,4	Hb A + Hb F + Hb S (20%)

Numération	
Vérification	Formule réalisée au microscope
Leucocytes	10.77
Globules blancs corrigés	8.25
Globules rouges	↓ 1.56
Hémoglobine	↓↓ 5.2
Hématocrite	↓ 14.5
MCV	92.9
MCH	33.3
MCHC	35.9
RDW	↑ 21.6
Réticulocytes	↑ 6.26
Réticulocytes absolus	97.7
Plaquettes	341

Hémoglobine anormale/thalassémies	
Hb A	15
Hb A2 (par élec. capillaire)	↑ 5.9
Hb F	↑ 7.2
Séparation des Hbs à pH 9,4	Hb F + Hb A + Hb S (72%)

LDH 2650 UI/L

Blood groups

Génotypage érythrocytaire	
RH2 C	Negatif
RH3 E	Negatif
RH4 c	Positif
RH5 e	Positif
KEL1 K	Negatif
KEL2 k	Positif
KEL3 Kpa	Negatif
KEL4 Kpb	Positif
KEL6 Jsa	Negatif
KEL7 Jsb	Positif
FY1 Fya	Negatif
FY2 Fyb	Negatif
JK1 Jka	Positif
JK2 Jkb	Negatif
MNS1 M	Negatif
MNS2 N	Positif
MNS3 S	Negatif
MNS4 s	Positif
LU1 Lua	Negatif
LU2 Lub	Positif
DI1 Dia	Negatif
DI2 Dib	Positif
CO1 Coa	Positif
CO2 Cob	Negatif
DO1 Doa	Negatif
DO2 Dob	Positif
DO4 Hy	Positif
DO5 Joa	Positif
LW5 Lwa	Positif
LW7 Lwb	Negatif
SC1 Sc1	Positif
SC2 Sc2	Negatif
HEA commentaire	Système FY : Présence du polymorphisme correspondant à l'allèle FY*2 à l'état homozygote. Présence de la mutation -67 T>C (mutation GATA) dans la région promotrice des allèles FY*2 à l'état homozygote. Phénotype érythrocytaire attendu: FY:-1,-2. Système RH: Présence de la mutation c.733C>G à l'état hétérozygote au niveau de l'exon 5 de l'allèle RHCE*ce.

Sounds complicated.
Any forbidden drugs ?

“Start / Stop” drugs

Corticosteroids :

CONTRA-INDICATION !! – Severe ACS

Pas si HbS>60%

Hydroxyurea

Reduce or hold in case of low reticulocyte count (RPI<2,5-3)

Carefull in case of renal failure

Benzodiazepines :

Risk of respiratory depression when combined with opiods

“Start / Stop” drugs

G6PD defic
35% of C

Acide acétylsalicylique (Aspirine)	😐
Acide ascorbique (Vitamine C)	😐
Acide nalidixique$	✖
Acide pipémidique	☹
Antipyrine (voir Phénazone)	☹
Aspirine (voir Acide acétylsalicylique)	😐
Bleu de méthylène (voie injectable)*	✖
Carbutamide$	☹
Chloroquine	☹
Ciprofloxacine	☹
Dapsone	✖
Dimercaprol	☹
Enoxacine	☹
Fluméquine	☹
Glibenclamide	☹
Glibornuride$$	☹
Gliclazide	☹
Glimépiride	☹
Glipizide	☹
Hydroxychloroquine	☹
Lévofloxacine	☹
Loméfloxacine	☹
Métamizole sodique (voir Noramidopyrine)$ $	✖
Moxifloxacine	☹
Nitrofurantoïne	✖

Noramidopyrine (Métamizole sodique)$ $	✖
Norfloxacine (voie orale)	☹
Ofloxacine (voies orale et injectable)	☹
Paracétamol	😐
Péfloxacine	☹
Phénazone (voie cutanée et nasale)	☹
Phytoménadione (voir Vitamine K)	☹
Prilocaïne	☹
Primaquine*	✖
Quinine	☹
Rasburicase	✖
Spiramycine	☹
Streptokinase*	☹
Sulfacétamide$$	☹
Sulfadiazine (voie orale)	✖
Sulfadiazine (voie cutanée)	☹
Sulfadoxine	☹
Sulfafurazole	✖
Sulfaguanidine$	✖
Sulfaméthizol	☹
Sulfaméthoxazole	✖
Sulfasalazine	✖
Triméthoprime**	😐
Vitamine C (voir Acide ascorbique)	😐
Vitamine K_1 (Phytoménadione)	☹

Take-home messages

1. Rapid and aggressive pain management
2. Prevention and early detection of potentially lethal complication as ACS
3. DO NOT TRANSFUSE

4. **Rare diseases suffer from amateurism**
   Collaboration with expert centers serves patients

Thank You

Martin Colard
02 555 26 27

Martin.Colard@HUBruxelles.be

Red Blood Cells and Iron Disorders Unit

F.S. Benghiat, M. Colard, V. De Wilde, A. Theunissen, L. Dedeken, C. Devalck, E. Garforth, S. Diallo, B. Gulbis, JF. Lalière, A. Minet, G. Mpawenayo, A. Ngoma, P. Vachaudez