Delirium de Réanimation

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Encephalopathy

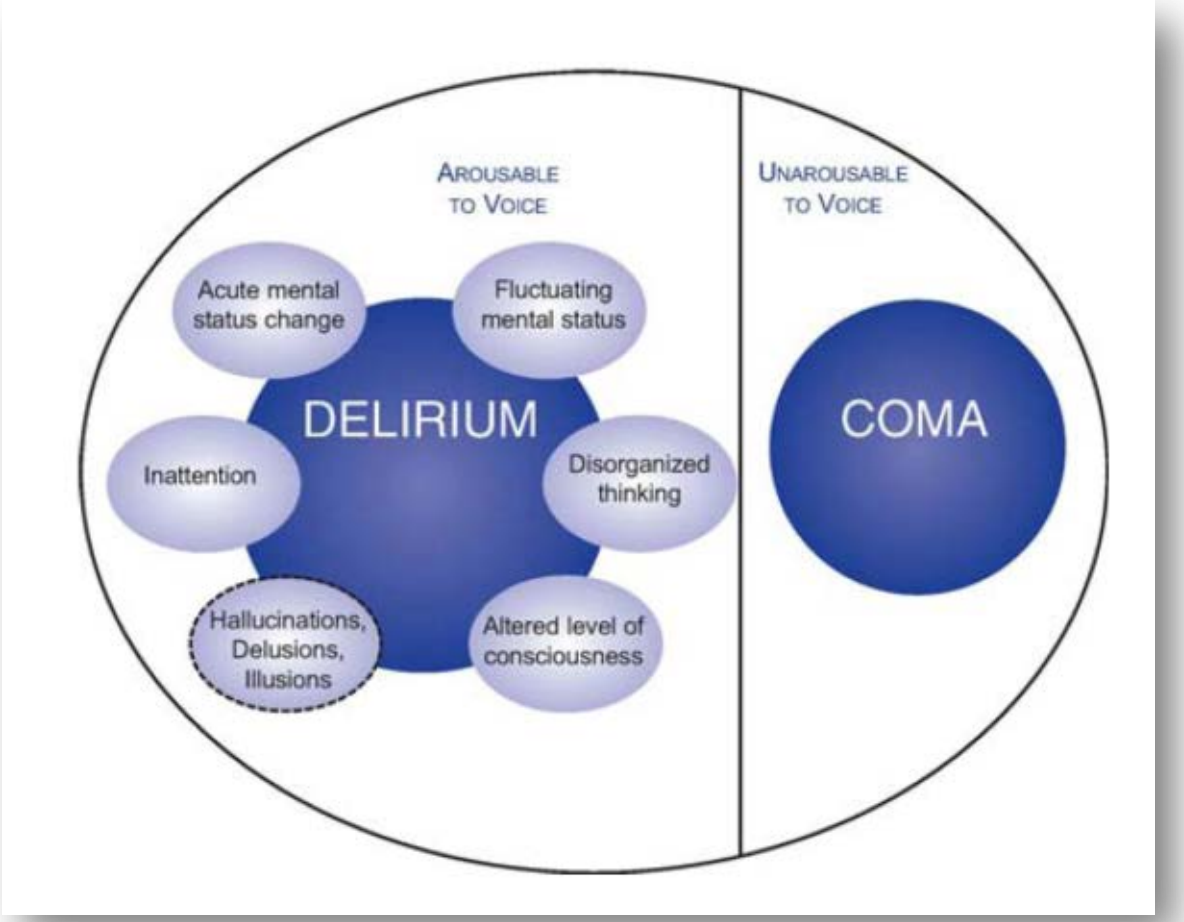
Disorder of consciousness

- Coma
- Delirium

+

Abnormal Electroencephalogram

Encephalopathy



Complete the neurological examination

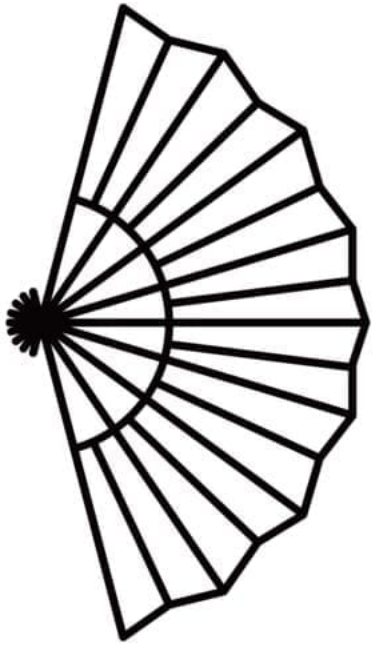
- Focal neurological sign
- Abnormal movements (seizures…)
- Neck stifness
- Flapping (delirium)
- Brainstem reflexes (coma)
- Dysautonomia

General examination

- Vital signs
- Risk factors for encephalopathy
- Seek for the medical cause

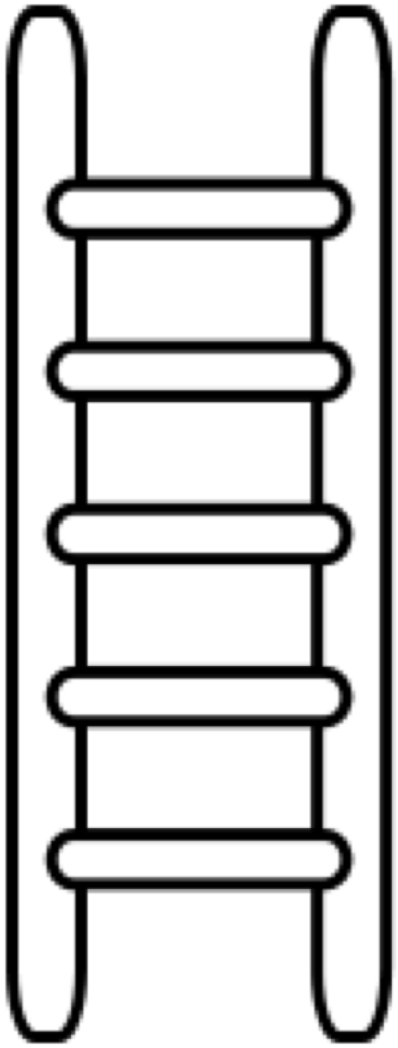
Consequence of medical condition, substance intoxication or withdrawal

Subtypes of delirium



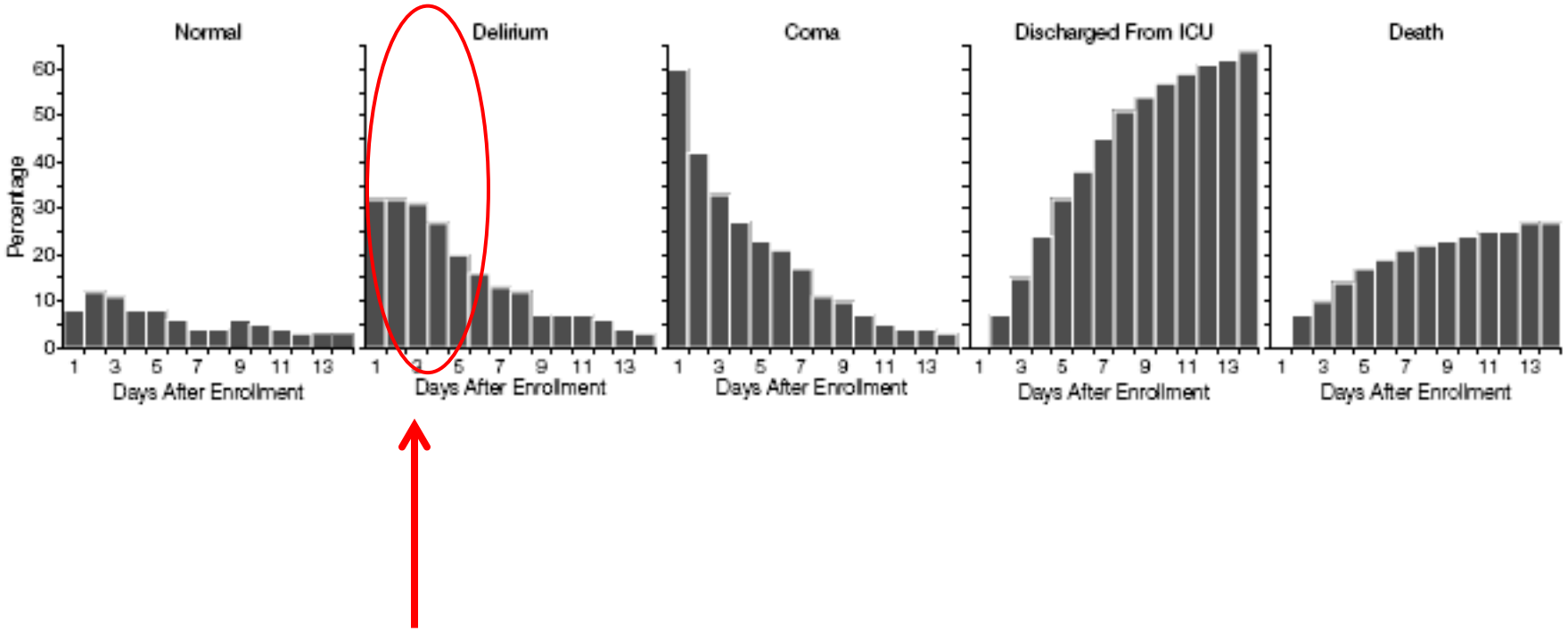
- **Hyperactive delirium:** agitation, agression, hallucination and disorientation
- **Hypoactive delirium:** prostration, motor slowness apathy, lethargia and withdrawal from interactions
- **Mixed delirium:** fluctuation between hyperactive and hypoactive subtypes

Hypoactive delirium



- Hypoactive delirium (HD) is **the most frequent subtype** of delirium
- HD can be easily misdiagnosed, necessity of routine detection by validated delirum scales
- **Age, dementia and severity of critical illness** increase the risk of HD
- HD is associated with **increased mortality** and impaired cognitive or functional outcomes
- **No specific treatment than those proposed in delirium**

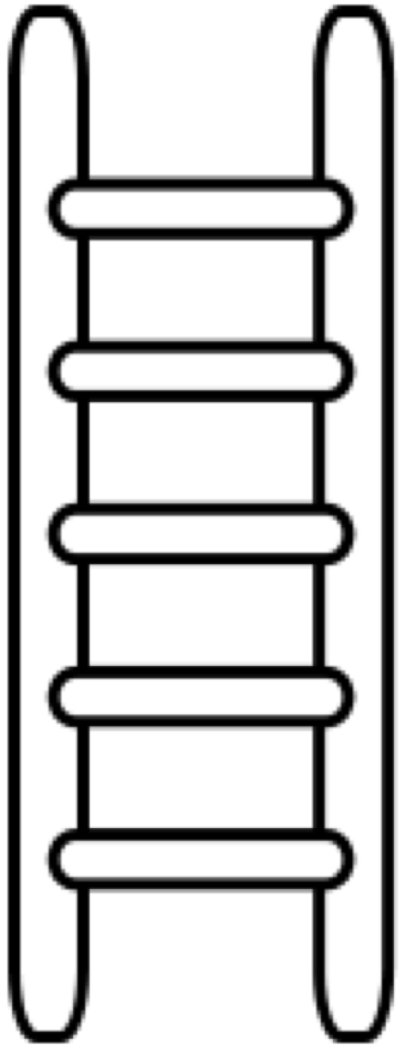
Time distribution



Early occurrence

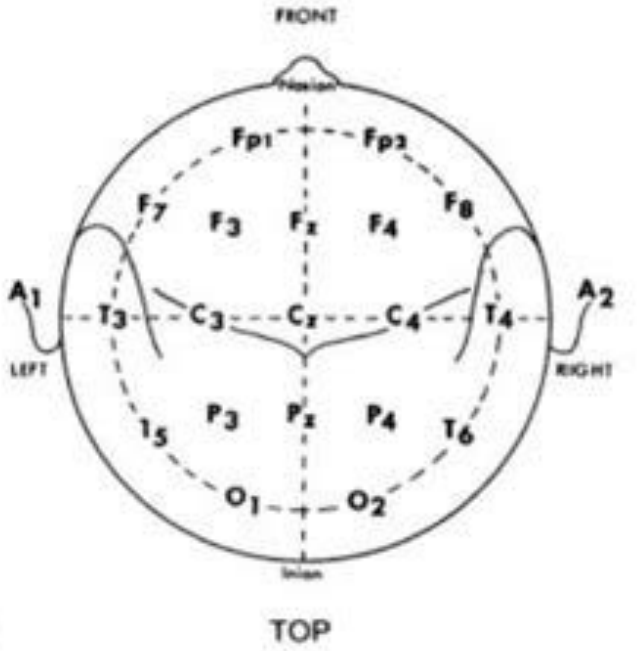
Ely et al – JAMA - 2004

EEG features

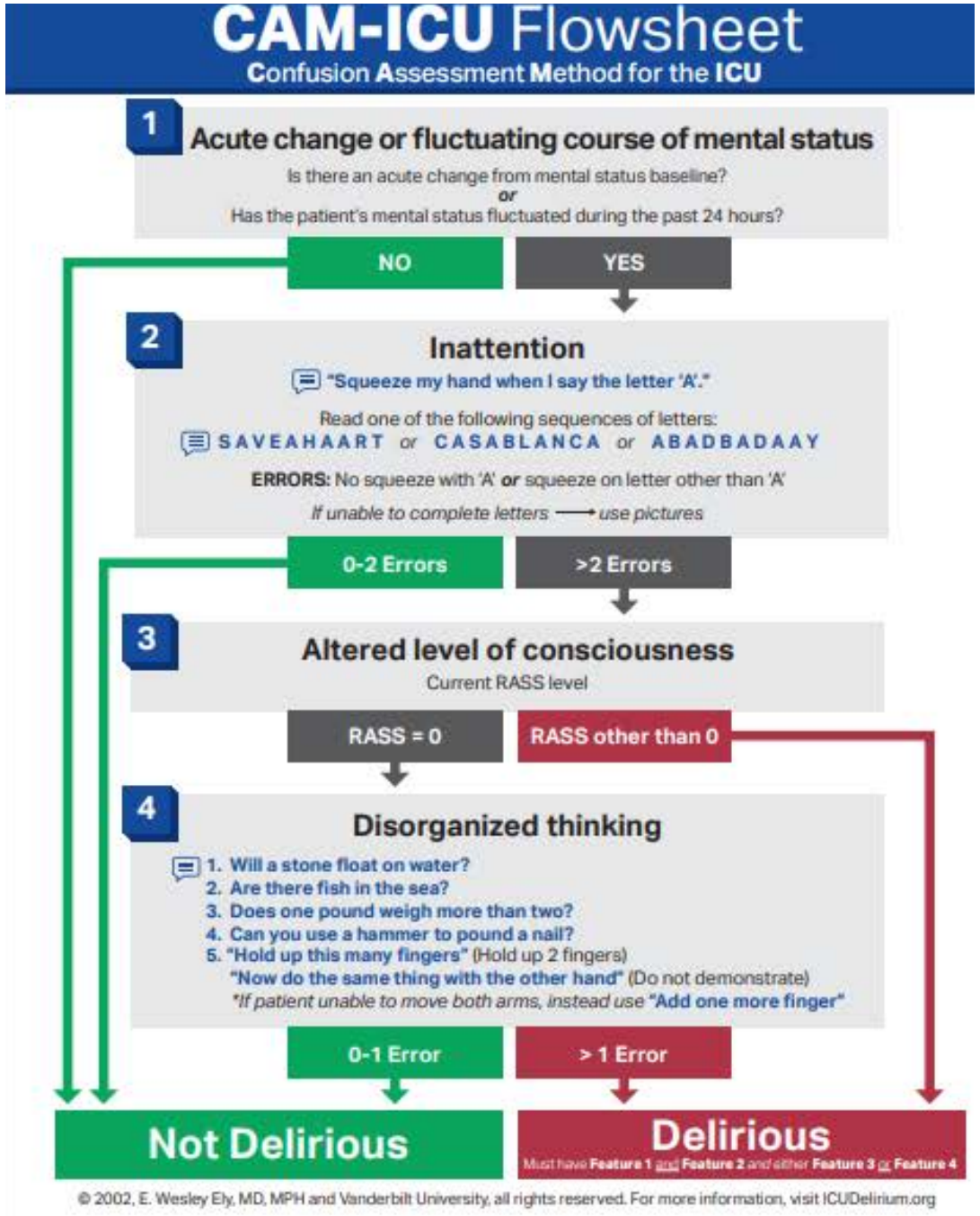


- **Most frequent EEG features**: Generalized slowing with increased theta and delta activity
- **Marker of severe encephalopathy**: Periodic discharges, triphasic waves, burst suppression, electrographic seizures less frequent but markers of severity
- **Delirium is characterized** by decreased variability in quantitative EEG and impaired connectivity.
- **EEG correlates of delirium**: Electrographic seizure more frequently seen in ICU patients with delirium
- **Prognostic predictors**: Absence of reactivity ++++
- **Delirium predictor**: Generalised slowing and absent reactivity

When doing an EEG in delirium?



- No clear recommendation
- Standard versus continuous EEG?
- Abnormal movement suggesting seizure
- Pro-epileptogenic factors (neurotoxic drugs, withdrawal…)
- Persistent encephalopathy
- Treating electrographic seizure (Yes?)
- Evaluating risk of delirium
- Prognostic evaluation



Kurtz et al – Current opinion - 2024

ICU Delirium Screening Checklist

The Intensive Care Delirium Screening Checklist

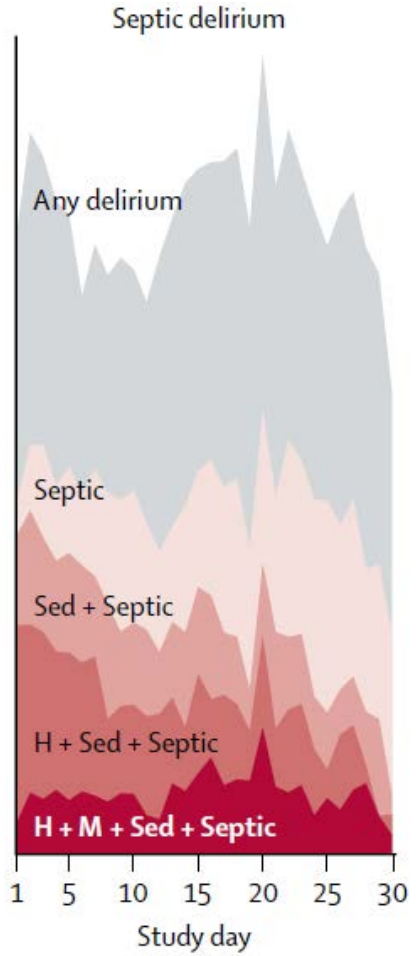
Checklist Item	Description
Altered level of consciousness[a]	
A	No response
B	Response to intense and repeated stimulation
C	Response to mild or moderate stimulation
D	Normal wakefulness
E	Exaggerated response to normal stimulation
Inattentiveness	Difficulty following instructions or easily distracted
Disorientation	To time, place, or person
Hallucination-delusion-psychosis	Clinical manifestation or suggestive behavior
Psychomotor agitation or retardation	Agitation requiring use of drugs or restraints, or slowing
Inappropriate speech or mood	Related to events or situation, or incoherent speech
Sleep/wake cycle disturbance	Sleeping <4 hours/day, waking at night, sleeping all day
Symptom fluctuation	Symptoms above occurring intermittently
Total score	0 to 8

Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study

	Prevalence among participants (N=1040)	Frequency among delirium days (N=4187)	Duration among participants affected
Any delirium	740 (71%)	4187 (100%)	4 (2–7)
Hypoxic	579 (56%)	2247 (54%)	3 (1–5)
Septic	534 (51%)	2405 (57%)	3 (2–6)
Sedative-associated	663 (64%)	2634 (63%)	3 (1–5)
Metabolic	260 (25%)	1149 (27%)	3 (1–6)
Unclassified	224 (22%)	591 (14%)	2 (1–3)

Data are n (%) or median (IQR).

Table 2: Prevalence and duration of delirium phenotypes



Girard et al – LRM - 2018

Predeleric score

Formula for PRE-DELIRIC model

Risk of delirium = 1/(1+exp–(–6.31

+ 0.04 × age

+ 0.06 × APACHE-II score

+ 0 for non-coma or 0.55 for drug induced coma or 2.70 for miscellaneous coma or 2.84 for combination coma

+ 0 for surgical patients or 0.31 for medical patients or 1.13 for trauma patients or 1.38 for neurology/neurosurgical patients

+ 1.05 for infection

+ 0.29 for metabolic acidosis

+ 0 for no morphine use or 0.41 for 0.01-7.1 mg/24 h morphine use or 0.13 for 7.2-18.6 mg/24 h morphine use or 0.51 for >18.6 mg/24 h morphine use

+ 1.39 for use of sedatives

+ 0.03 × urea concentration (mmol/L)

+ 0.40 for urgent admission))

The scoring system's intercept is expressed as –6.31; the other numbers represent the shrunken regression coefficients (weight) of each risk factor.

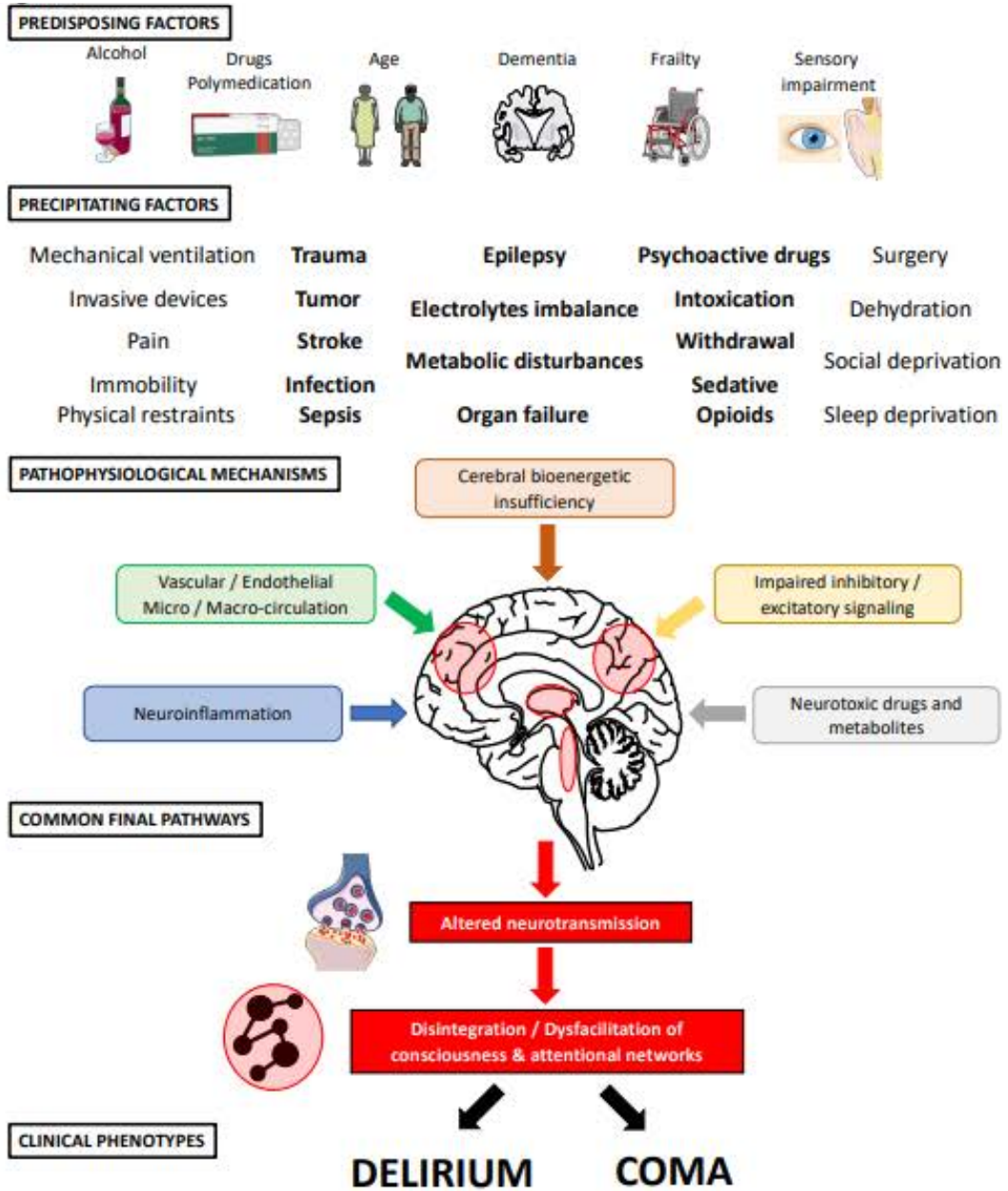
Van den Bogaard et al – BMJ - 2012

Causes

1. Primary CNS disorders
2. Epilepsia
3. Organ failure (Renal, Liver, Heart, Respiratory..)
4. Metabolic disturbances/ Dehydratation
5. Hypoxemia/acido-basis disturbances
6. Drugs side-effects (AB etc..)
7. Withdrawal (druges, alcohol…)
8. Deficiencies (Vitamines)
9. Endocrinopathies
10. Infection
11. Pain/Retention/Discomfort/Sleep deprivation/anxiety…

Brain Imaging
EEG
CSF
Standard biological tests

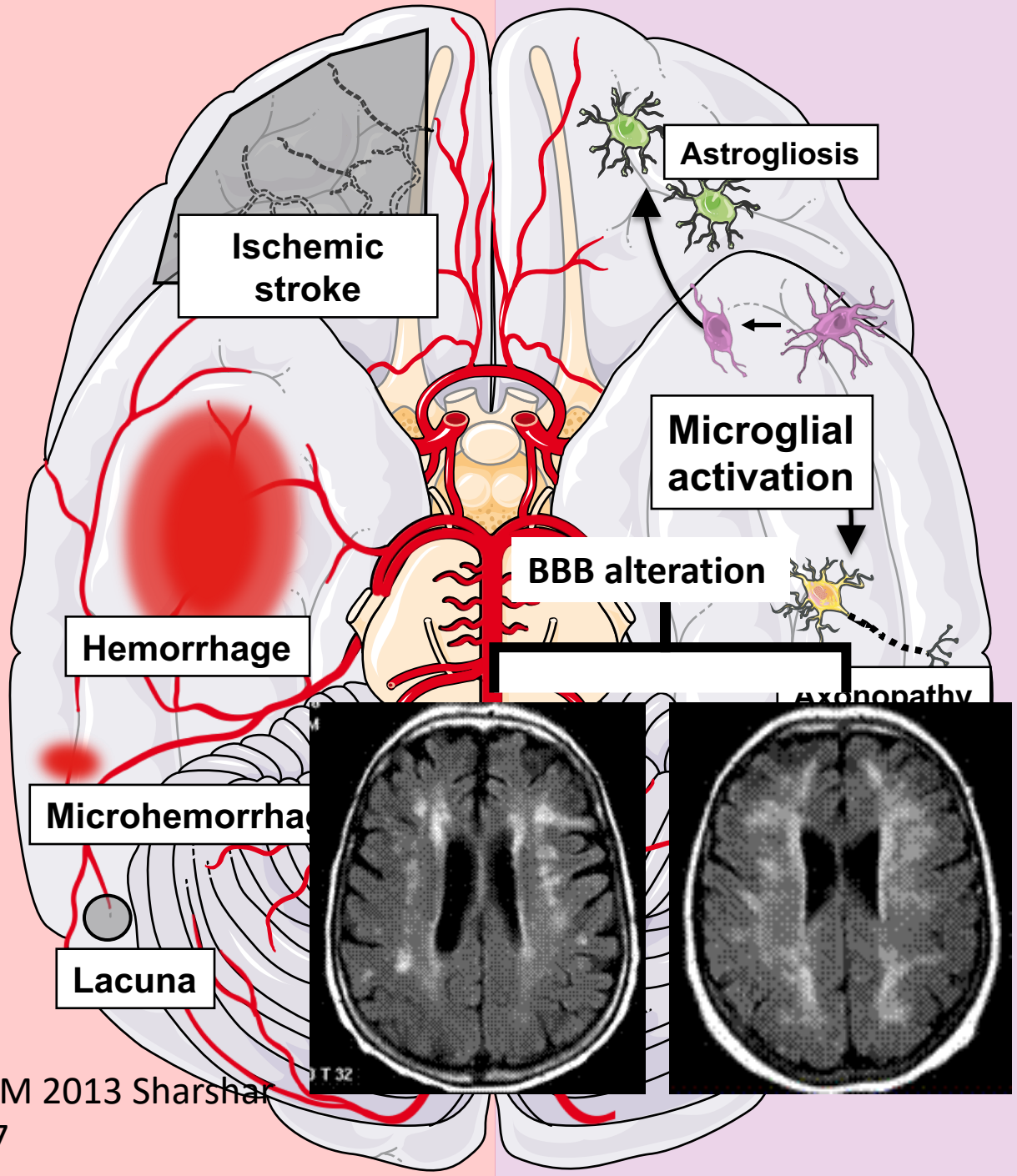
Risk factors and pathophysiology



Kurtz et al – Current opinion - 2024

Pathophysiology of SAE

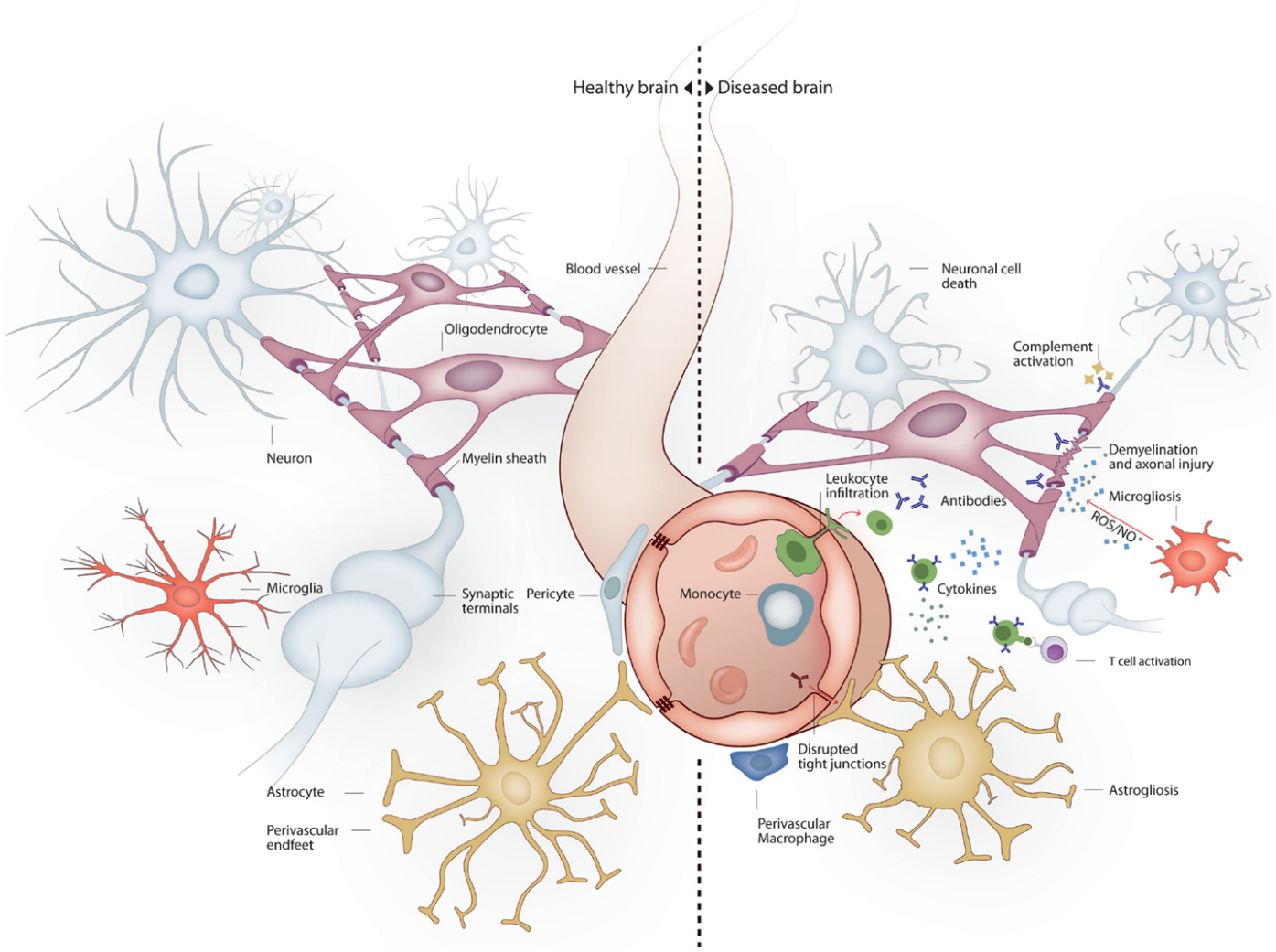
Vascular changes

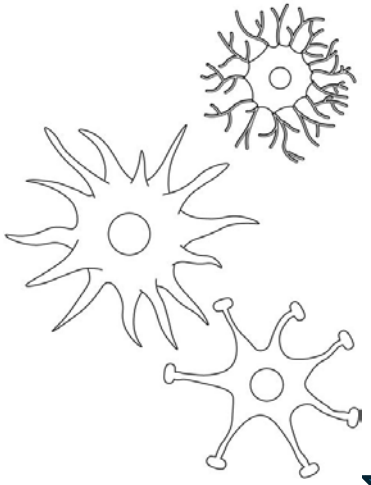


Neuroinflammatory changes

Polito CCM 2013 Sharshar
ICM 2007

Neuroinflammatory process





Neuroprotective

Neurotoxic

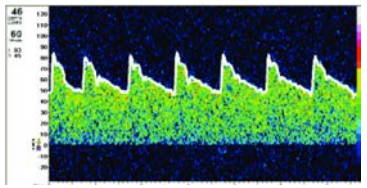
New event

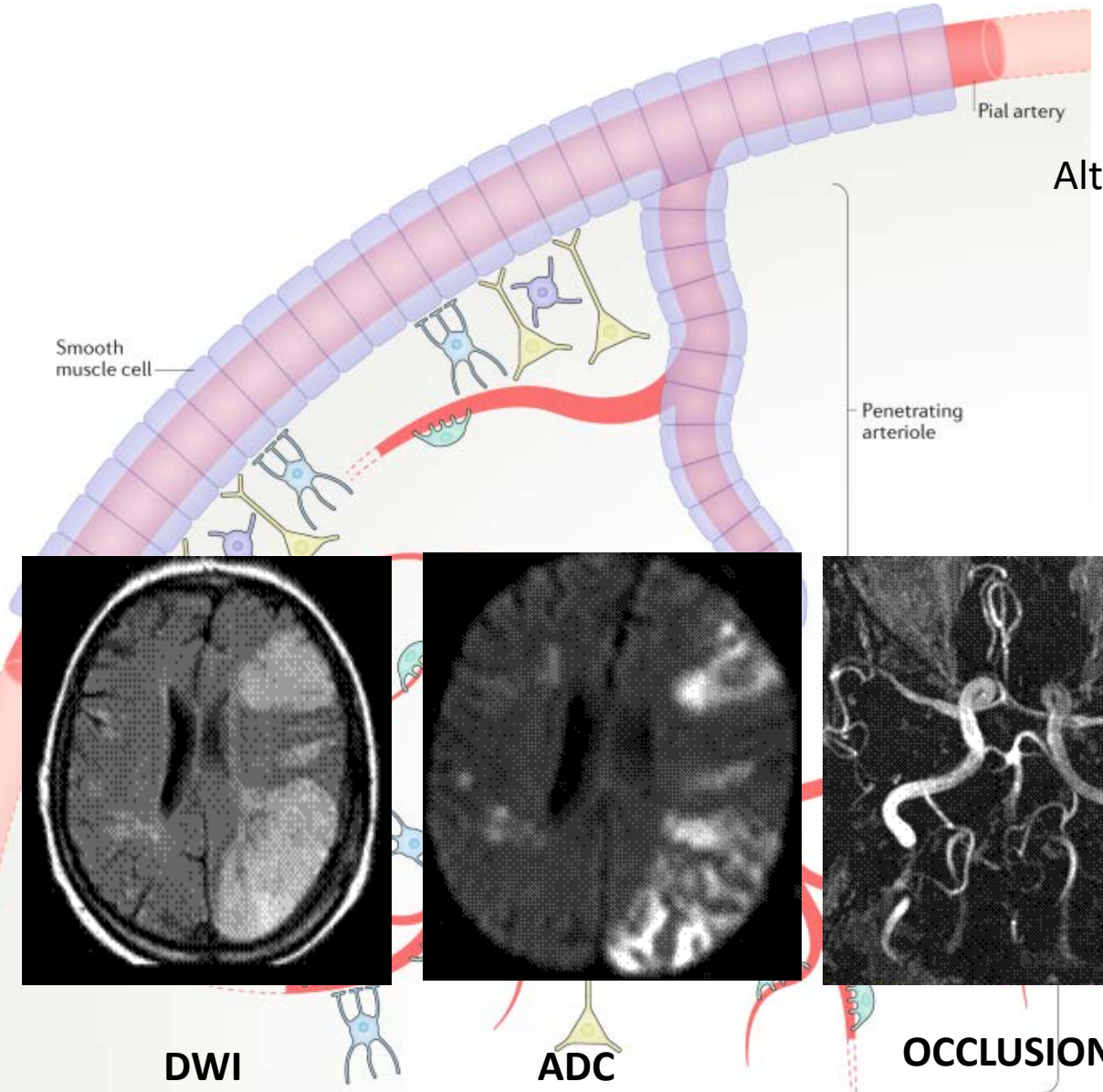
Priming

No biomarker of microglial immuno-phenotype

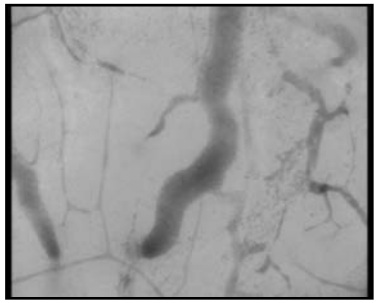
Ischemic process in SAE

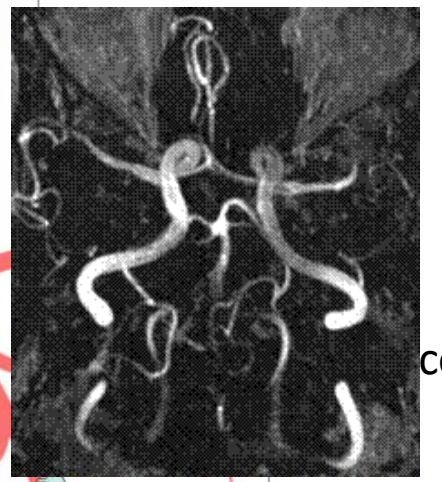
Systemic HD changes
Autoregulation





Altered microperfusion





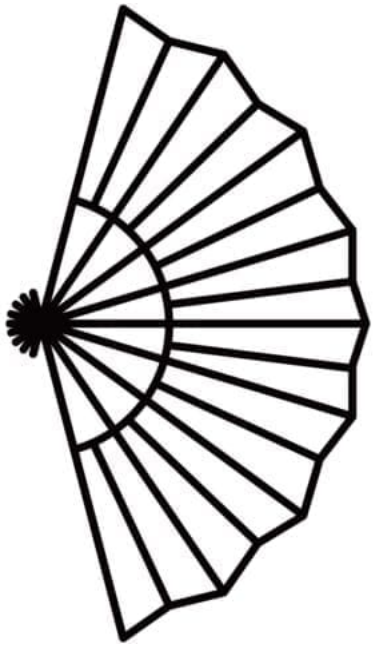
coupling

FLAIR **DWI** **ADC** **OCCLUSION**

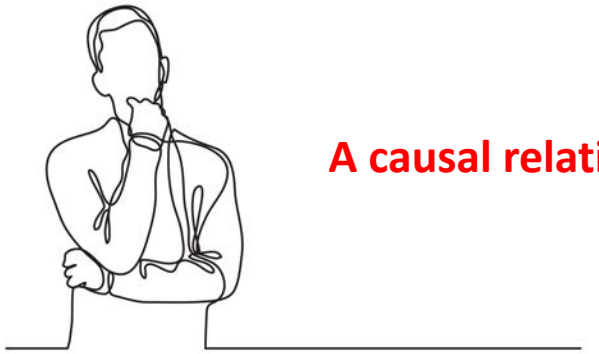
When doing a brain imaging?

- No clear recommendation
- Focal neurological signs
- Abnormal movements
- No obvious causes
- Persistent delirium

Outcomes

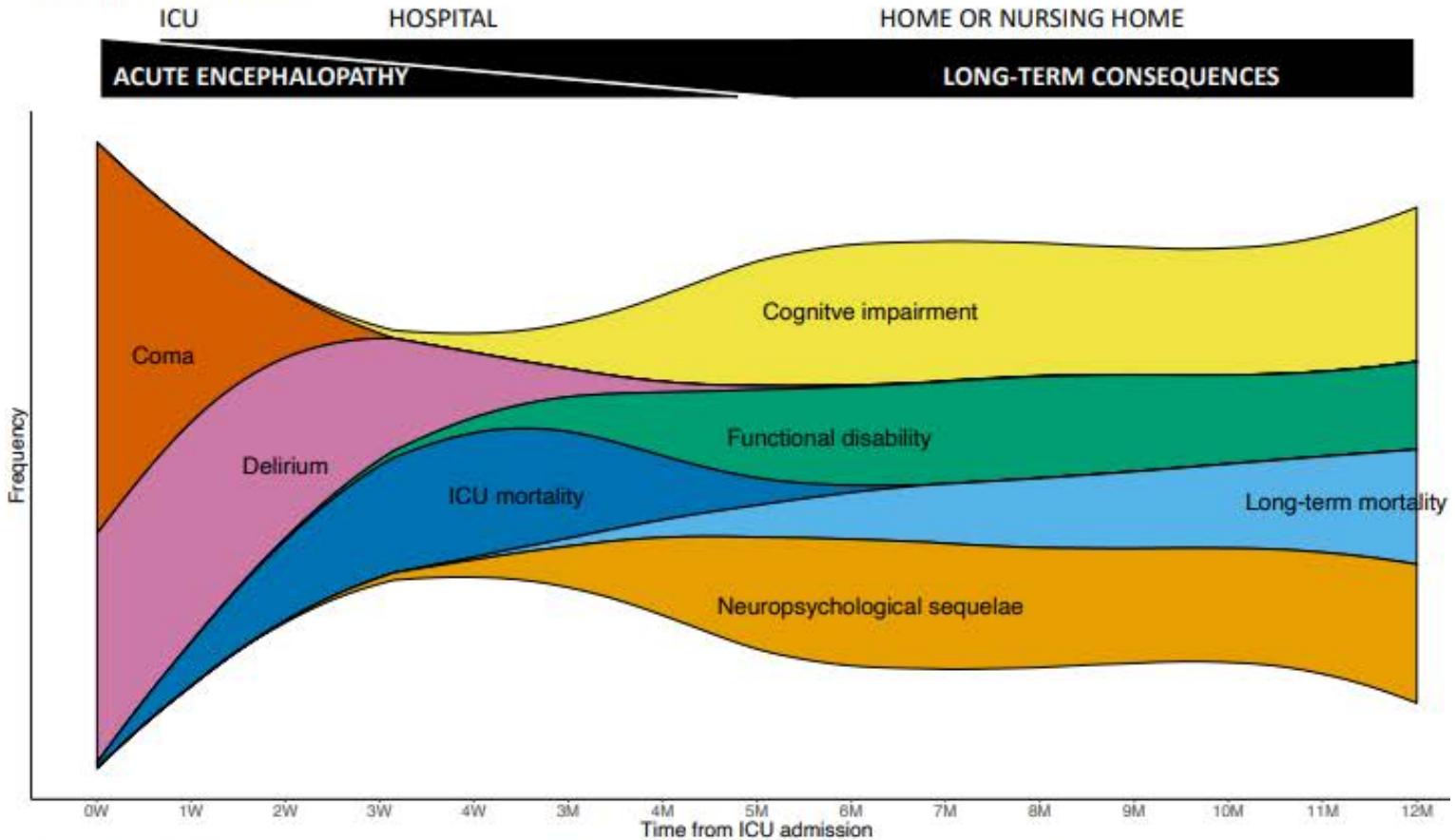


- **Increased Mortality**: ICU, in-Hospital, at one-year
- **Long-term cognitive impairment**: proportional relationship with delirium duration
- **Long-term psychological disorders**: delirium is a risk factor of PTSD



A causal relationship?

PATIENTS' TRAJECTORIES

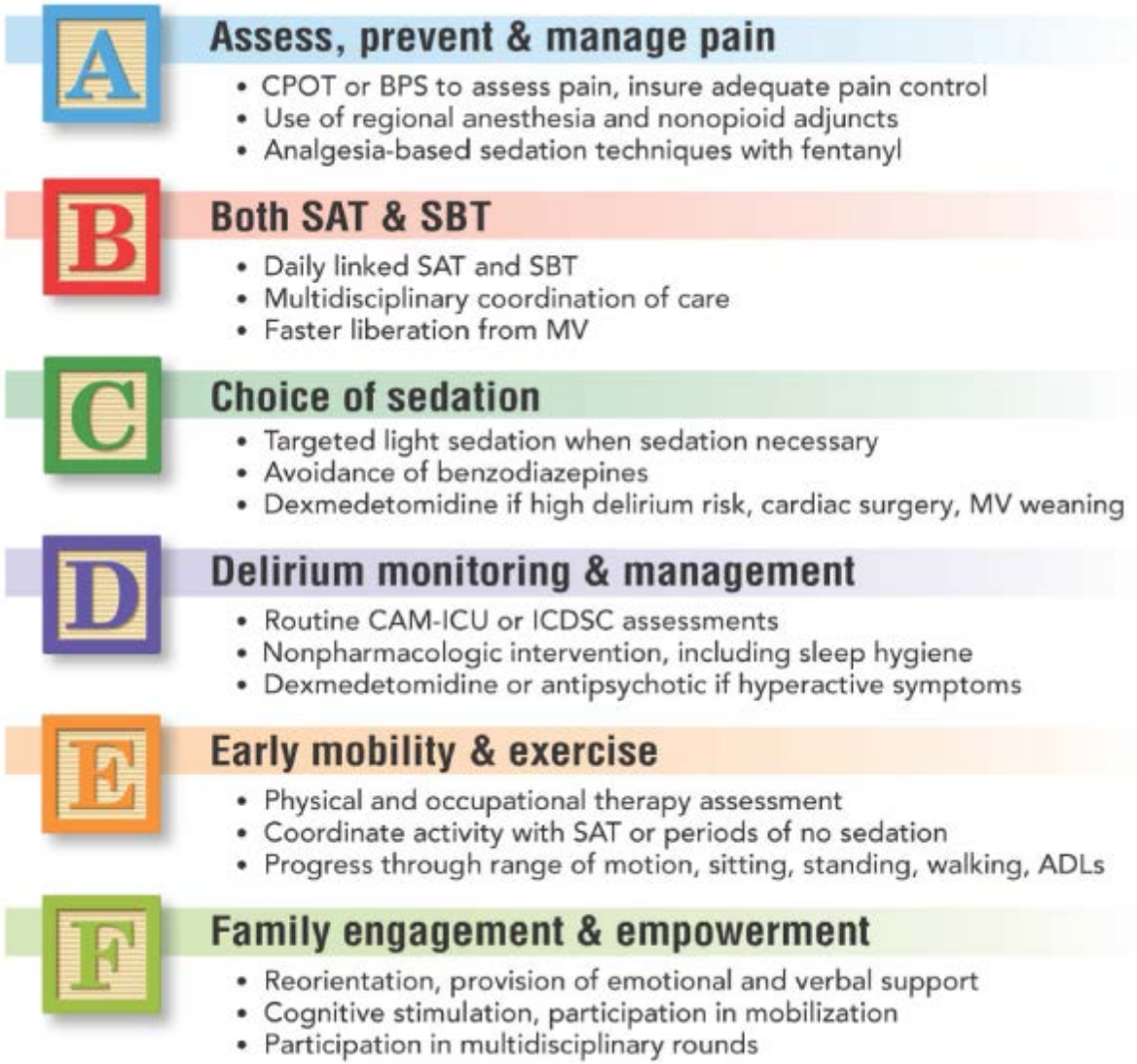


USEFUL SCORES

RASS or SAS	RASS or SAS	4AT	Cognition: MMSE, MoCA, RBANS
GCS & FOUR	FOUR	MMSE or MoCA	Anxiety & Depression: HADS, BDI
CAM-ICU(-7) or ICDSC	CRS-r		Post-traumatic stress disorder: PCL-5
	CAM-ICU(-7) or ICDSC		Quality of life: EQ-5D-3/5L, SF-12/36
			Functional independance: ADL/IADL

Kurtz et al – Current opinion - 2024

ABCDEF Bundle

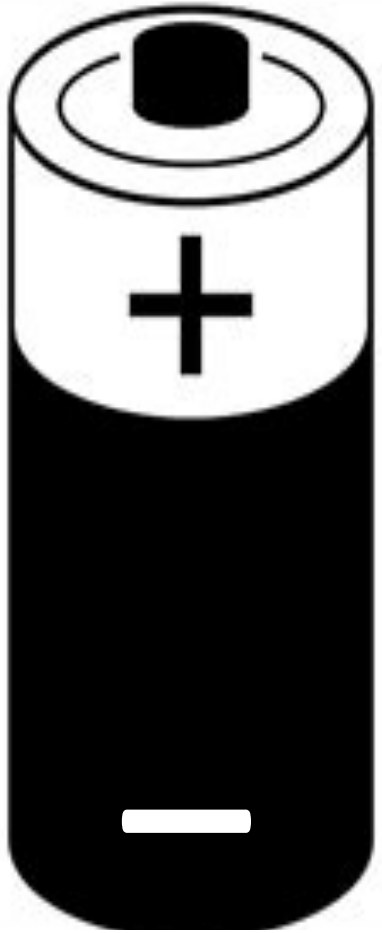


Early Mobilization in ICU

No effect
Good effect
Not tested

Intervention	Mortality	Prevention of delirium	Duration of delirium	Duration of MV/LOS	Long-term psychological disorders	Long-term cognitive disorders	Long-term Quality of Life
ICU/RCT/2009			Reduction	Reduction			
Surgical ICU/RCT/2016	Trend for hopital mortality		Reduction	Reduction of lOS			
ICU/RCT/2023		Yes	Reduction	Reduction		Yes	Trend to better QoL (physical)
ICU/RCT/2024							

Non-pharmacological intervention in ICU



- Family participation
- ABCDEF bundle
- Delirium early detection protocol
- Multicomponent
- Light noise blocking (improves sleep)

- Bright light therapy
- Architectural intervention
- Flexible family visitation (Rosa et al JAMA 2029)
- Massage
- Quiet time protocol
- Cognitive stimulation

Kang et al – Aust Crit Care - 2023

PREVENTION

Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium

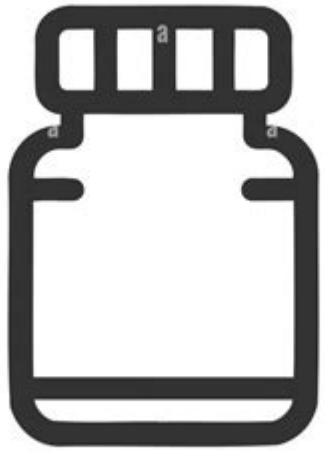
The REDUCE Randomized Clinical Trial

	2-mg Haloperidol (n = 732)	Placebo (n = 707)
Primary analysis, days alive at 28 days, median (IQR)	28 (28 to 28)	28 (28 to 28)
Survival, No. (%)		
28 d	610 (83.3)	585 (82.7)
90 d	579 (79.1)	556 (78.6)
28-Day end points		
Incidence of delirium, No. (%)	244 (33.3)	233 (33.0)
No. of delirium- and coma-free, median (IQR), d[b]	26 (17 to 28)	26 (19 to 28)
No. of delirium-free, median (IQR), d[b]	28 (22 to 28)	28 (23 to 28)
No. of coma-free, median (IQR), d[b]	27 (22 to 28)	27 (23 to 28)
No. of days to occurrence of delirium, median (IQR)[b]	3 (2 to 6)	3 (2 to 6)
Duration of mechanical ventilation, median (IQR), d	2 (0 to 6)	2 (0 to 5)

Van den Boogaard et al – JAMA - 2018

Haloperidol for treating delirium

Intervention	Mortality	Duration of delirium	Duration of MV/LOS	Long-term psychological disorders	Long-term cognitive disorders	Long-term Quality of Life
ICU/RCT/2018	ICU/hospital/ 3-months					
ICU/RCT/2023 AID-ICU	3-months					
ICU/RCT/2023 AID-ICU (Pre-planned Bayesian)	Hospital	Coma & delirum	Days alive without MV			
ICU/RCT/2023 AID-ICU (ancillary)	1-year					
ICU/RCT/2023 Euridice			Trends to reduce LOS			
ICU/RCT/2024 MIND-USA	3 and 12-months					



- Dose: 2,5 mg/8h in average
- Side-effects (ECG)
- Contraindicated in **catatonia**

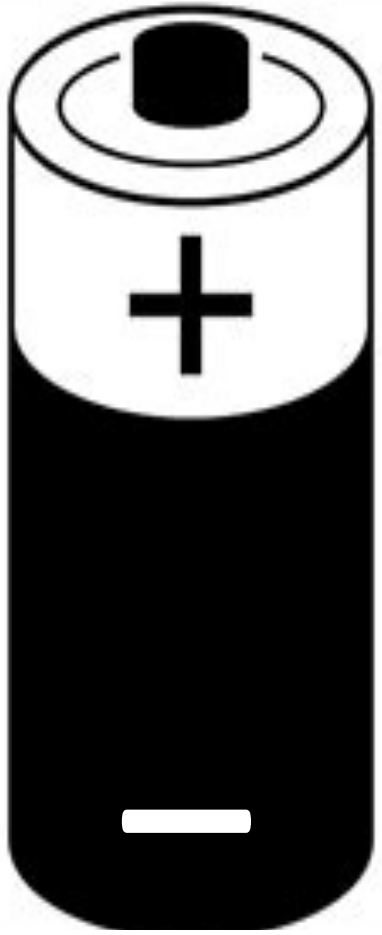
- Motoric immobility (catalepsy, waxy flexibility, stupor)
- Excessive motor activity (purposeless, not influenced by external stimuli)
- Extreme negativism (rigid posture, resistance to instructions, gegenhalten, mutism)
- Peculiarities of voluntary movement (grimacing, bizarre postures, stereotyped movements)
- Echolalia or echopraxia

Dexmedetomidine for preventing or treating delirium

Intervention	Mortality	Delirium prevention	Delirium duration	Duration of MV/LOS
ICU/RCT/2016 SPICE III	ICU/hospital/ 3-months			
METANALYSIS				
MIDEX&PRODEX	Hospital		More cooperative with Dex	Days alive without MV
DEX vs MID	1-year			
DEX-LORAZEPAM				
DEX-SEPSIS				
DEX-AGITATED DELIRIUM				MV
DEX-ELDERLY-CARDIAC SURGERY				

No effect Good effect Not tested

Other drugs for preventing or treating delirium

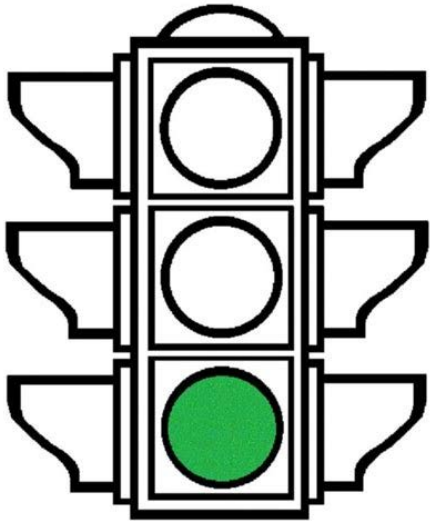


- Minocycline (to b confirmed)
- Thiamine
- Reducing sedation
- BZD (Dex?) for alcoohol withdrawal

- Statins
- Rivastigmine
- Melatonin

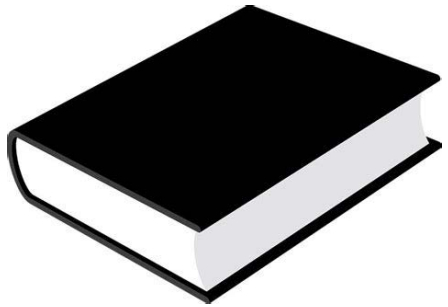
The KISS trial

Kang et al – Aust Crit Care - 2023



- Control of the risk factors
- Treatment of the cause
- Think of alternative diagnosis

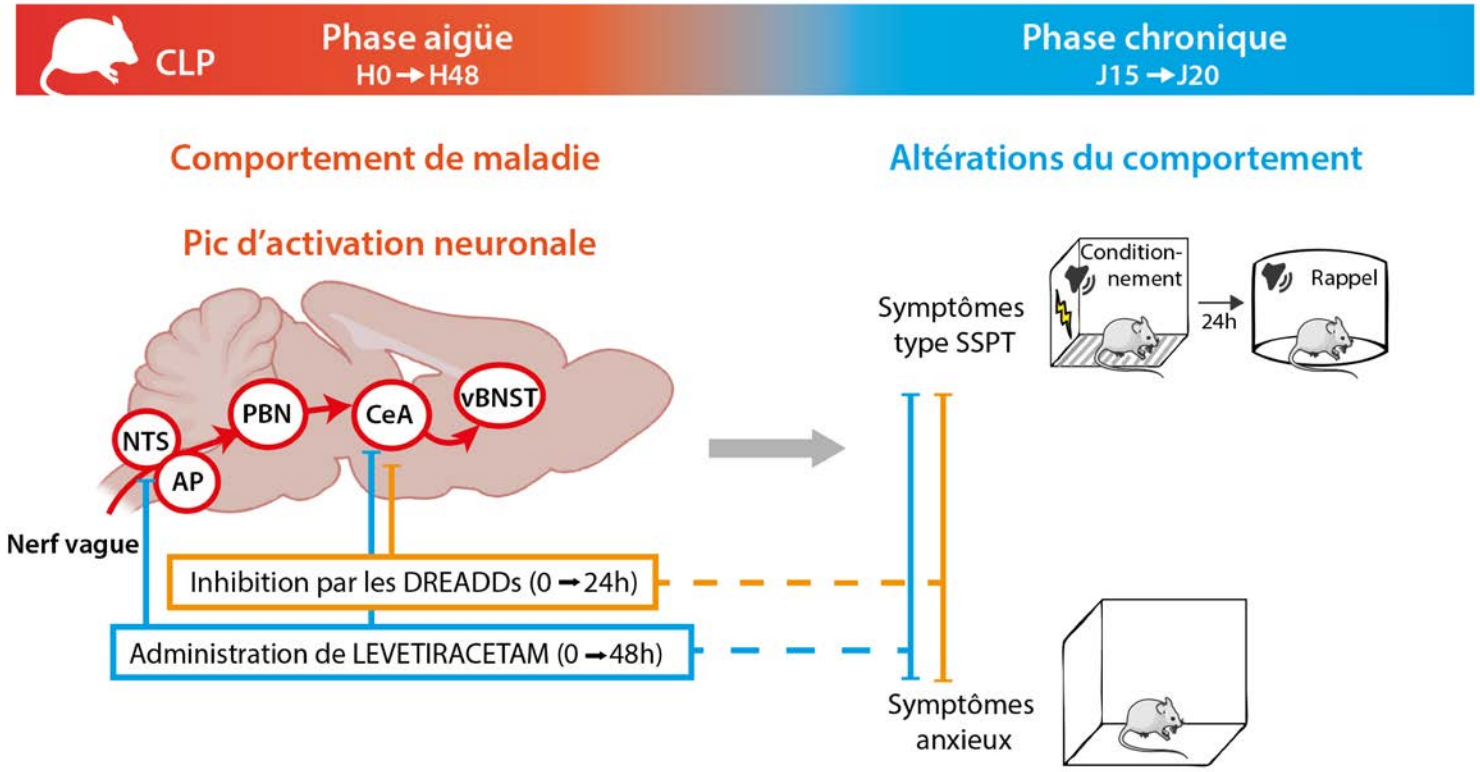
Conclusions



- **A frequent and severe complication** of critical illness and ICU management
- **Multifactorial**
- Associated with **short and long-term bad outcomes,** especially **hypoactive delirum**
- **To be detected routinely** with validated scales
- Prevention based on **reducing risk factors** (sedation and immobility).
- **Etiological treatment** +++
- Interest of **Dexmedetomitine** for helping discontinuation of sedation.
- **Antipsychotic drugs** if only agitation (or hallucination) but contra-indicated in catatonia (a differential diagnosis of delirium)

Quelques réflexions….

Dysfonction amygdalienne



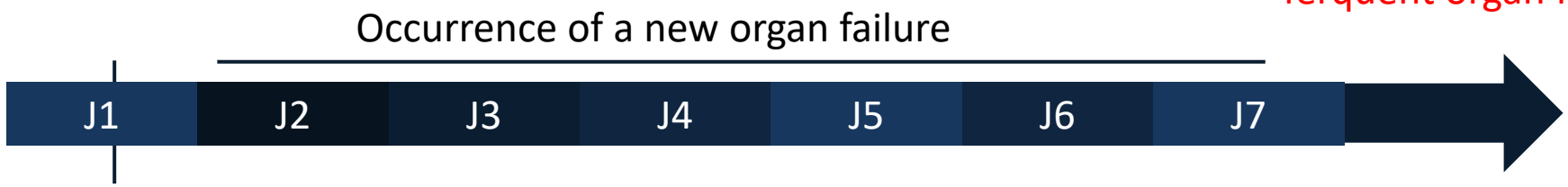
Bourhy et al – Brain - 2022

KISS **trial:** Keppra in septic shock

PHRC

ANXIETY (Panicu study)

Respiratory failure and delirium were the two most ferquent organ failure



Anxiety assessment

STAI
- ≥40
- <40

TABLE 4. Adjusted Analyses of the Association of State-Trait Anxiety Inventory State Questionnaire (From 20 to 80) Score With New Organ Failure After Day 1

Variables	OR (95% CI)	*p*
Model adjusted for SAPS II and SOFA at admission		
STAI-State ≥ 40	1.94 (1.18–3.18)	0.009
SAPS II (per point value)	1.03 (1.01–1.05)	0.005
SOFA score (per point value)	1.21 (1.05–1.39)	0.009
Model adjusted for SAPS II and SOFA at admission and dyspnea variables[a]		
STAI-State ≥ 40	1.72 (1.03–2.87)	0.038
SAPS II (per point value)	1.03 (1.01–1.05)	0.007
SOFA score (per point value)	1.22 (1.05–1.40)	0.007
Dyspnea Visual Analogic Scale (per point value)	1.06 (0.98–1.15)	0.13
$Paco_2$ ≥ 45 mm Hg	1.27 (0.69–2.36)	0.45
Subgroup analysis according to SOFA value at admission, adjusted for SAPS II		
STAI-State ≥ 40 for patients without organ dysfunction at admission	2.02 (1.01–4.06)	0.048
STAI-State ≥ 40 for patients with organ dysfunction at admission	2.13 (1.03–4.39)	0.040
Interaction test		0.99

OR = odds ratio, SAPS = Simplified Acute Physiology Score, SOFA = Sequential Organ Failure Assessment, STAI-State = State-Trait Anxiety Inventory State questionnaire (from 20 to 80).

[a]Post hoc analysis.

C-index for the model adjusted for SAPS II and SOFA at admission: 0.698.

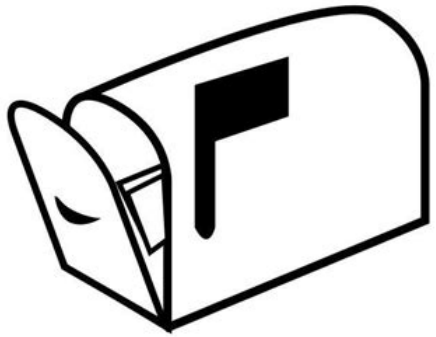
C-index for the model with SAPS II and SOFA only: 0.676.

C-index difference, 0.02; bootstrap 95% CI, 0.0002–0.070; *p* 0.048.

Continuous net reclassification index, 0.297; bootstrap 95% CI, 0.081–0.516; *p* 0.005.

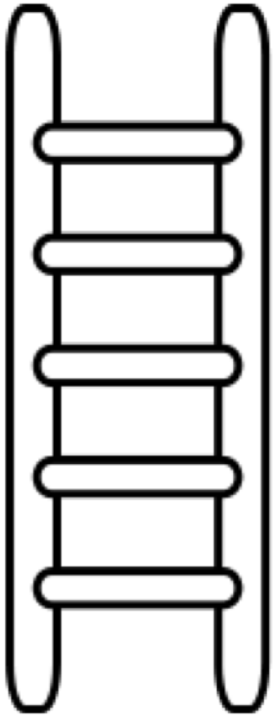
C-index for the model adjusted for SAPS II and SOFA at admission and dyspnea variables: 0.703.

Mazeraud et al Crit care Med 2020



TANDEX trial: treatment of anxiety by DEX

Deep sedation



- It is required in more than **30% of critically ill patients** over the first 7 days
- It is required in **most severe critically ill patients** who are at risk of **neurological deterioration**
- Deep sedation can **mask neurological deterioration**
- It is associated with **increased mortality**
- It is associated with **delayed awakening, delirium and long-term psycho-cognitive disorders**

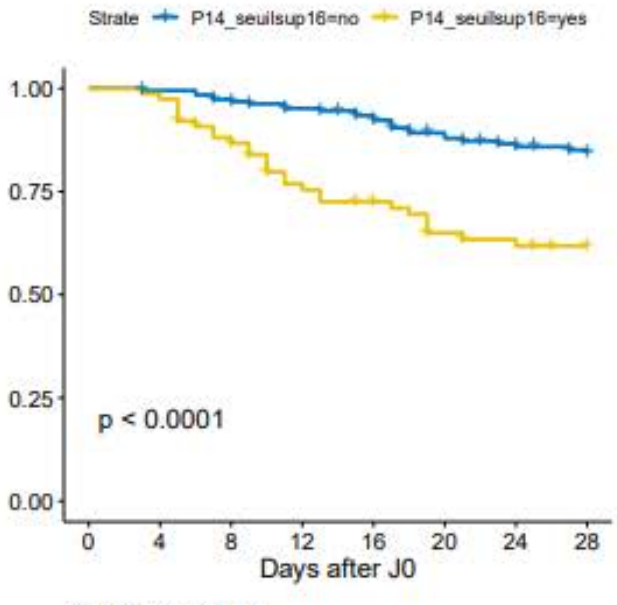
- ICU-mortality is associated
  - absent cough reflex,
  - heteregenous pattern of abolition of brainstem reflexes
  - increased SSEP intracranial interlatency are asssociated with
- altered mental status after discontinuation of sedation is related
  - early abolition of oculocephalic reflex

ProReTro multicenter observational study

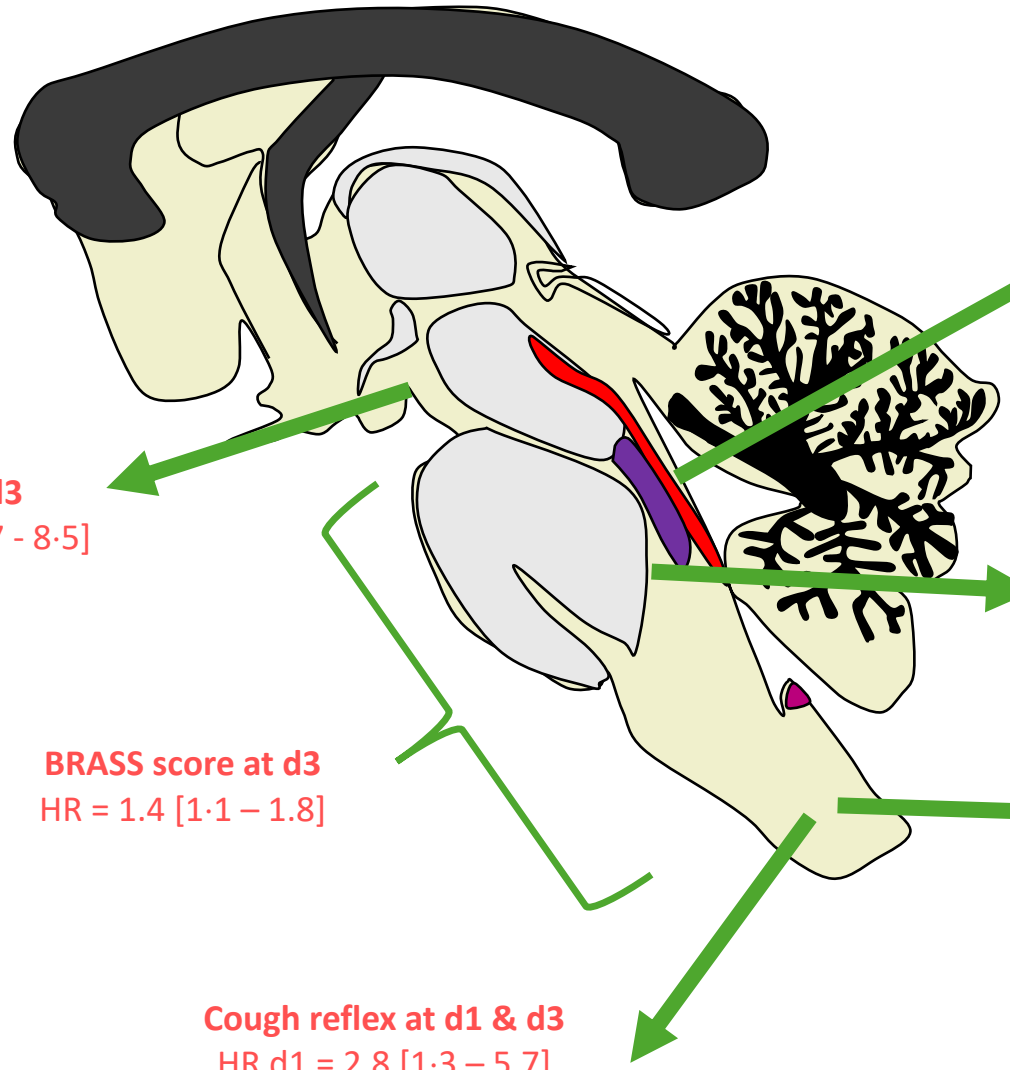
Multimodal assessment at day 3 of deep sedation
261 patients (brain injured: 139 (53%)
Primary outcome: medullar SSEP P14> 16 ms associated with day 28 mortality

P14 latency at Day 3	Survivor (n=211)	Dead (n=53)
< 16 ms	77%	49%
> 16 ms	23%	51%

	Hazard ratio	IC	p
P14 latency 16 ms	2.98	[1.71-5.18]	0.0001
SAPS-II	1.01	[0.99-1.03]	0.41
GCS at admission	1.02	[0.95-1.09]	0.59
Brain injury	0.64	[0.31-1.30]	0.22



ProReTro multicenter observational study



OCR at d1 & d3
HR d1 = 2·4 [1·2-4·6]
HR d3 = 2·1 [1·1-3·7]

PLR at d3
HR = 3.9 [1·7 - 8·5]

P14-N20 IPL at d3
HR = 2·4 [1·2 - 4·6]

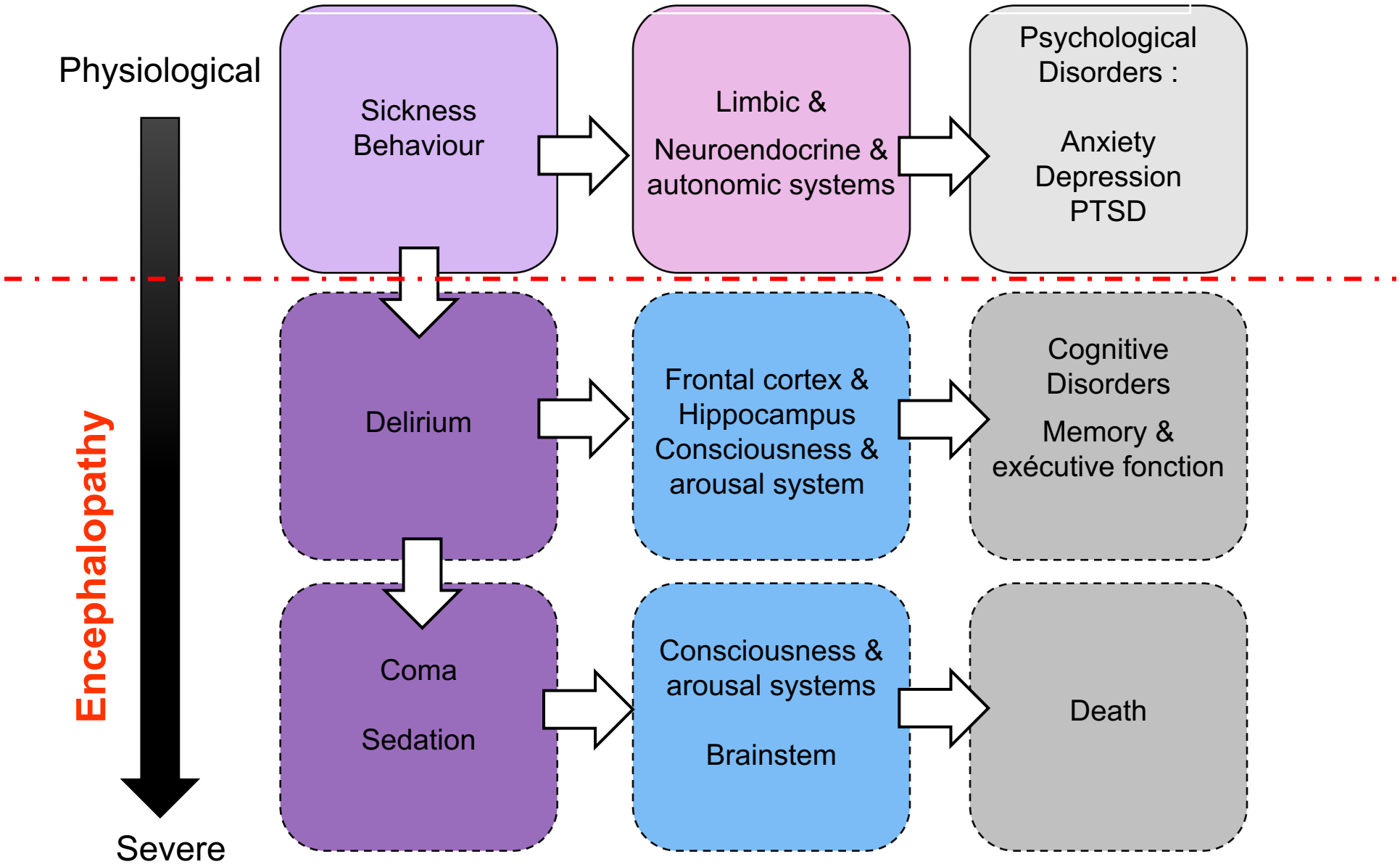
BRASS score at d3
HR = 1.4 [1·1 – 1.8]

P14 at d3
HR = 3·0 [1·7-5·2]

Cough reflex at d1 & d3
HR d1 = 2.8 [1·3 – 5.7]
HR d3= 2·8 [1·4 – 5.5]

Delayed awakening
Mortality

The Paradigm



Sharshar & Annane – Lancet Respiratory Medicine - 2015

Clinical case

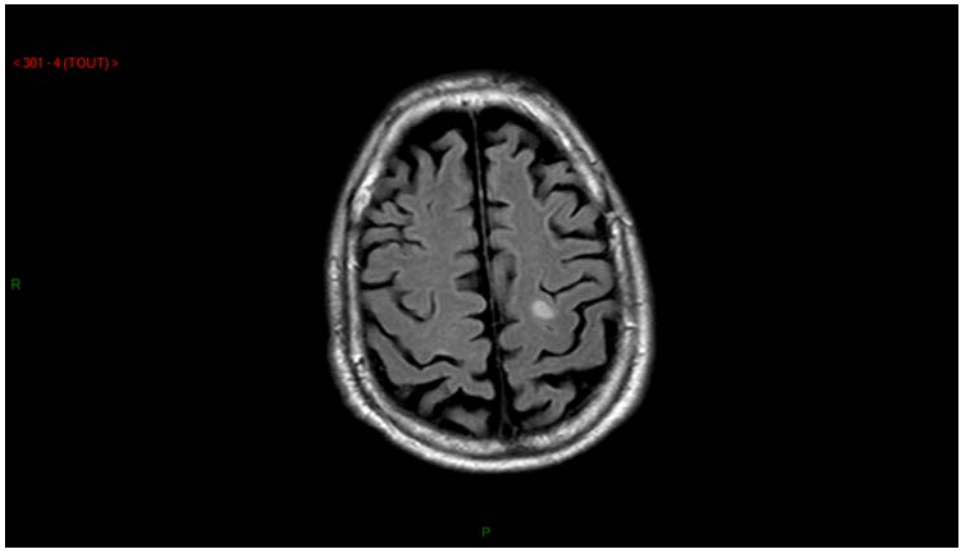
A 55 years old man was hospitalised for a septic shock. Blood culture were positive to *Staphylococcus aureus* and CSF analysis showed an aseptic meningitis. At admission, neurological examination was normal as well as MRI of the brain and spine. Transoesophageal cardiac ultrasound only showed a thrombus in the left atria. He also underwent surgery for a septic arthritis of the right knee. A right jugular catheter could not be put. A goitre was also noticed. Vasopressor and mechanical ventilation were discontinued the 3rd and 5th days from admission. The patient was treated with methicillin and heparin.

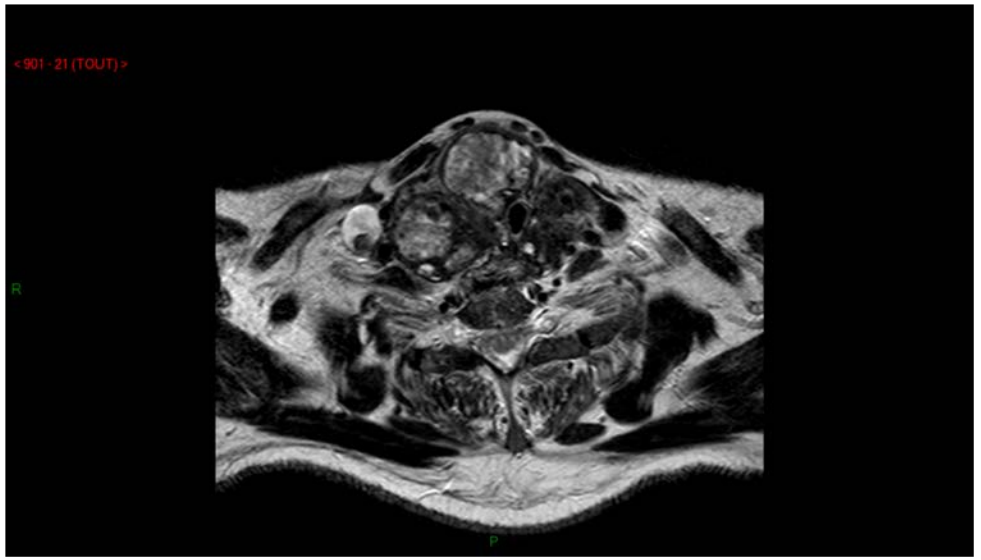
Day 8, the patient developed agitation and delirium. Neurological examination showed

1. **A weakness of the right arm,**
2. **A slight right central facial palsy,**
3. **A ptosis and miosis of the right eye.**
4. **The right arm was also oedematous.**
5. The brain CT scan and CSF analysis were normal. EEG showed a slow cortical activity. Biochemical screening showed a moderate renal insufficiency. Blood culture were negative.

Clinical case

1. Left pre-rolandic lesion
2. Thrombosis of right jugular vein
3. Orbenin overdose





Clinical case

- Mme X…, 53 years old, traited with CS et I- for LED, is admitted for ARF related to a thrombotic microangiopathy. Occurrence of a hyperactive delirium: « **on me vole mon enfant, les médecins me volent mon enfant…** »

Thank you
For your Attention !

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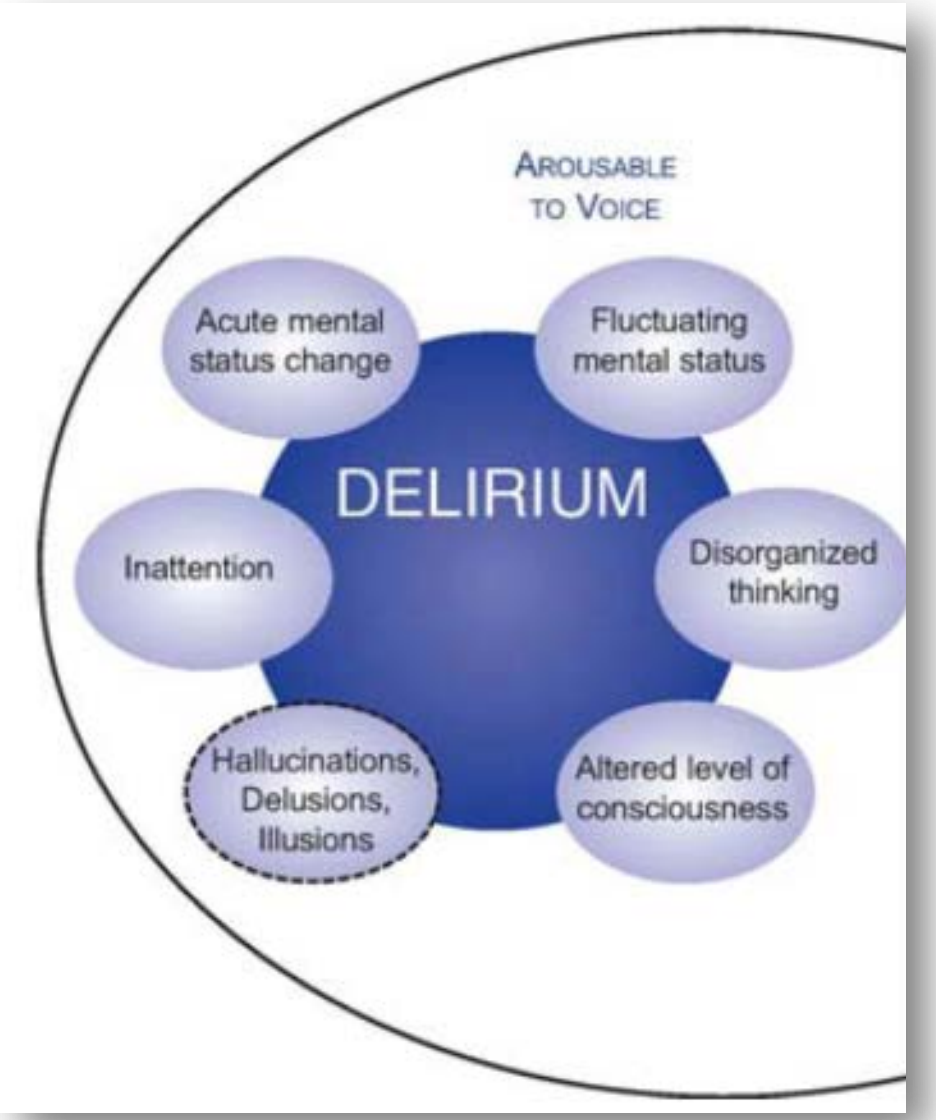
First conclusion

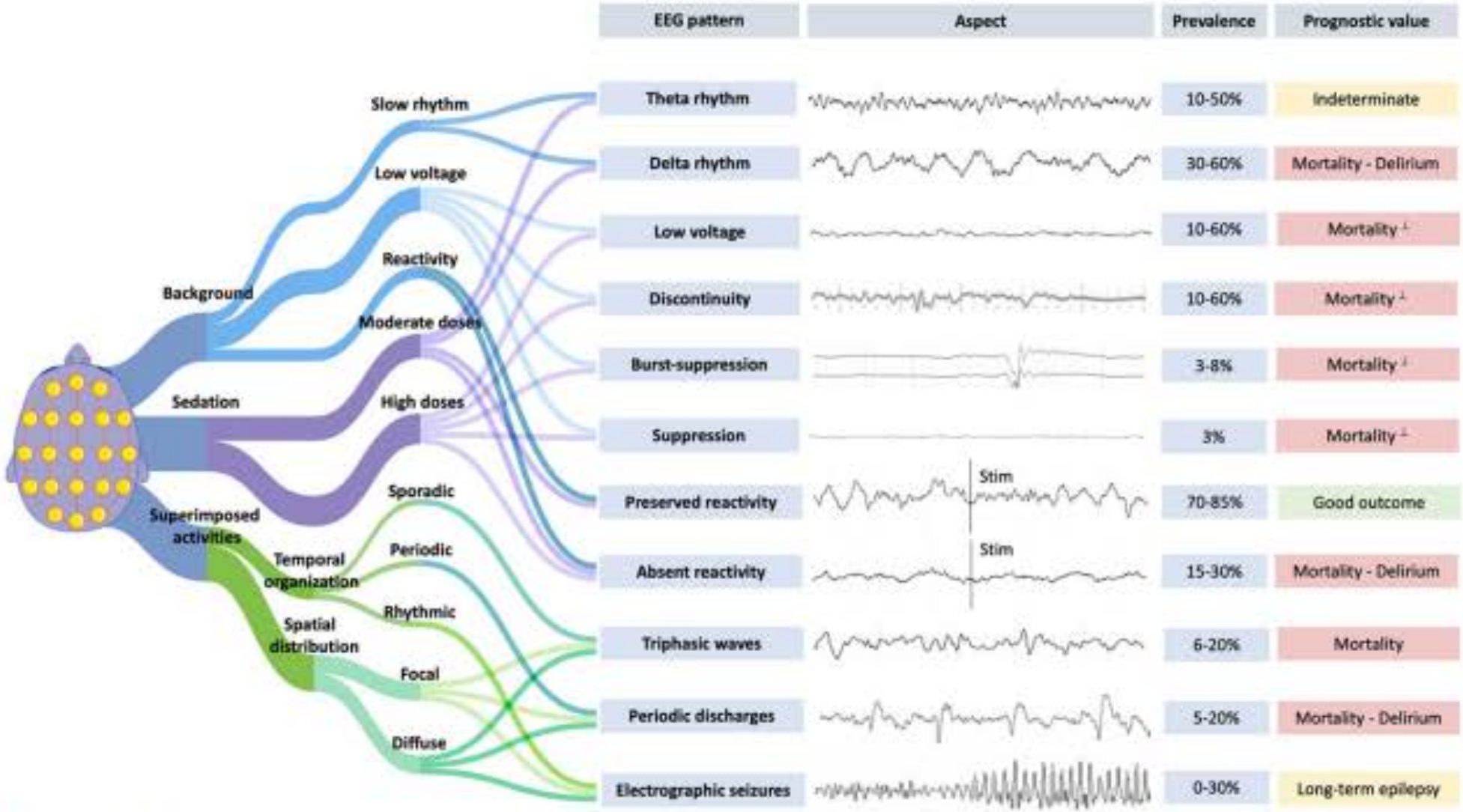


Morandi et al., ICM 2008

- **Prevalence**
  - Historically: 60 to 80%
  - Nowadays: 25 to 45% (MV or shock)
- **Phenotypes**
  - Hyperactive, hypoactive or mixed
  - Hypoactive more frequent in elderly and worst outcome
- **Validated scores**
  - CAM-ICU, ICU-DSC…
- **Risk factors**
  - Predeleric score
  - Age, prexisting mental/neurological disorders, sepsis, sedation, metabolic disorders, drug overdoses or withdrawal…
- **Complications**
  - Increased short and long-term mortality
  - Increased long-term psychocognitive impairment

Ely et al – JAMA – 2001; Girard et al – Lancet – 2008; Ely et al – JAMA «- 2004;Bergeron et al – ICM – 2001; Girard et al – NEJM – 2018; Salluh et al – BMJ - 2015

EEG in septic patients



Sonneville R – Crit Care - 2023