DELIRIUM IN ICU

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DELIRIUM

DSM IV

A. **Alteration of consciousness: decreased interaction with the environment, attention and concentration difficulties**

B. **Impairment of one or more cognitive functions:**

- **Speech**
- **Memory**
- **Disorientation in space and time**
- **Thinking/judgement**

C. **Onset sudden or rapidly progressive, fluctuating symptoms**

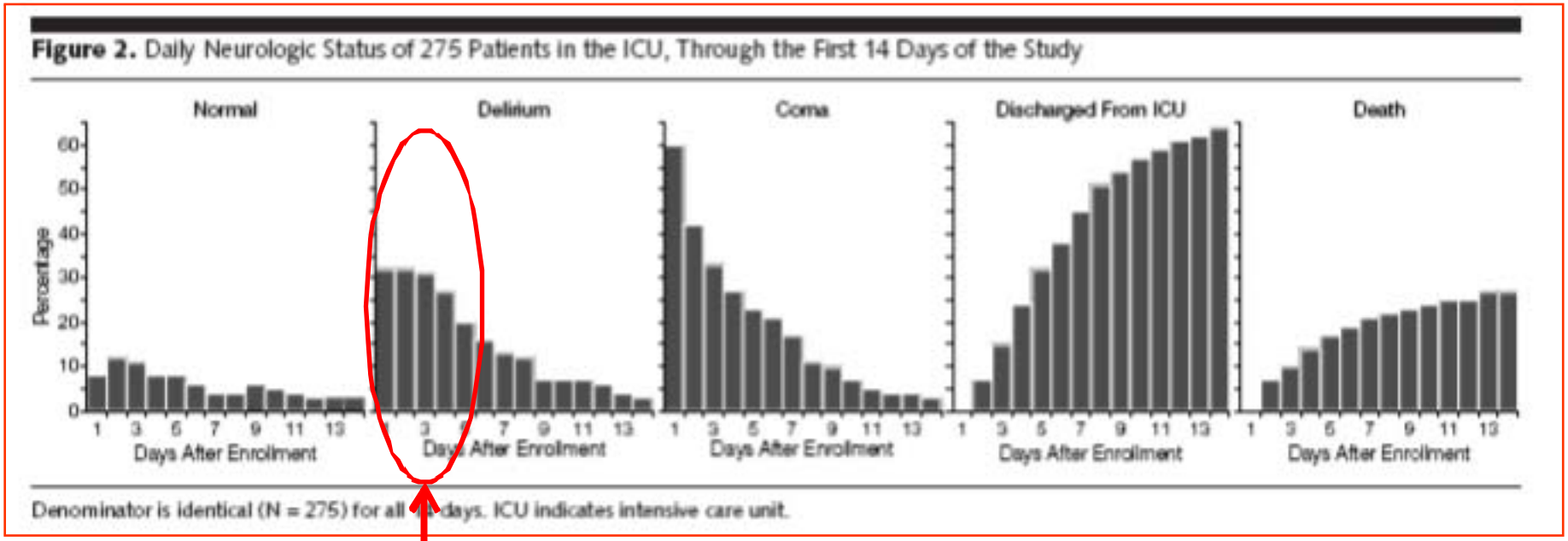
D. **Secondary to:**

- **Medical illness**
- **Drugs toxicity**
- **Withdrawal**

INCIDENCE

Auteur, année	Population Réa, n	Critère (échelle)	Fréq.
Dubois, ICM 2001	Med-chir, n=216	Delirium (ICDSC)	19%
Ely, CCM 2001	Med, n=48	Delirium (CAM-ICU)	60%
Ely, Crit care 2003	Med non ventilés, n=261	Delirium (CAM-ICU)	48%
Woods, ICM 2004	Med, n=143	Agitation (MAAS)	16%
Ely, JAMA 2004	Med et USIC, n=224	Delirium (CAM-ICU)	82%
Jaber, Chest 2005	Med-chir, n=211	Agitation (Ramsay)	52%
Ely, ICM 2007	Chir-Trauma, n=100	Delirium (CAM-ICU)	70%
Ely, JAMA 2007	Med-chir, n=106	Delirium (CAM-ICU)	80%
Ouimet, ICM 2007	Med-chir, n=820	Delirium (ICDSC)	32%

DISTRIBUTION



Early occurrence

Ely et al – JAMA - 2004

MORTALITY

Figure 3. Kaplan-Meier Analysis of Delirium in the Intensive Care Unit and 6-Month Survival

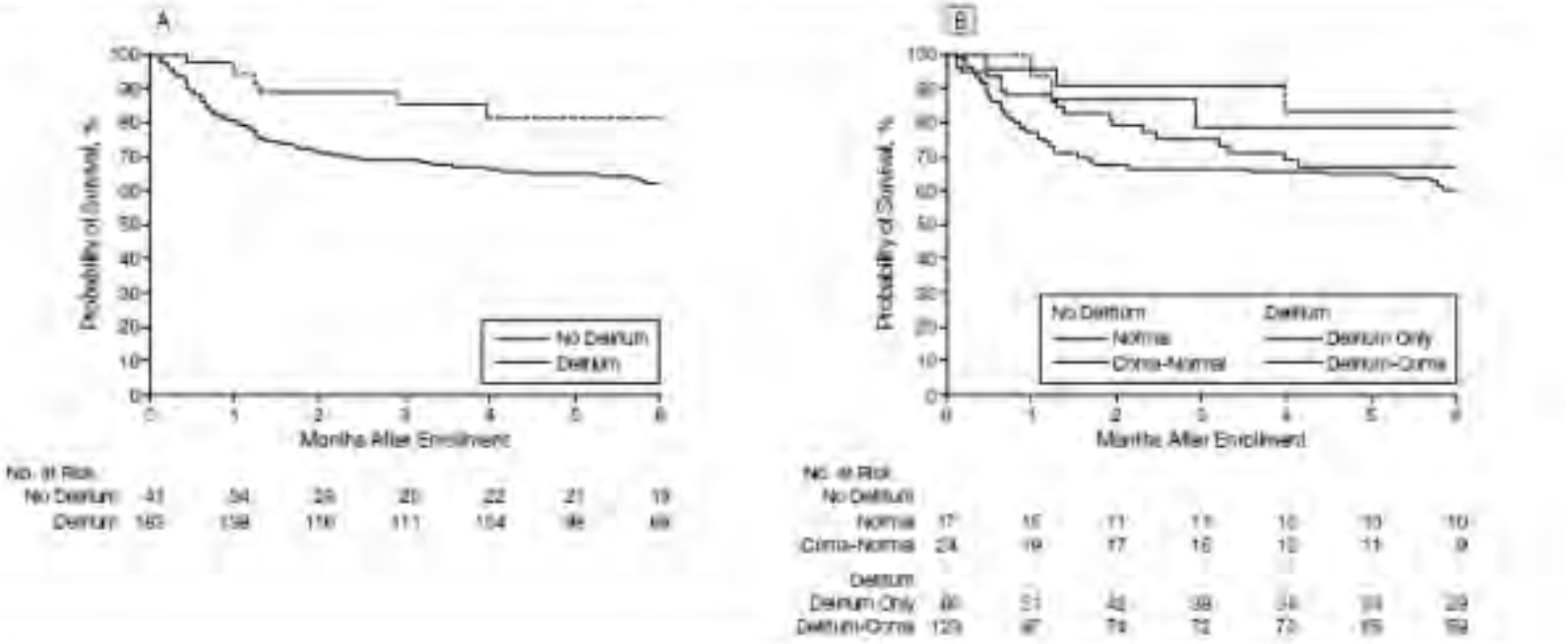
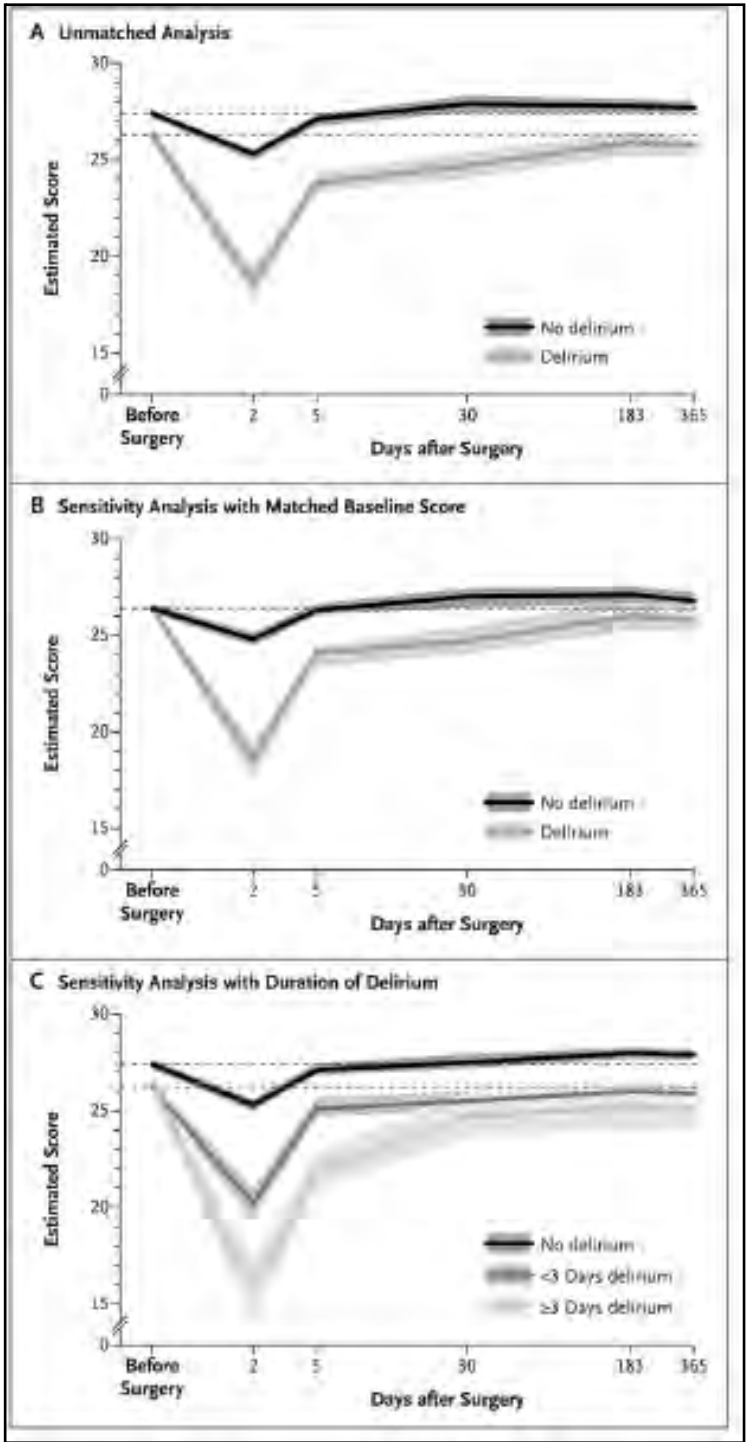


Table 3. Delirium Status and Clinical Outcomes Including 6-Month Mortality and Lengths of Stay

	No Delirium	Delirium	Adjusted *P* Value
	6-Month Mortality		
No.	41	183	
Rate, No. (%)	6 (15)	63 (34)	
Adjusted HR (95% CI)*	Reference	3.2 (1.4-7.7)	.008

Ely et al – JAMA - 2004

MID-TERM COGNITIVE DECLINE



225 Post-operative patients

Saczynski et al – NEMJ - 2012

MID-TERM COGNITIVE DECLINE

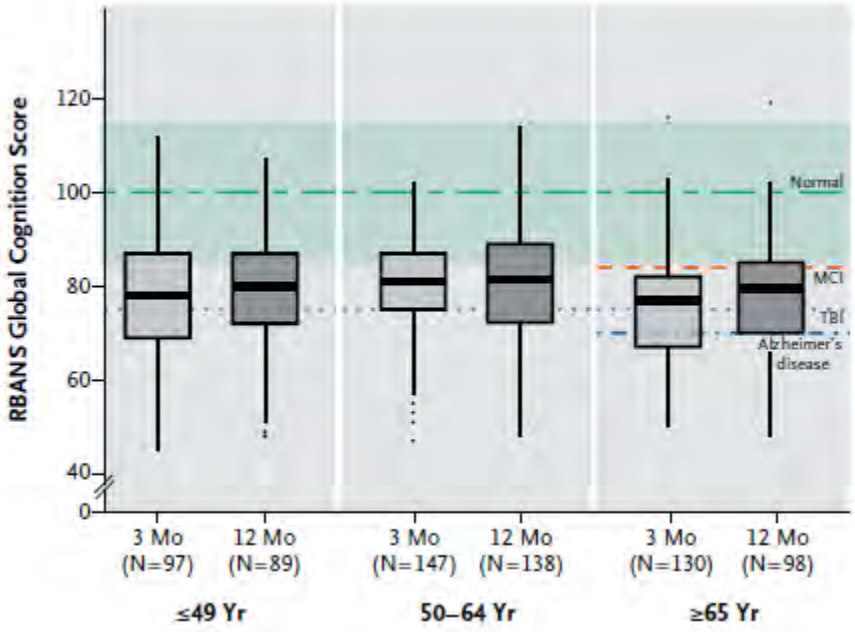
Cognitive outcomes during follow-up

	Follow-up Assessment	
Outcome, % (n/total)	3 months (n=76)*	12 months (n=52)*
No impairment	21% (16/76)	29% (15/52)
Mild/moderate impairment	17% (13/76)	35% (18/52)
Severe impairment	62% (47/76)	36% (19/52)

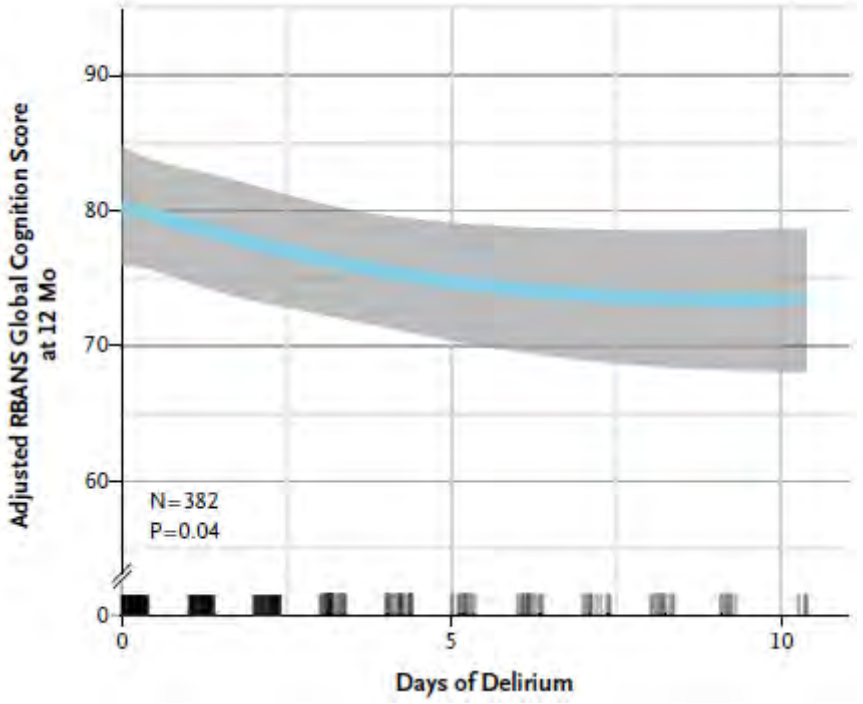
77 Medical ICU patients

Girard et al – Crit Care Med - 2010

Long-Term Cognitive Impairment after Critical Illness

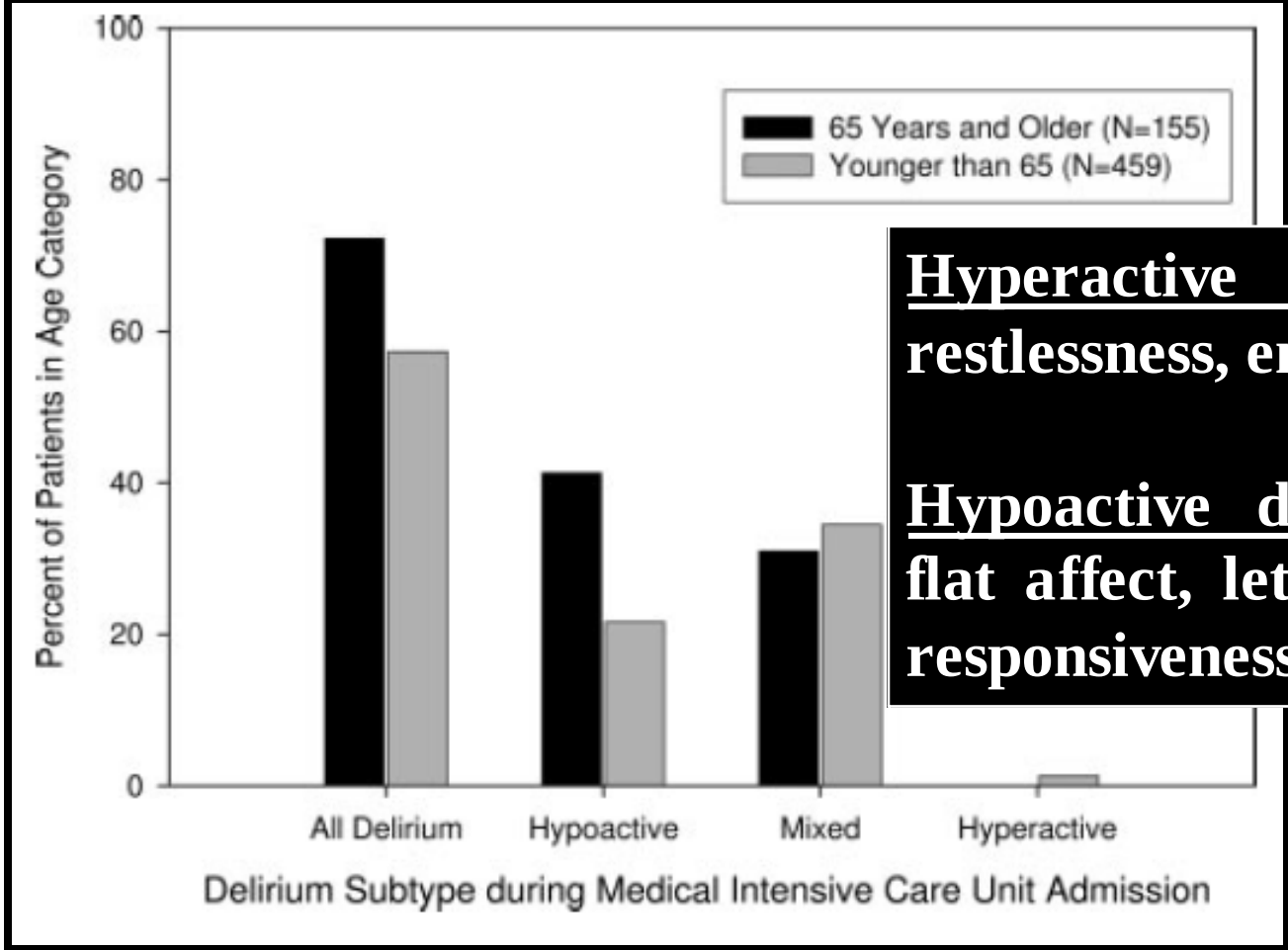


Global Cognition Scores in Survivors of Critical Illness.



Pandharipande et al – NEJM - 2013

DELIRIUM TYPES



Hyperactive delirium: agitation, restlessness, emotional lability

Hypoactive delirium: withdrawal, flat affect, lethargy and decreased responsiveness

All agitated patients are not confused
Most confused patients are not agitated

However, there are some common causes and risk factors between agitation and delirium

DELIRIUM SCALES

Sedation/Agitation :

- **RAMSAY**
- **Richmond Agitation Sedation Scale (RASS)**
- **Adaptation to the Intensive Care Unit Environment (ATICE)**

Delirium :

- **Confusion Assessment Method for the ICU (CAM-ICU)**
- **Intensive Care Delirium Screening Check-list (ICDSC)**

MUST BE COMPLETD BY

1. **A FULL NEUROLOGICAL EXAMINATION (focal sign, neck stiffness…)**
2. **EEG**

CAM-ICU : Échelle d'évaluation des états confusionnels en réanimation

1

RASS supérieure à -4 (entre -3 et +4)

Aller à l'étape 2

RASS égale -4 ou -5

Stop

Ré-évaluer le patient plus tard

2

Évaluation de la confusion (échelle CAM-ICU) : 1 et 2 et (3 ou 4)

1 Altération ou variation

- Modification de l'état mental basal ?
- Variation du RASS au cours des 24 dernières heures ?

Non → STOP Absence de confusion

Oui

et

2 Inattention

Lire les dix lettres suivantes : « **A B R A C A D A B R A** »
Erreur : Si le patient ne serre pas la main sur une lettre « A »
ou si il la serre sur tout autre lettre que « A ».
En cas d'incertitude sur le résultat faire le test des images.

< 3 erreurs → STOP Absence de confusion

≥ 3 erreurs

et

3 Niveau de conscience altéré (vrai « RASS »)

Si RASS = 0 aller à l'étape suivante.

si RASS ≠ 0 → Confusion

RASS = 0

ou

4 Pensée incohérente

1) Est-ce qu'une pierre flotte sur l'eau ? (ou : Est-ce qu'une feuille flotte sur l'eau ?)
2) Y a t'il des poissons dans la mer ? (ou : Y a t'il des éléphants dans la mer ?)
3) Est-ce qu'un kilogramme pèse plus que 2 kilogrammes ? (ou : Est-ce que 2 kg pèsent plus que 1 kg ?)
4) Peut-on utiliser un marteau pour enfoncer un clou ? (ou : Pouvez-vous utiliser un marteau pour couper du bois ?)
5) **Dire** : « Montrez autant de doigts que moi » (en montrant 2 doigts au patient). « Maintenant faites pareil avec l'autre main » (sans répéter le nombre de doigts). Si un bras est indisponible dire « Ajouter un doigt ».

≥ 2 erreurs → Confusion

< 2 erreurs → STOP Absence de confusion

Échelle RASS

Niveau	Description	Définition
+ 4	Combatif	Combatif, danger immédiat envers l'équipe.
+ 3	Très agité	Tire, arrache tuyaux ou cathéters et/ou agressif envers l'équipe.
+ 2	Agité	Mouvements fréquents sans but précis et/ou désadaptation au respirateur
+ 1	Ne tient pas en place	Anxieux ou craintif, mais mouvements orientés, peu fréquents, non vigoureux, non agressif.
0	Éveillé et calme	
- 1	Somnolent	Pas complètement éveillé, mais reste éveillé avec contact visuel à l'appel (> 10s).
- 2	Diminution légère de la vigilance	Reste éveillé brièvement avec contact visuel à l'appel (< 10s).
- 3	Diminution modérée de la vigilance	N'importe quel mouvement à l'appel (ex: ouverture des yeux), mais pas de contact visuel.
- 4	Diminution profonde de la vigilance	Aucun mouvement à l'appel, n'importe quel mouvement à la stimulation physique (friction non nociceptive de l'épaule ou du sternum).
- 5	Non réveillable	Aucun mouvement, ni à l'appel, ni à la stimulation physique (friction non nociceptive de l'épaule ou du sternum).

www.delirriumicu.org
Traduction : d.journois@invivo.edu

ICU Delirium Screening Checklist

Items

Altered level of consciousness (if A or B, do not complete patient evaluation for the period)

A: No response, score: none

B: Response to intense and repeated stimulation (loud voice and pain), score: none

D: Normal wakefulness, score: 0

E: Exaggerated response to normal stimulation, score: 1

Inattention (score: 0 to 1)

Disorientation (score: 0 to 1)

Hallucination-delusion-psychosis (score: 0 to 1)

Psychomotor agitation or retardation (score: 0 to 1)

Inappropriate speech or mood (score: 0 to 1)

Sleep/wake cycle disturbance (score: 0 to 1)

Symptom fluctuation (score: 0 to 1)

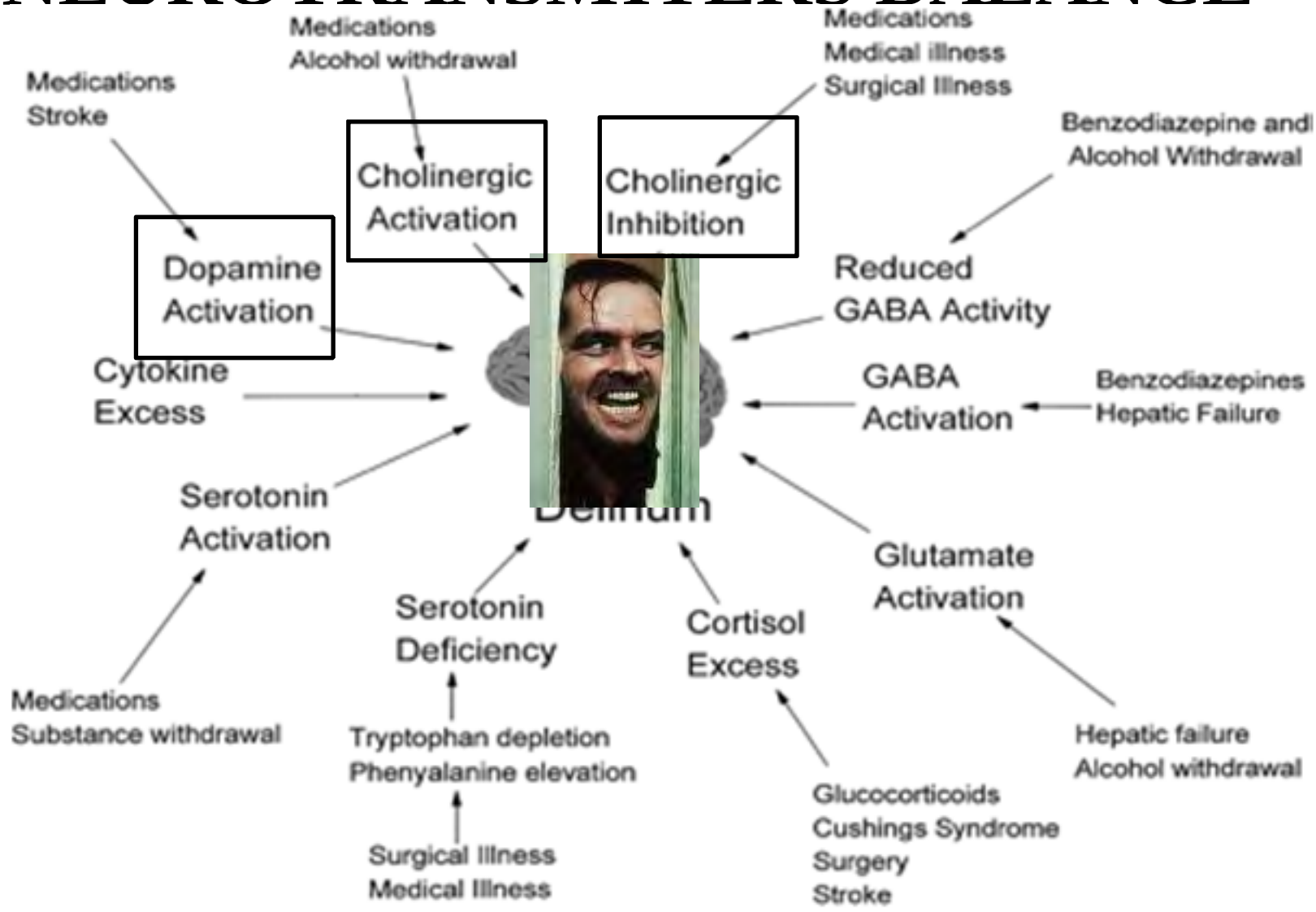
Total (score: 0 to 8)

DIFFERENTIAL DIAGNOSES

Table 1 | Differentiating features of conditions that mimic delirium

Feature	Condition			
	Delirium	**Alzheimer disease**	**Psychotic disorders**	**Depression**
Descriptive features	Confusion and inattention	Memory loss	Loss of contact with reality	Sadness, anhedonia
Onset	Acute	Insidious	Acute or slow	Slow
Course	Fluctuating, often worse at night	Chronic, progressive (but stable over the course of a day)	Chronic, with exacerbations	Single or recurrent episodes; can be chronic
Duration	Hours to months	Months to years	Months to years	Weeks to months
Consciousness	Altered	Normal	Normal	Normal
Attention	Impaired	Normal, except in late stages	May be impaired	May be impaired
Orientation	Fluctuates	Poor	Normal	Normal
Speech	Incoherent	Mild errors	Normal or pressured	Normal or slow
Thought	Disorganized	Impoverished	Disorganized	Normal
Illusions and hallucinations	Common (often visual)	Rare, except in late stages	Common	Not usually
Perceptions	Altered	Altered or normal	Altered	Normal
Psychomotor changes	Yes	No	Yes	Yes
Reversibility	Usually	Rarely	Rarely	Possibly
EEG reading	Moderate to severe background slowing	Normal or mild diffuse slowing	Normal	Normal

DELIRIUM: IMPAIRED NEUROTRANSMITERS BALANCE



BRAIN STRUCTURES

- **Hippocampus and frontal cortex**
  - **Acute brain dysfunction**
  - **Long-term cognitive dysfunction**
  - **But not mortality**
- **Concept of Brainstem Dysfunction**
  - **Mortality**
  - **Impaired arousal**

RISK FACTORS

HOST FACTORS	FACTORS OF CRITICAL ILLNESS	IATROGENIC FACTORS
Age (older)	Acidosis	Immobilization
Alcoholism	Anemia	Medications (opioids, bzd)
APOE4	Fever/infection/sepsis	Antibiotic
(Pre) Dementia	Hypotension	Steroids
Depression	Metabolic disturbances (for example, sodium, calcium, BUN, bilirubin)	Sleep disturbances
Hypertension	Withdrawal syndrome	Dehydration, dyspnea
Smoking	Respiratory disease/ congestive heart failure	
Vision/hearing impairment	High severity of illness	

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 Boqaard et al – BMJ - 2012

The association of intraoperative factors with the development of postoperative delirium.

Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TH.

PATIENTS AND METHODS:

We studied 1,341 patients > 50 years admitted for major elective noncardiac surgery.

RESULTS:

- Postoperative delirium: 117 (9%) patients.
- Route of anesthesia and intraoperative hemodynamic complications were not associated with delirium.
- Delirium was associated with greater intraoperative blood loss, more postoperative blood transfusions, and postoperative hematocrit <30%.
- After adjusting for preoperative risk factors, **postoperative hematocrit <30% was associated with an increased risk of delirium (odds ratio = 1.7, 95% confidence interval 1.1-2.7).**

Am J Med - 1998

POST-OPERATIVE DELIRIUM

	No Delirium	DELIRIUM		
		Hypoactive	Mixed	
	n=98	n=50	n=23	p value
PRE-OPERATIVE VARIABLES				
Clinical				
Age (years)	61±6	71±9	65±9	p=0.002
Co-Morbidities(Charlson Index[a])	1.9±1.5	4.2±2.3	5.0±2.1	p=0.146
Cognitive Function (Mini-Cog[b])	4.6±0.7	2.7±1.6	2.7±1.5	p=0.971
Functional Status (Barthel Index[c])	99±3	90±11	93±11	p=0.173
Laboratory				
Albumin (g/dL)	3.9±0.5	3.3±0.7	3.4±0.7	p=0.753
Hematocrit (%)	44±4	36±8	41±6	p=0.002
Sodium (mEq/L)	139±3	137±3	139±3	p=0.422
Potassium (mEq/L)	4.3±0.5	4.1±0.5	4.2±0.5	p=0.580
Creatinine (mg/dL)	1.1±0.5	1.2±0.7	1.2±0.7	p=1.000
Glucose (mg/dL)	115±41	119±44	112±34	p=0.756
OPERATIONS				
Abdominal	38% (37/98)	58% (29/50)	48% (11/23)	p=0.457
Cardiac	46% (45/98)	26% (13/50)	26% (6/23)	p=1.000
Non-Cardiac Thoracic	8% (8/98)	10% (5/50)	13% (3/23)	p=0.701
Vascular	8% (8/98)	6% (3/50)	13% (3/23)	p=0.372
OUTCOME MEASURES				
ICU Stay (days)	4.6±2.6	8.8±8.7	9.2±5.5	p=0.970
Hospital Stay (days)	8.0±4.6	14.4±11.2	14.5±9.6	p=0.998
Institutionalization	3% (3/98)	42% (21/48)[e]	26% (6/22)[e]	p=0.296
30-Day Mortality	1% (1/98)	14% (7/50)	4% (1/23)	p=0.421
6-Month Mortality	2% (2/96)[d]	32% (16/50)	9% (2/23)	p=0.041

Robinson et al – Arch Surg - 2011

IMPLICATION OF SEDATION, SLEEP and SEPSIS IN ICU DELIRIUM

SEDATION
(very confusing!)

SEDATIVES ET ANALGESICS

Table 2. Daily and Cumulative Doses of Sedative and Analgesic Medications

Drug	Daily ICU Dose, Mean (SD), mg			Cumulative ICU Dose, Mean (SD), mg*		
	No Delirium (n = 41)	Delirium (n = 183)	*P* Value†	No Delirium (n = 41)	Delirium (n = 183)	*P* Value†
Lorazepam	1.12 (2.2)	4.8 (12.8)	.01	9.0 (20.0)	49.2 (131.3)	.001
Propofol	36.6 (258.6)	48.4 (172.9)	.19	362.1 (1265.4)	591.2 (3942.2)	.20
Morphine	5.8 (17.0)	17.3 (163.8)	.79	48.0 (147.0)	168.1 (1321.9)	.66
Fentanyl	0.53 (1.7)	0.78 (1.7)	.22	3.1 (10.3)‡	8.7 (22.9)‡	.12

Abbreviation: ICU, intensive care unit.
*In the persistently comatose patients, the mean (SD) cumulative doses of these medications were: lorazepam, 15 (27) mg; propofol, 318 (1434) mg; morphine, 107 (345) mg; and fentanyl, 3 (12) mg.
†By Wilcoxon rank sum test for no delirium vs delirium.
‡Fentanyl is commonly reported to be 100 times more potent than morphine.[54] Therefore, using a dose conversion factor of 0.01, the median cumulative "morphine equivalent" dose of fentanyl given to patients in the no delirium and delirium groups would equate to 310 mg and 870 mg, respectively. While this mathematical conversion may be flawed or confounded in vivo, such large values are plausible considering fentanyl's initially short duration of action,[18] the potential for rapid tolerance to fentanyl,[62-64] and the administration of fentanyl as a continuous infusion rather than an intermittent bolus.

Ely et al – JAMA - 2004

Richard R. Riker, MD
Yahya Shehabi, MD
Paula M. Bokesch, MD
Daniel Ceraso, MD
Wayne Wisemandle, MA
Firas Koura, MD
Patrick Whitten, MD
Benjamin D. Margolis, MD
Daniel W. Byrne, MS
E. Wesley Ely, MD, MPH
Marcelo G. Rocha, MD
for the SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group

Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients

A Randomized Trial

JAMA. 2009;301(5):489-499

Table 2. Efficacy Outcomes in Patients Treated With Dexmedetomidine vs Midazolam

Outcome	No. (%) Dexmedetomidine (n = 244)	No. (%) Midazolam (n = 122)	*P* Value
Time in target sedation range (RASS score −2 to +1), mean, %[a]	77.3	75.1	.18
Patients completing all daily arousal assessments	225 (92)	103 (84.3)	.09
Patients requiring study drug interruption to maintain RASS score −2 to +1	222 (91)	112 (91.8)	.85
Duration of study drug treatment, median (IQR), d	3.5 (2.0-5.2)	4.1 (2.8-6.1)	.01
Time to extubation, median (95% CI), d[b]	3.7 (3.1-4.0)	5.6 (4.6-5.9)	.01
ICU length of stay, median (95% CI), d[b]	5.9 (5.7-7.0)	7.6 (6.7-8.6)	.24
Delirium			
Prevalence	132 (54)	93 (76.6)	<.001
Mean delirium-free days[c]	2.5	1.7	.002
Open-label midazolam use			
No. treated	153 (63)	60 (49)	.02
Dose, median (IQR), mg/kg[d]	0.09 (0.03-0.23)	0.11 (0.03-0.28)	.65
Fentanyl use			
No. treated	180 (73.8)	97 (79.5)	.25
Dose, median (IQR), µg/kg[d]	6.4 (1.8-26.3)	9.6 (2.9-28.6)	.27

From: **Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation: Two Randomized Controlled Trials**

JAMA. 2012;307(11):1151-1160. doi:10.1001/jama.2012.304

Table 3. Patients' Arousability, Ability to Communicate Pain, and Ability to Cooperate With Nursing Care

	Adjusted Mean Estimate (95% CI)			
	Dexmedetomidine	Preferred Usual Care	*P* Value[a]	Estimate of Difference (95% CI)
Dexmedetomidine vs midazolam (MIDEX)	(n = 249)	(n = 251)		
Total VAS score[b]	49.7 (45.5 to 53.8)	30.0 (25.9 to 34.1)	<.001	19.7 (15.2 to 24.2)
Can the patient communicate pain?	46.3 (41.7 to 50.9)	24.2 (19.7 to 28.8)	<.001	22.1 (17.1 to 27.1)
How arousable is the patient?	58.2 (53.7 to 62.6)	40.7 (36.3 to 45.1)	<.001	17.5 (12.7 to 22.3)
How cooperative is the patient?	44.8 (40.3 to 49.2)	25.1 (20.8 to 29.5)	<.001	19.7 (14.8 to 24.5)
Dexmedetomidine vs propofol (PRODEX)	(n = 251)	(n = 247)		
Total VAS score[b]	51.3 (46.9 to 55.7)	40.1 (35.7 to 44.6)	<.001	11.2 (6.4 to 15.9)
Can the patient communicate pain?	49.3 (44.5 to 54.2)	35.4 (30.5 to 40.4)	<.001	13.9 (8.7 to 19.1)
How arousable is the patient?	59.1 (54.7 to 63.4)	47.8 (43.4 to 52.3)	<.001	11.2 (6.5 to 16.0)
How cooperative is the patient?	47.2 (42.3 to 52.2)	38.0 (33.0 to 43.0)	<.001	9.2 (3.9 to 14.5)

Abbreviation: VAS, visual analogue scale.
[a] Analysis of covariance with effects for treatment, country, and baseline values.
[b] A higher score represents a better outcome.

A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial

Thomas Strøm, Torben Martinussen, Palle Toft

Lancet 2010; 375: 475–80

	No sedation (n=55)	Sedation (n=58)	p value
Days without mechanical ventilation (from intubation to day 28)	13·8 (11·0); 18·0 (0–24·1)	9·6 (10·0); 6·9 (0–20·5)	0·0191*†
Length of stay (days)			
Intensive care unit	13·1 (5·7–··)‡	22·8 (11·7–··)‡	0·0316*§
Hospital	34 (17–65)	58 (33–85)	0·0039*§¶
Mortality			
Intensive care unit	12 (22%)	22 (38%)	0·06
Hospital	20 (36%)	27 (47%)	0·27
Drug doses (mg/kg)‖			
Propofol (per h of infusion)**	0 (0–0·515)	0·773 (0·154–1·648)	0·0001
Midazolam (per h of infusion)	0 (0–0)	0·0034 (0–0·0240)	<0·0001
Morphine (per h of mechanical ventilation)	0·0048 (0·0014–0·0111)	0·0045 (0·0020–0·0064)	0·39
Haloperidol (per day of mechanical ventilation)	0 (0–0·0145)	0 (0–0)	0·0140
Tracheostomy	16 (29%)	17 (29%)	0·98
Ventilator-associated pneumonia	6 (11%)	7 (12%)	0·85

Delirium (DSM IV) **20%** **4%** **0.04**

Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial.

OBJECTIVE:
To compare protocolized sedation with protocolized sedation plus daily sedation interruption in critically ill patients.

INTERVENTION:
Continuous opioid and/or benzodiazepine infusions and random allocation
to protocolized sedation (n = 209) (control)
or to protocolized sedation + daily sedation interruption (n = 214).

RESULTS:
Rates of delirium were not significantly different between groups (53.3% vs 54.1%; relative risk, 0.98; 95% CI, 0.82-1.17; P = .83).

Mehta et al – JAMA - 2012

SEDATIVES METABOLISM

OBJECTIVES:

To compare biological and drug treatment characteristics in patients with coma and/or delirium while in the ICU.

PATIENTS AND MEASUREMENTS:

In 99 patients receiving IV fentanyl, midazolam, or both, we evaluated:

1-drug doses, covariates likely to influence drug effects (age, body mass index, and renal and hepatic dysfunction);
2- delirium risk factors;
3- concomitant administration of CYP3A & P-glycoprotein substrates/inhibitors;
4- ABCB1, ABCG2, and CYP3A5 genetic polymorphisms;
5 - fentanyl and midazolam plasma levels.

CONCLUSIONS:

Coma is associated with fentanyl and midazolam exposure; delirium is unrelated to midazolam and may be linked to inflammatory status.
These data suggest that iatrogenic coma and delirium are not mechanistically linked.

Skrobik et al – Crit Care Med - 2013

EFFECT OF SEDATION ON BRAINSTEM REFLEXES

EFFECTS OF SEDATION

- **Severe septic or critically ill patients often require sedation**
- **Sedation is a risk factor for delirium**
- **How to detect acute brain dysfunction in sedated critically ill patients?**

DESIGN

***Non brain injured** critical ill patients*

Reproducibility of neurological examination was satisfactory

Sharshar et al – Crit Care Med – 2011

NEUROLOGICAL ASSESSMENT

GLASGOW COMA SCALE

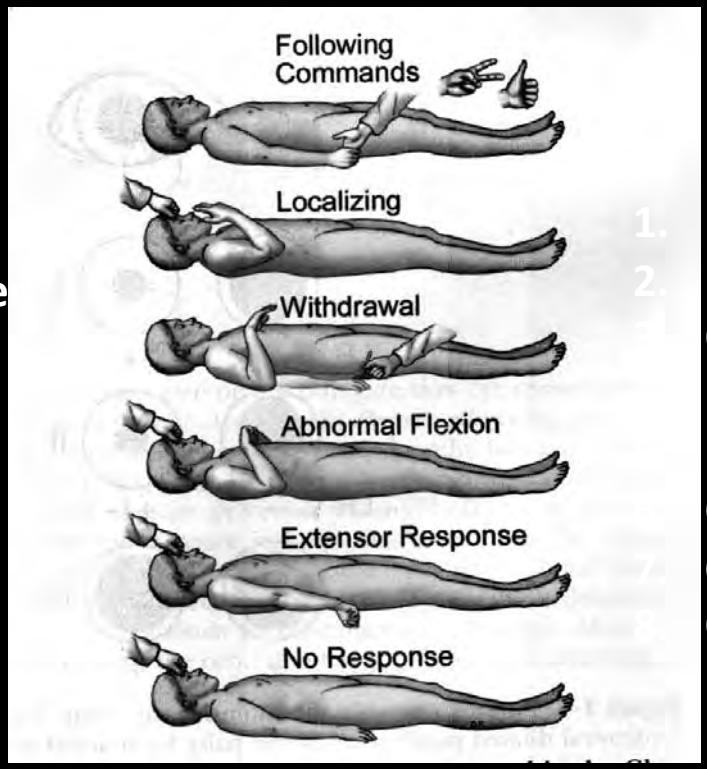
Eyes response

Motor response

Verbal response

FOCAL SIGNS

Comparison between right and left body
1. Motor responses to orde or painful stimulation
2. Limbs tone
3. Tendon reflexes
4. Plantar reflex



BRAINSTEM RESPONSES

1. **Eyes spontaneous movement**
2. **Eyes position**
Oculocephalogyre response
Pupillar size
Pupillar light reflex
Corneal reflex
Grimace
Cough reflex

NEUROLOGICAL EXAMINATION

12-24H OF SEDATION	Fitting set	Validation set
Number of patients	72	72
Midazolam (mg/kg)	0.9 (0.6 to 1.8)	1.3 (0.8 to 2.0)
Subfentanyl (µg/kg)	2.0. (0.8 to 4.0)	2.0 (0.7 to 4.6)
sedation to inclusion (hours)	12 (12-24)	12 (12-24)
ATICE (from 0 to 20)	9 (9 to 10)	9 (9 to 10)
RASS	Not tested	-4 (-4 to -2)
Blinking to strong light (%)	31 (43)	28 (39)
Absent eye movement (%)	66 (93)	67 (93)
Myosis (%)	45 (63)	38 (54)
Pupillary light response (%)	51 (71)	58 (82)
Corneal reflex (%)	65 (90)	66 (92)
Oculocephalic response (%)	32 (47)	33 (46)
Cough response (%)	36 (51)	60 (83)
Grimacing (%)	41 (57)	48 (69)

28-DAYS MORTALITY

Multiple logistic model

RESPONSES ASSESSED BETWEEN THE 12Th AND 24th H OF SEDATION

	Fitting set		Validation set	
	OR (95%CI)	P	OR (95%CI)	P
SAPS-II at inclusion	1.06 (1.02 to 1.09)	0.003	1.03 (1.00 to 1.07)	0.051
Absent cough response	7.80 (2.00 to 30.4)	0.003	5.44 (1.35 to 22.0)	0.017
C-index (SE)	0.836 (0.055)		0.743 (0.067)	

Sharshar et al – Crit Care Med - 2011

ALTERED MENTAL STATUS (after discontinuation of sedation)

Multiple logistic model

RESPONSES ASSESSED BETWEEN THE 12Th AND 24th hours of sedation

	Fitting set		Validation set	
Criteria	Confusion or coma		Delirium or coma	
	OR (95%CI)	P	OR (95%CI)	P
SAPS-II at inclusion	1.04 (1.00 to 1.07)	0.058	1.03 (0.99 to 1.08)	0.10
Absent oculocephalic response	4.49 (1.34 to 15.1)	0.015	5.64 (1.63 to 19.5)	0.006

Sharshar et al – Crit Care Med - 2011

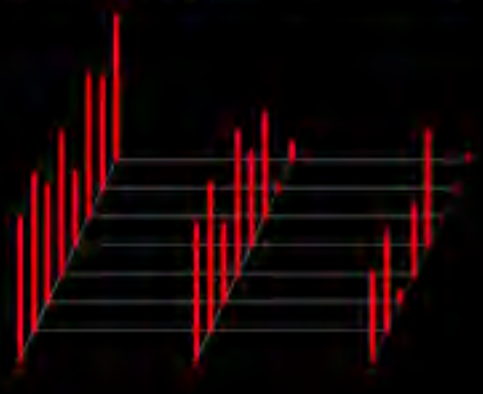
NEUROLOGICAL EXAMINATION

1. **Feasible, reproducible and interpretable**
2. **Enables to detect focal neurological sign**
3. **Enables to estimate critical illness severity (cough reflex)**
4. **Enables to identify patient at risk to develop delirium after sedation discontinuation (Oculocephalogyre response) – Titration of sedation?**

Sharshar et al – Crit Care Med - 2011

NEUROLOGICAL PROFILES

n (%)	Class1 68 (35%)	Class 2 81(41%)	Class 3 48 (24%)	p
GCS Eyes response	1 (2 to 3)	1 (1 to 1)	1 (1 to 1)	< 0.0001
GCS Motor response	4 (4 to 6)	1 (1 to 1)	1 (1 to 1)	< 0.0001
Myosis	30 (44)	46 (57)	39 (81)	0.026
Pupillar light reflex	64 (94)	70 (86)	28 (58)	< 0.0001
Corneal reflex	68 (100)	77 (95)	31 (65)	< 0.0001
Oculocephalogyre reflex	55 (81)	45 (56)	2 (4)	< 0.0001
Grimace	63 (93)	61 (75)	0 (0)	< 0.0001
Cough reflex	65 (96)	68 (84)	24 (50)	< 0.0001



Rohaut et al - Submitted

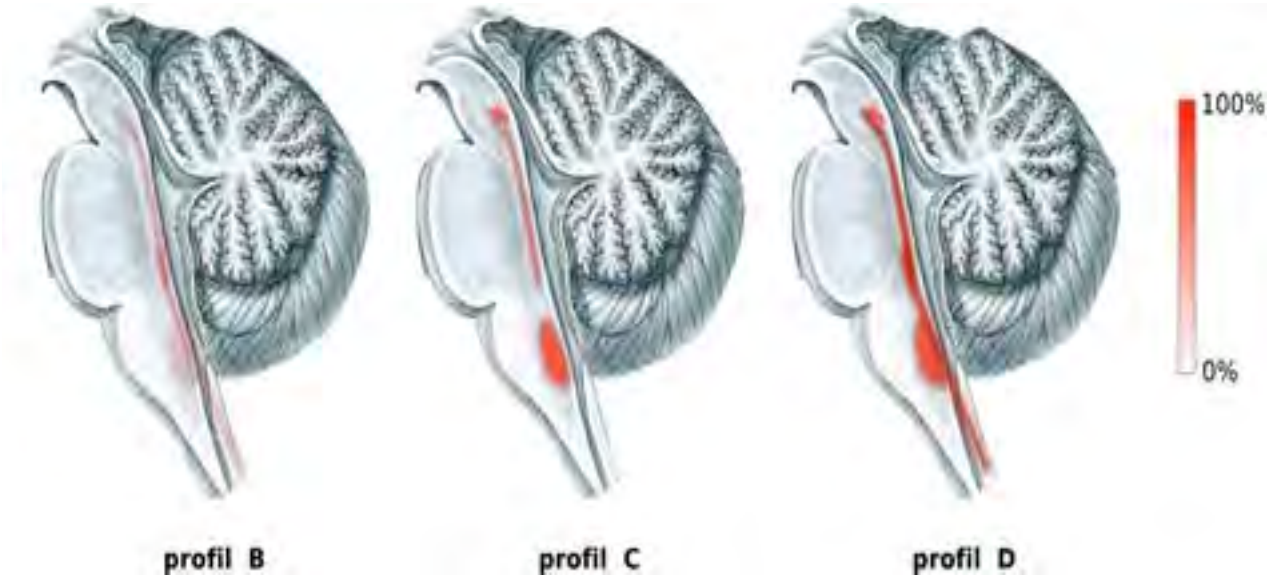
NEUROLOGICAL PROFILES

	Class 1	Class 2	Class 3	p
Median (IQR); n (%)	84 (48)	74 (33)	36 (19)	
Midazolam infusion rate	4.9 (3.1)	6.1 (4.0)	6.0 (4.1)	0.17
Midazolam cumulative dose	1.7 (1.6)	1.6 (1.7)	1.5 (1.3)	0.83
Sufentanyl infusion rate	10.1 (7.6)	13.8 (11.0)	13.1 (10.6)	0.073
Sufentanyl cumulative dose	3.6 (3.1)	3.6 (4.3)	3.5 (3.3)	0.71
Age	61 (51 to 78)	68 (55 to 80)	74 (63 to 82)	0.009
Sexe (%)	32 (47)	30 (37)	18 (38)	0.42
SAPS-II	47 (33 to 60)	56 (40 to 75)	58 (47 to 72)	0.006
RASS	-2 (-4 to -2)	-5 (-5 to -4)	-5 (-5 to -5)	< 0.0001
Sepsis (%)	48 (71)	61 (77)	37 (79)	0.54
Coma (%)	7 (11)	13 (19)	11 (28)	0.08
Delirium (%)	25 (41)	35 (51)	19 (51)	0.45
Coma & Delirium (%)	29 (47)	43 (62)	27 (71)	0.041
ICU mortality (%)	15 (22)	23 (30)	30 (62)	< 0.0001

Rohaut et al - Submitted

HYPOTHESES

Continuum?
Reversibility?



Continuum : process posteriorly spreading from the *area postrema*
(deprived from BBB, neuro-inflammatory signaling)

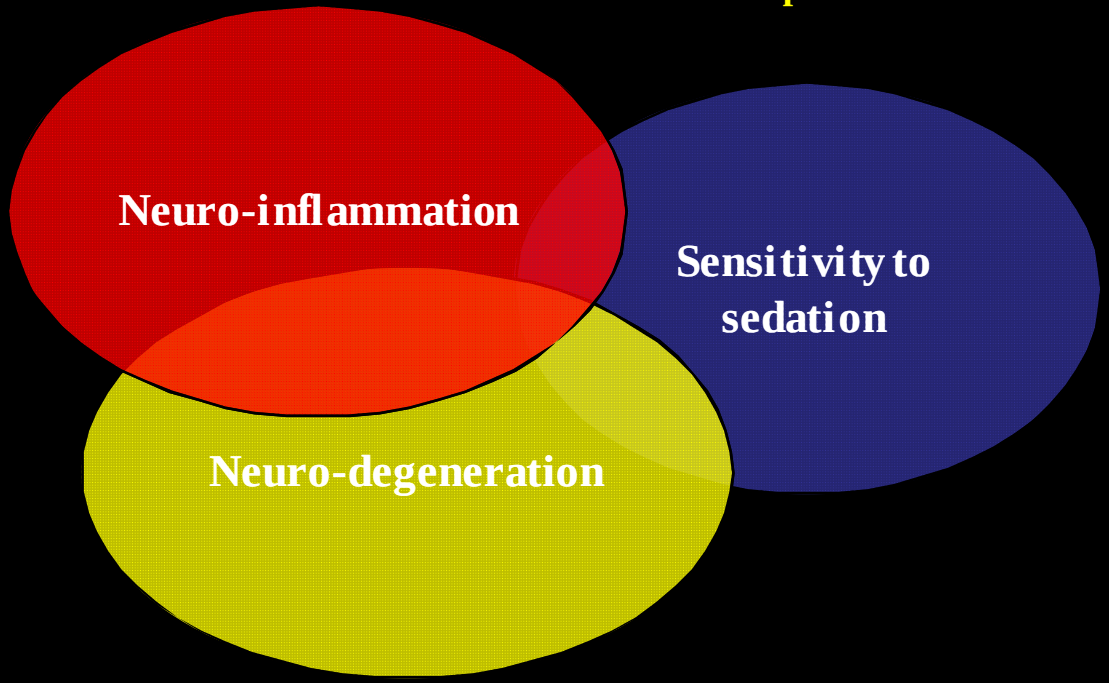
HYPOTHESES

- Difference in SAPS-II
- Neuro-inflammatory process starting at the level of the area postrema (posterio localisation, no BBB)

- No difference in term of sedatives dose

- effect of sedation reduction on profil C or D?

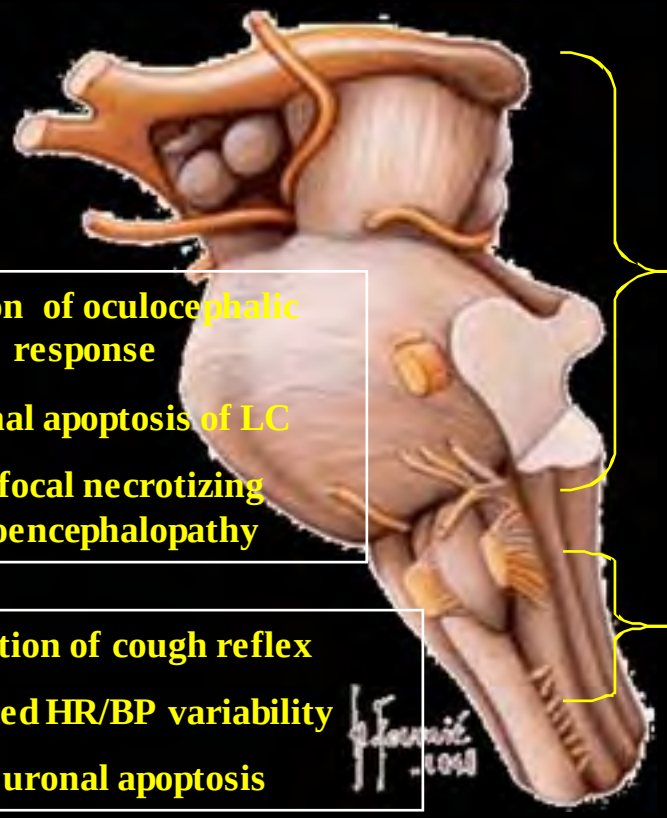
-Animal studies



- Difference in age

- Aging? Animal studies?

CONCEPT OF BRAINSTEM DYSFUNCTION



Abolition of oculocephalic response

Neuronal apoptosis of LC

Multifocal necrotizing leukoencephalopathy

Abolition of cough reflex

Impaired HR/BP variability

Neuronal apoptosis

RAAS dysfunction → Delirium

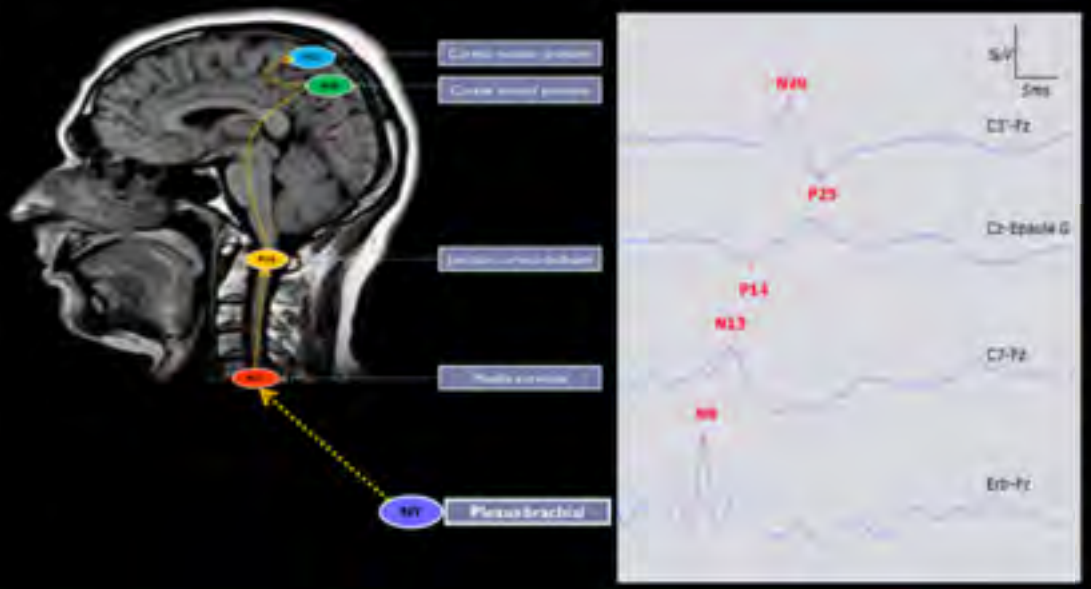
Autonomic dysfunction → Death

Autonomic dysfunction → Hemodynamic failure

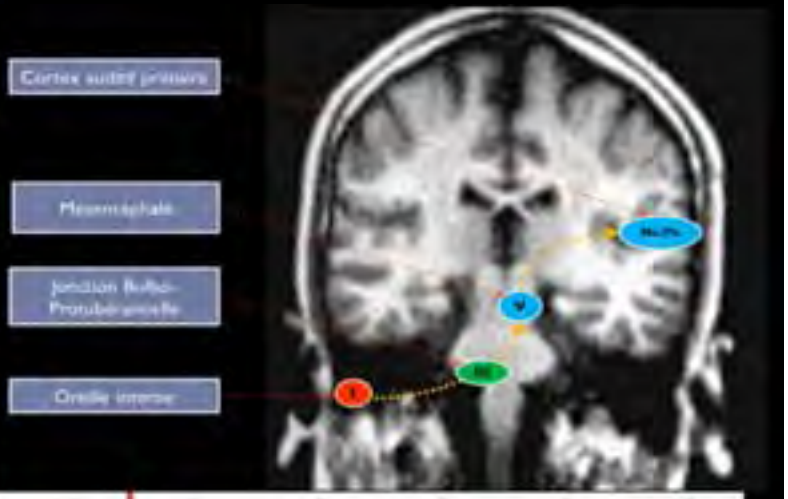
Autonomic dysfunction → Maladaptative immune response

Sharshar et al – CCM – 2002; Sharshar et al – Lancet – 2004; Pandharipande et al – CC - 2011; Annane et al – AJRCCM – 1999; Tracey et al – Nature Review Neuroci

EVOKED POTENTIALS



Réponses successives obtenues après stimulation du nerf médian au poignet: *N9, N13, P14 , N20 et P25*
- Intervalle N9-N13: temps de Conduction radiculaire
- Intervalle P14-N20: temps de Conduction intracrânien
- Intervalle N20-P25: temps de Conduction transcortical



Réponses successives obtenues après stimulation auditive à 70dB:
- *Pics I, II, III , IV et V*
- Intervalle III-V: temps de conduction protubérantielle

EVOKED POTENTIALS

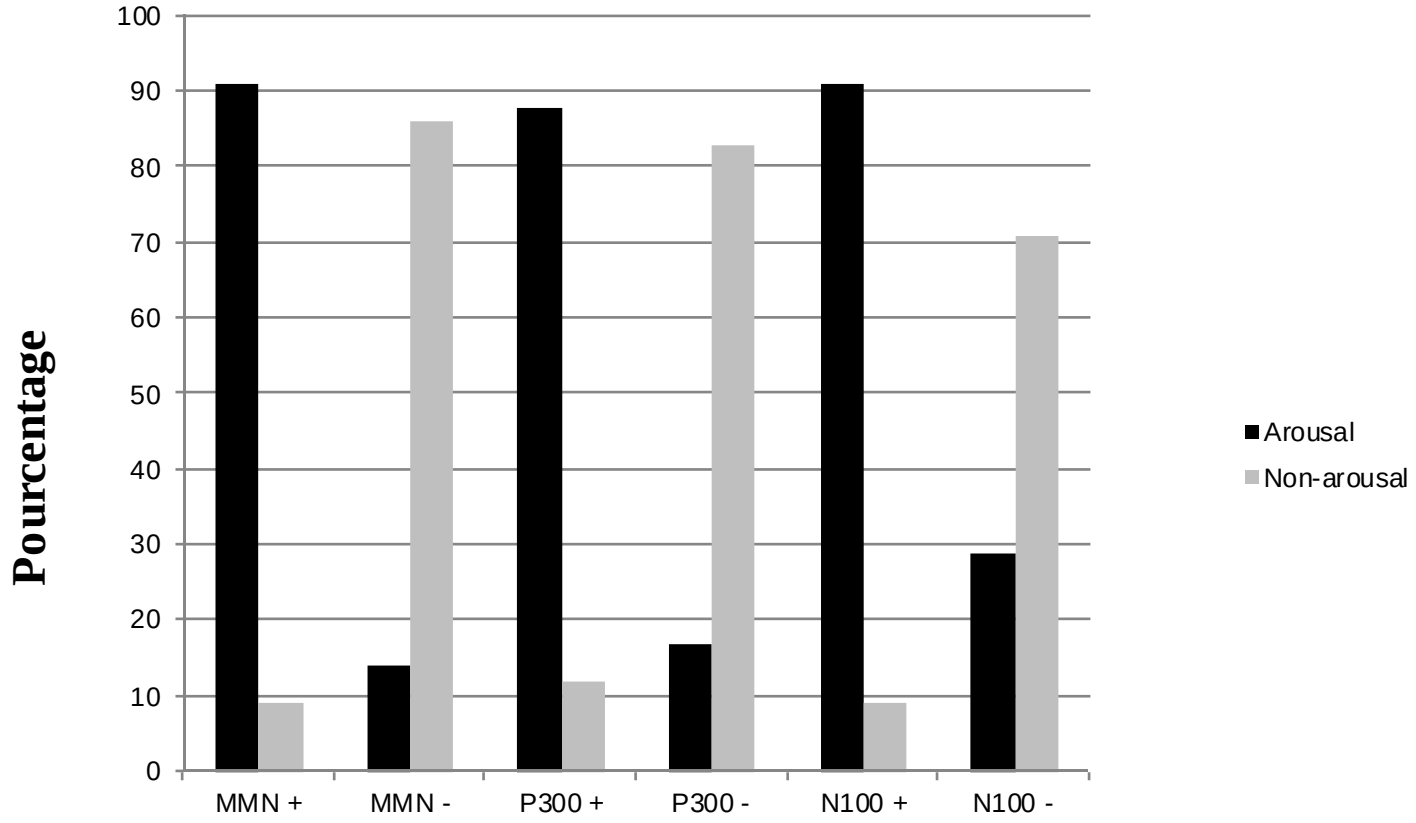
Increased Latency (%)	All patients N=60	Survivors N= 36 (60)	Dead N=24 (40)	Without Delirium N= 15 (25)	Delirium N= 26 (43)
P14	29 (48)	12 (33)	17 (71)	3 (20)	10 (12)
N20	33 (56)	15 (42)	18 (75)	6 (40)	11 (23)
P14-N20	26 (43)	13 (36)	13 (54)	8 (53)	6 (31)
III	21 (35)	10 (28)	11 (46)	5 (33)	6 (19)
V	26 (43)	13 (36)	13 (54)	5 (33)	12 (19)
III-V	14 (23)	8 (22)	6 (25)	2 (13)	9 (8)
Cough reflex	19 (32)	6 (17)	13 (54)	5 (33)	5 (19)
OCR reflex	31 (52)	15 (42)	16 (67)	6 (40)	13 (23)

Sepsis: 55 (91); Age: 62 ± 15; SAPS-II: 50 ± 18

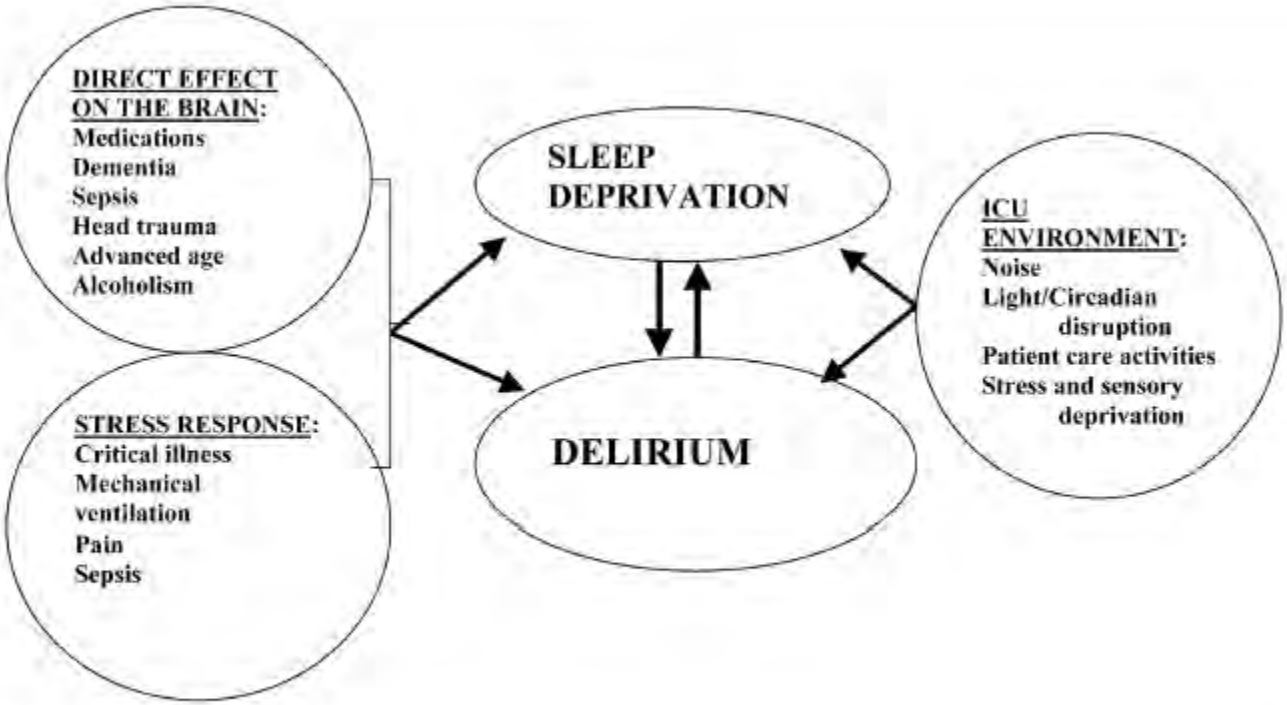
Azabou et al - Submitted

POTENTIELS EVOQUES COGNITIFS

N=40 critically ill sedated patients



SLEEP



Delirium and some associated risk factors. A possible relationship between delirium and some of its associated risk factors, including sleep deprivation. ICU, intensive care unit.

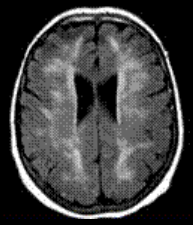
Weinhouse et al – Crit Care - 2013

SEPSIS

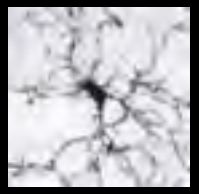
1. **Sepsis is an independant risk factors for agitation (*Jaber et al – ICM - 2003*)**
2. **Sepsis is a major cause of delirium (*Ely et al – JAMA - 2004*) ~ 50%**
3. **Encephalopathy is occuring in 32 to 60% of septic patients (*Eidelman et al -JAMA -1996*)**

PATHOPHYSIOLOGY

Neuroinflammatory process
(Delirium => neurodegenerative)



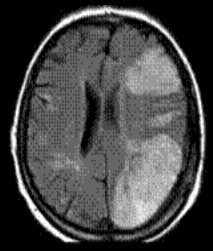
Cytokines
NO

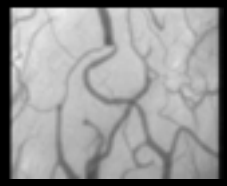


40% mortality

(Sharshar 2007, Polito 2011)

Ischemic process
(Delirium/focal => vascular dementia)

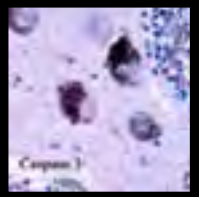




60% mortality

(Polito et al 2013, Sharshar 2007, Sharshar 2004)

Neurotoxic process (Delirium => neurodegenerative)



NEUROINFLAMMATORY PROCESS

EXPERIMENTAL OR CLINICAL DEMONSTRATION

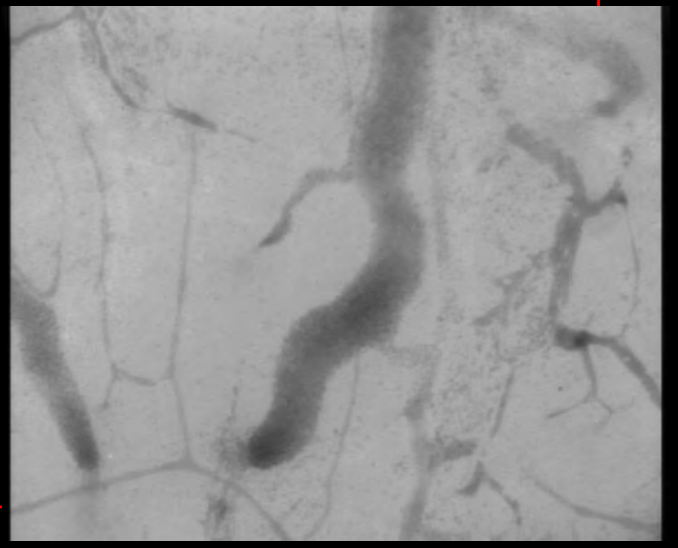
1. **Endothelial activation**
2. **Alteration of blood-brain barrier**
    1. **Role of TNFα**
    2. **Role of complement**
3. **Brain expression of cytokines and iNOS**
4. **Microglial activation**
    1. **Amplification of neuro-inflammatory process**
5. **Brain cells oxidative stress**
6. **Brain cell apoptosis**
7. **Alteration of neurotransmission**

STATINES

MINOCYCLINE

ISCHEMIC PROCESS

1. **Macrocirculatory dysfunction**
    1. Systemic hypotension or decreased blood flow
    2. Impaired autoregulation
2. **Microcirculatory dysfunction**
    1. Role of TNFa
    2. Role of complement
3. **Clotting disorder**



Taccone et al – Crit Care - 2010

CEREBRAL BLOOD FLOW

CONTROVERSIAL

Cerebral blood flow, cerebral vasomotor reactivity, autoregulation and cerebral metabolic rates have been shown to be decreased or preserved in experimental sepsis and in septic patients.

Should we monitor and "optimize" cerebral blood flow in patients with septic shock?

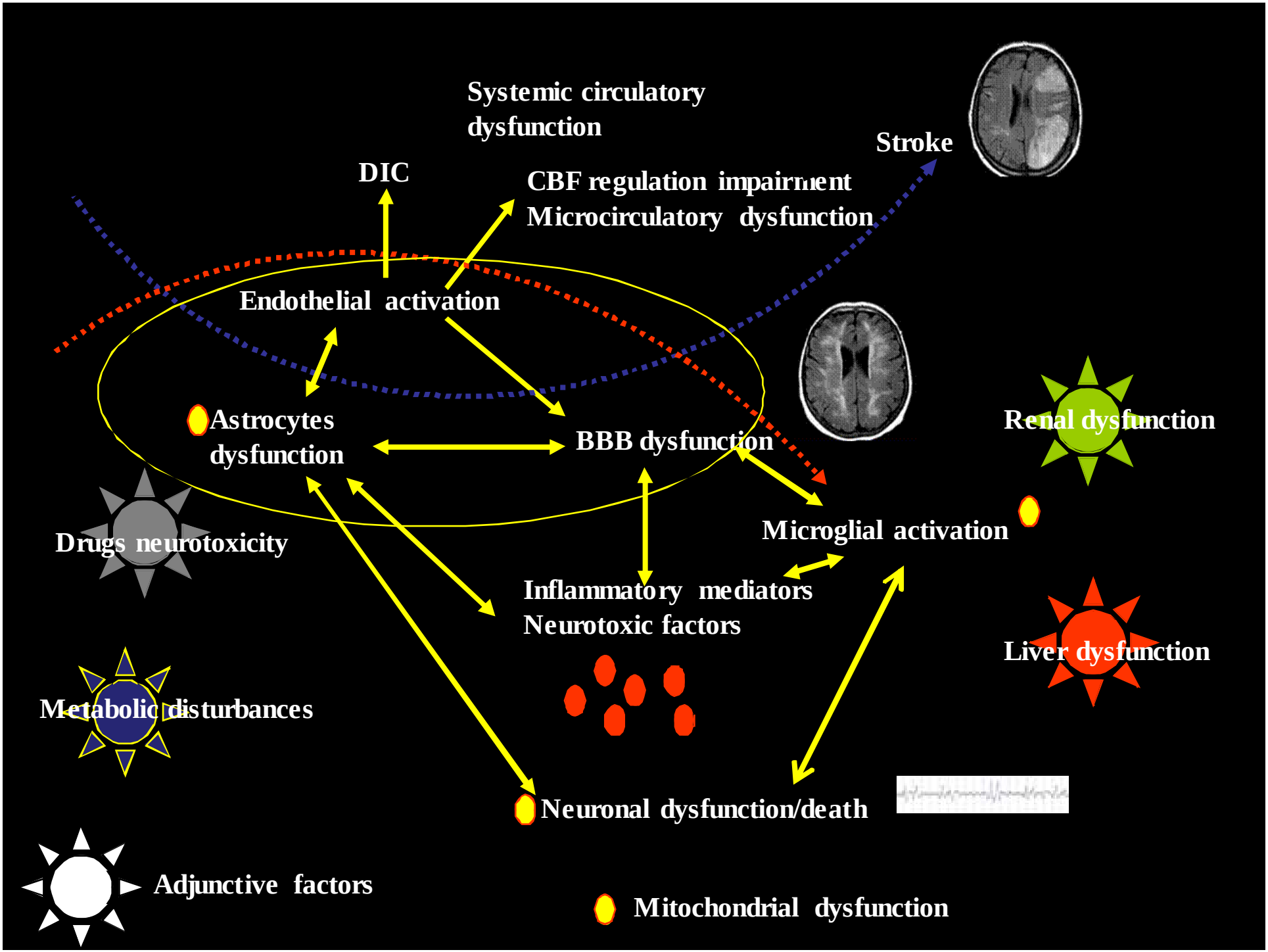
Crit Care - 2010; Siami et al - Crit Care Clin - 2008

NEUROTOXIC PROCESS

- **SAE is characterized by EEG abnormalities**
- **Some EEG patterns are associated with outcome**
- **SAE results from neurotransmission impairment**
- **Sepsis impairs long-term potentiation**
- **Evidence of neuronal apoptosis**

ANTI-EPILEPTIC DRUGS?
(Levetiracetam)

Sharshar et al – Lancet – 2004
Oddo et al – Crit Care Med - 2009


Systemic circulatory dysfunction
Stroke
DIC
CBF regulation impairment
Microcirculatory dysfunction
Endothelial activation
Astrocytes dysfunction
BBB dysfunction
Renal dysfunction
Drugs neurotoxicity
Microglial activation
Inflammatory mediators
Neurotoxic factors
Liver dysfunction
Metabolic disturbances
Neuronal dysfunction/death
Adjunctive factors
Mitochondrial dysfunction

TREATMENT

No specific treatment other than control of sepsis

Persistence or reappearance of delirium often indicates that the sepsis is uncontrolled

Cerebral effects of accepted treatments of septic shock

1. **Activated protein C ? (Effect on endothelial activation)**
2. **Corticosteroids? (decrease in PTSD, effect on BBB)**
3. **Insulin? (neuroprotective?)**

COMPORTEMENT DE MALADIE
REPONSE A L'AGRESSION
ENCEPHALOPATHIE

CONCEPT OF SICKNESS BEHAVIOR

- **Sickness behavior is a major, highly preserved and adaptive component of response to stress.**

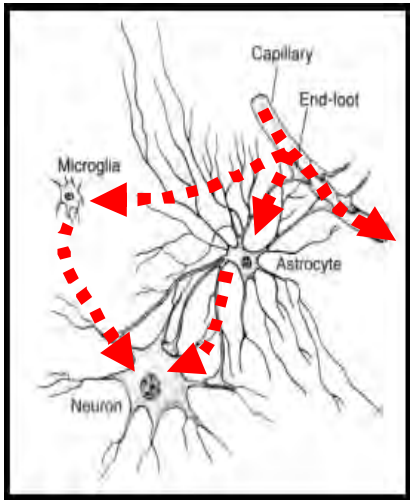
- **The sickness behavior includes stereotypical changes: anxiety, immobility, somnolence, starving, autonomic and neuroendocrine changes etc…**
- **It involves the amygdala and hippocampus and is mediating by specific structures: circumventricular organs and vagal nerve .**

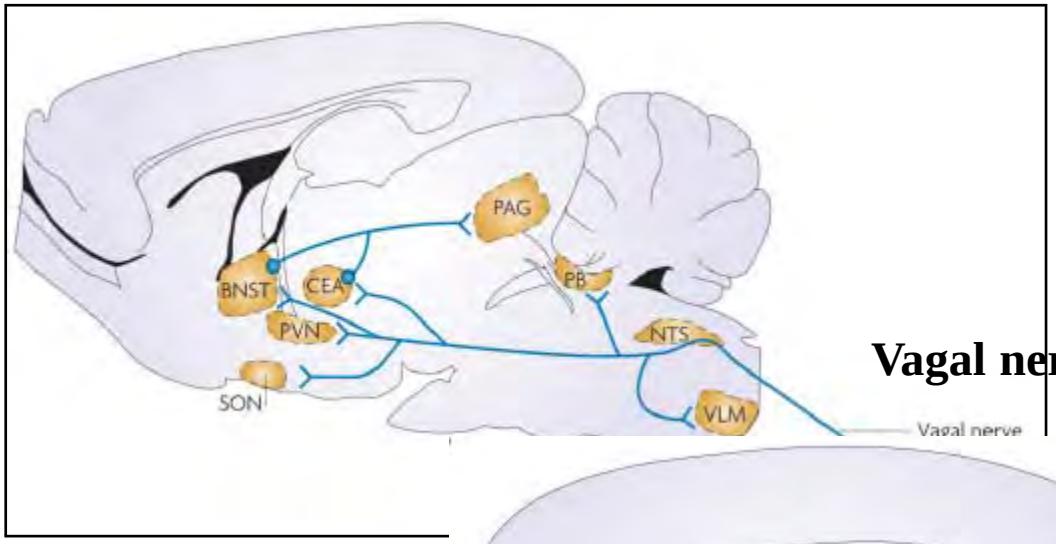
Dantzer et al – Nat Neurosci Rev-2008

PHYSIOLOGICAL BRAIN SIGNALLING

Sickness behavior

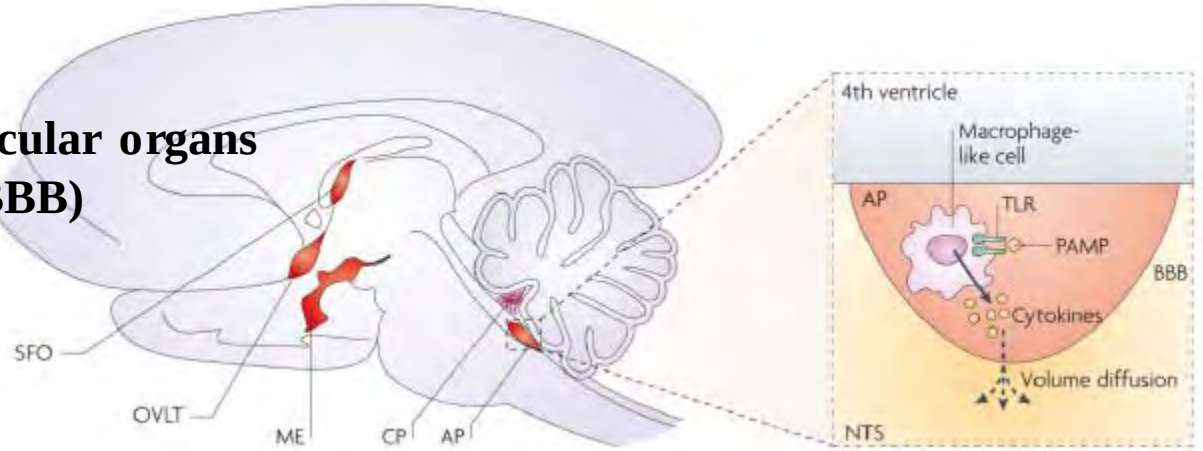
Adapted autonomic and neuroendocine response





Vagal nerve

Circumventricular organs (no BBB)



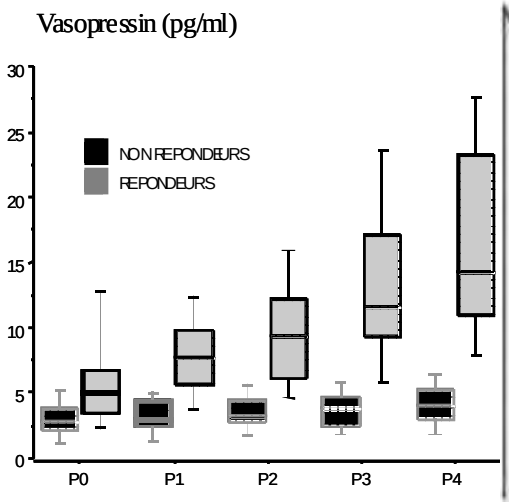
Delirium +

Dantzer et al – Nat Rev Sci - 2008

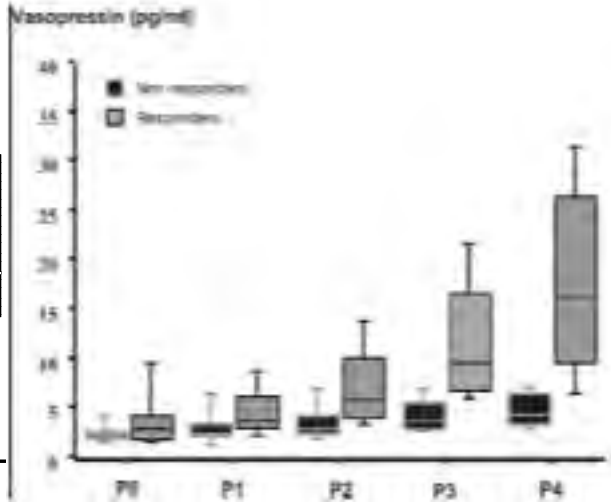
OVLT DYSFUNCTION

Impaired vasopressin secretion during an osmotic challenge and thirst perception in post-acute and recovery phases of septic shock; related to hyperplarisation of osmoreceptors, located in OVLT

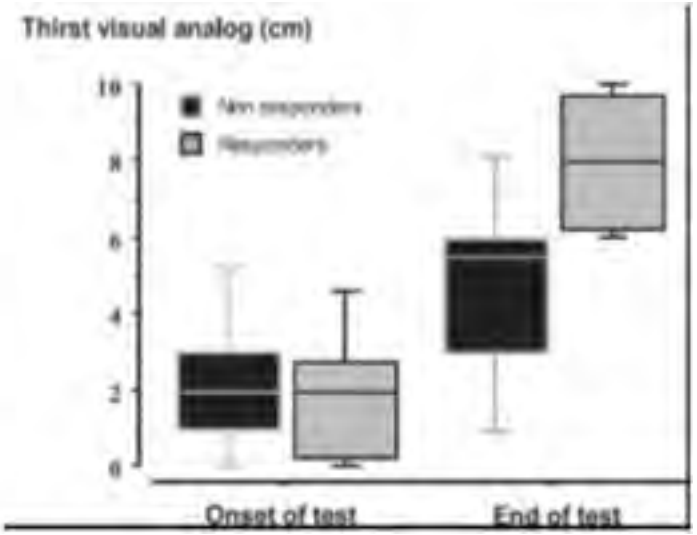
Post-acute phase

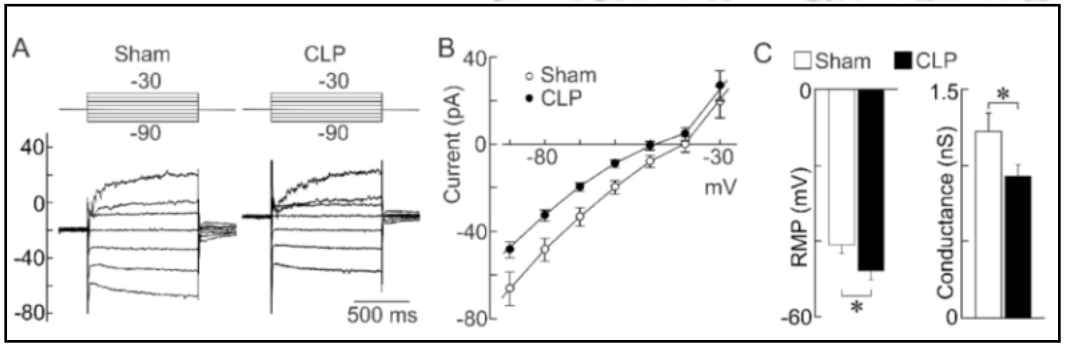


Recovery phase



Recovery phase

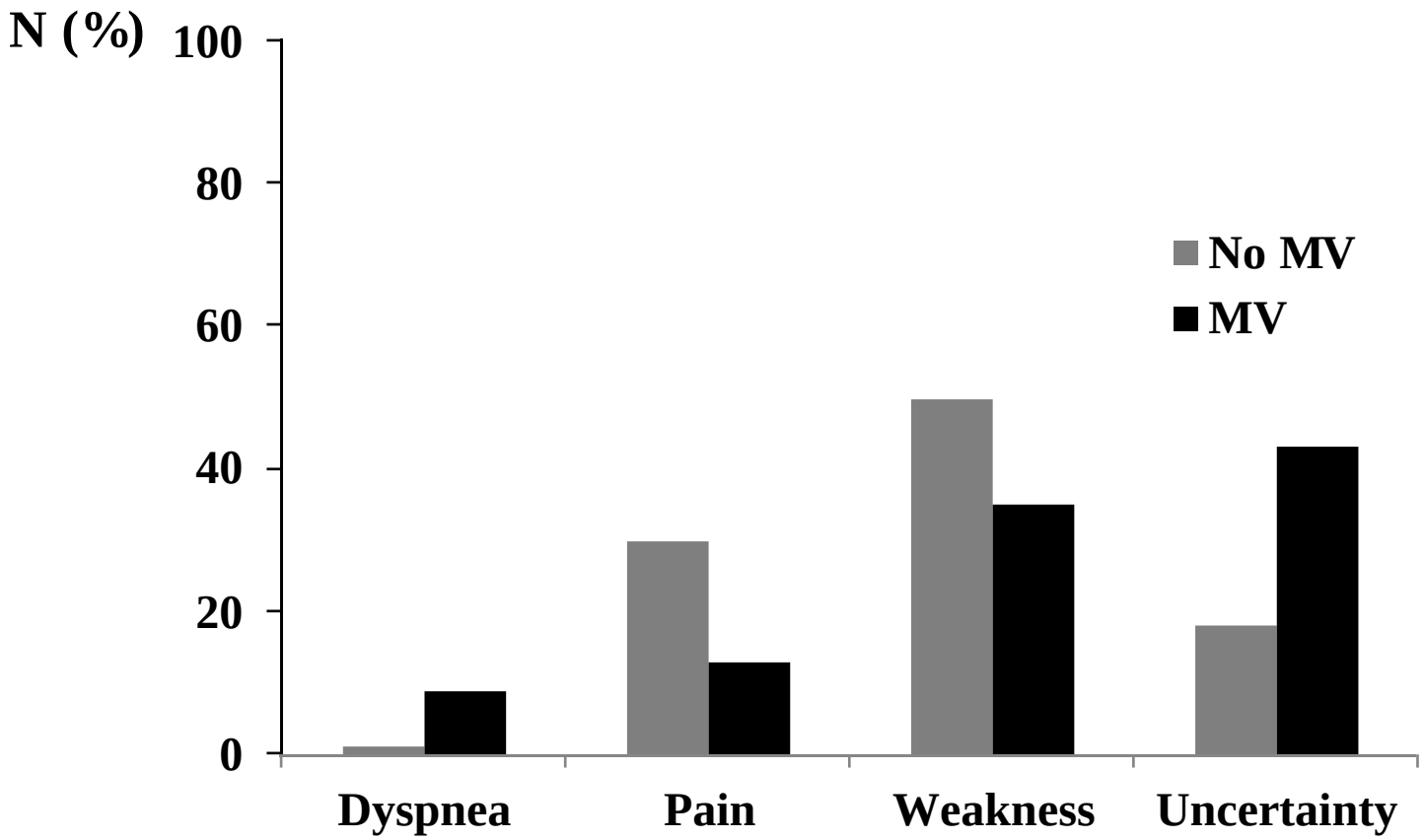




***Patch-Clamp*: Hyperpolarisation of OVLT neurons in CLP**

Siami et al – Crit Care Med – 2010
Siami et al – Plosone – 2013
Siami et al – in process

ANXIETY & FEAR
(*patients with GBS)*



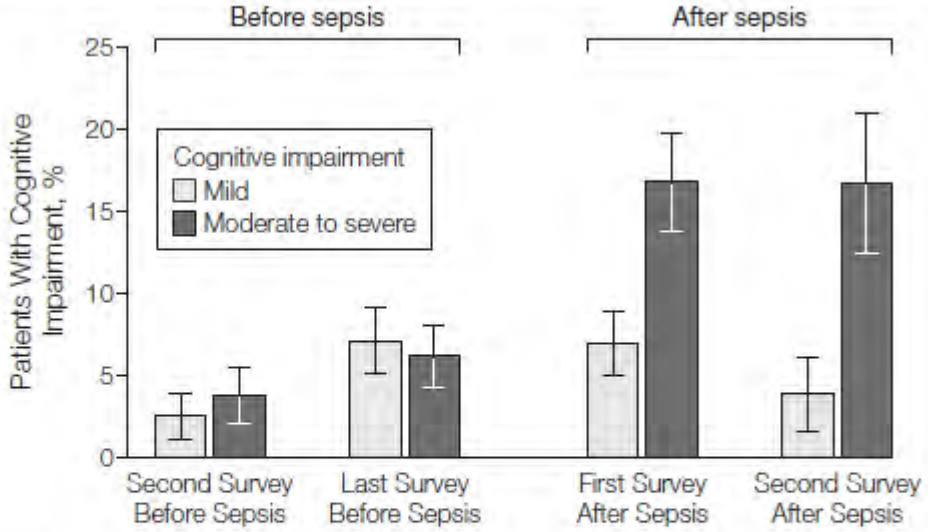
Sharshar et al – BMJopen access-2012

PANICU PROJECT:

TO ASSESS THE PROGNOSIS VALUE OF ANXIETY AT ADMISSION IN ICU

Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

Figure 2. Cognitive Impairment Among Survivors of Severe Sepsis at Each Survey Time Point

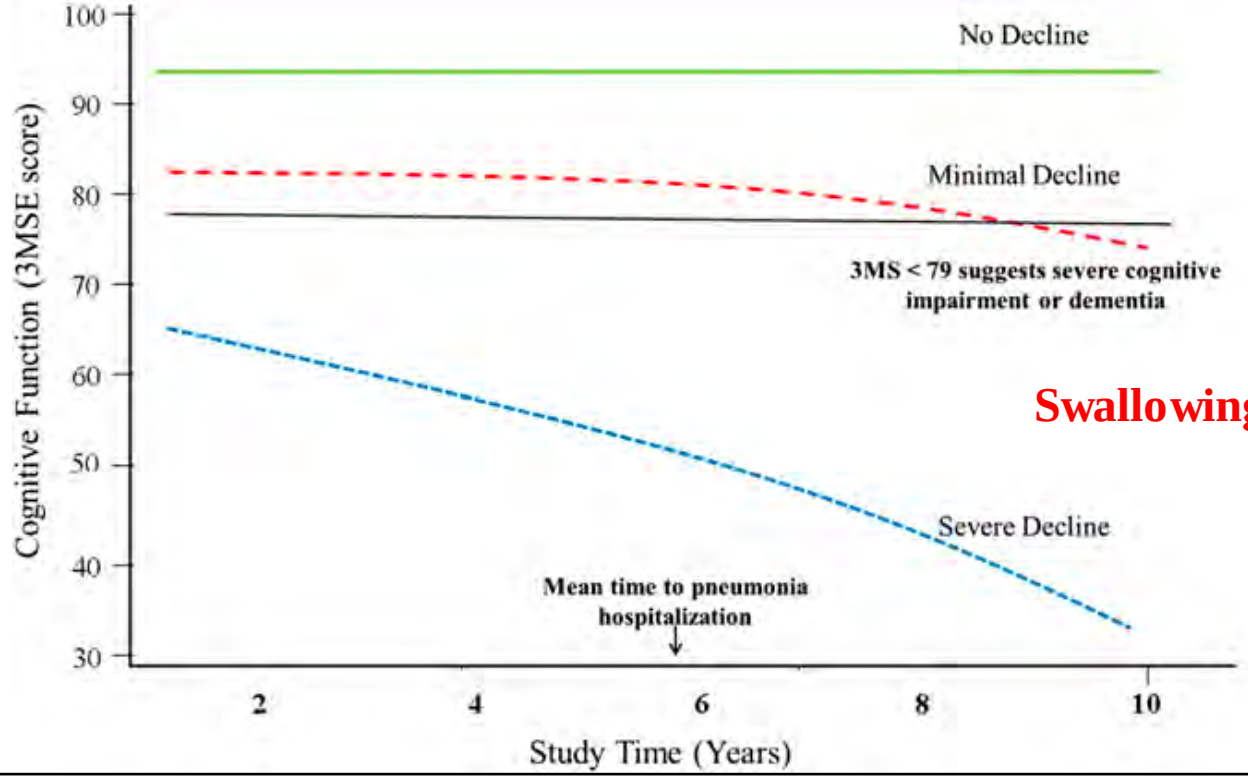


	Second Survey Before Sepsis	Last Survey Before Sepsis	First Survey After Sepsis	Second Survey After Sepsis
Time to sepsis admission, median (IQR), y	−3.1 (−3.7 to −2.7)	−1.1 (−1.7 to −0.7)	0.9 (0.4 to 1.4)	2.8 (2.3 to 3.4)
No. of patients	484	623	623	288

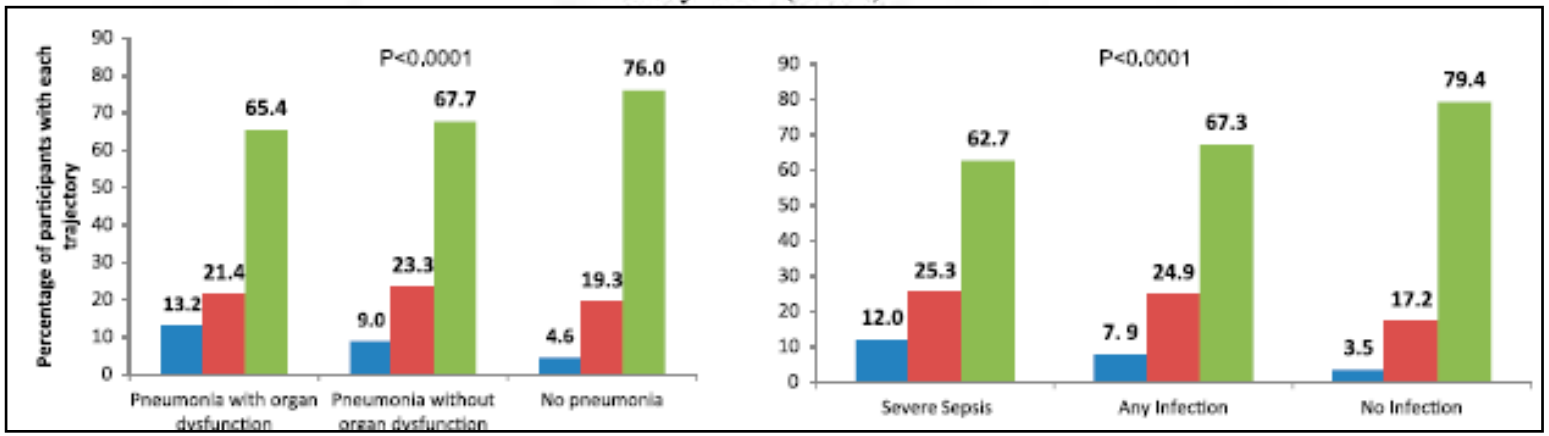
Error bars indicate 95% confidence intervals (CIs); IQR, interquartile range.
Interpretive Example: Compared with stable rates before severe sepsis, the prevalence of moderate to severe cognitive impairment increased from 6.1% (95% CI, 4.2%-8.0%) before severe sepsis to 16.7% (95% CI, 13.8%-19.7%) at the first survey after severe sepsis ($P < .001$ by χ^2 test; Table 2).

Iwashyna et at – JAMA - 2010

Bidirectional Relationship between Cognitive Function and Pneumonia

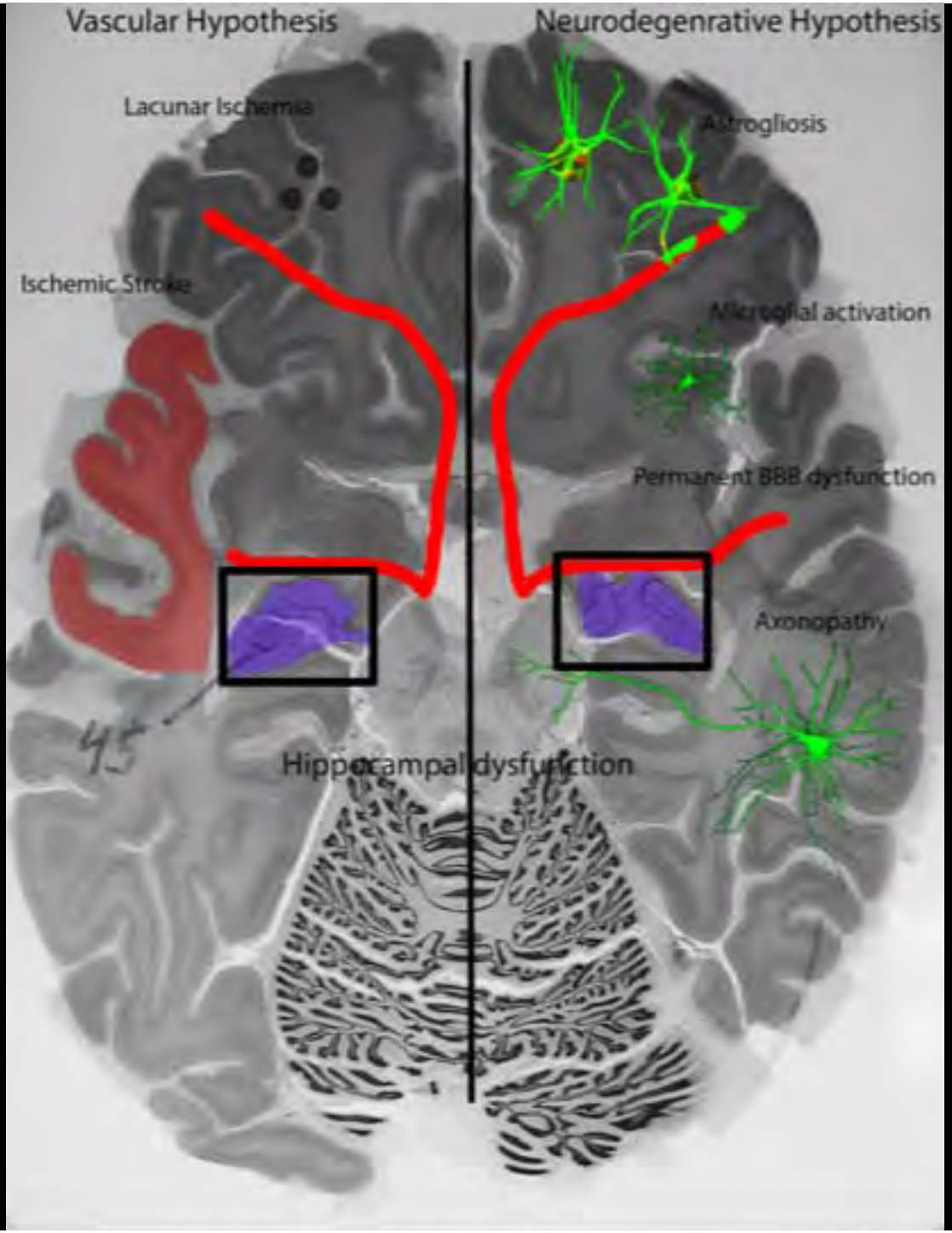


Swallowing dysfunction?



Shah et al- AJRCCM - 2013

MECHANISMS OF LONG-TERM COGNITIVE DECLINE IN SEPSIS



Effects of patient-directed music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilatory support: a randomized clinical trial.

OBJECTIVE:

To test whether listening to self-initiated patient-directed music (PDM) can reduce anxiety and sedative exposure during ventilatory support in critically ill patients.

DESIGN, SETTING, AND PATIENTS:

Randomized clinical trial that enrolled 373 patients from 12 intensive care units (ICUs).

INTERVENTIONS:

Self-initiated PDM (n = 126) with preferred selections tailored by a music therapist whenever desired while receiving ventilatory support, self-initiated use of noise-canceling headphones (NCH; n = 122), or usual care (n = 125).

RESULTS:

Patients in the PDM group had an anxiety score that was 19.5 points lower (95% CI, -32.2 to -6.8) than patients in the usual care group (P = .003).

PDM significantly reduced both measures of sedative exposure.

By the fifth study day, the PDM patients received 2 fewer sedative doses (reduction of 38%) and had a reduction of 36% in sedation intensity.

Chlan et al – JAMA 2012

SLEEP

OBJECTIVES:

To determine if a quality improvement intervention improves sleep and delirium/cognition.

DESIGN:

Observational, pre-post design.

PATIENTS:

300 medical ICU patients.

INTERVENTIONS:

This medical ICU-wide project involved a "usual care" baseline stage, followed by a quality improvement stage incorporating multifaceted sleep-promoting interventions implemented with the aid of daily reminder checklists for ICU staff.

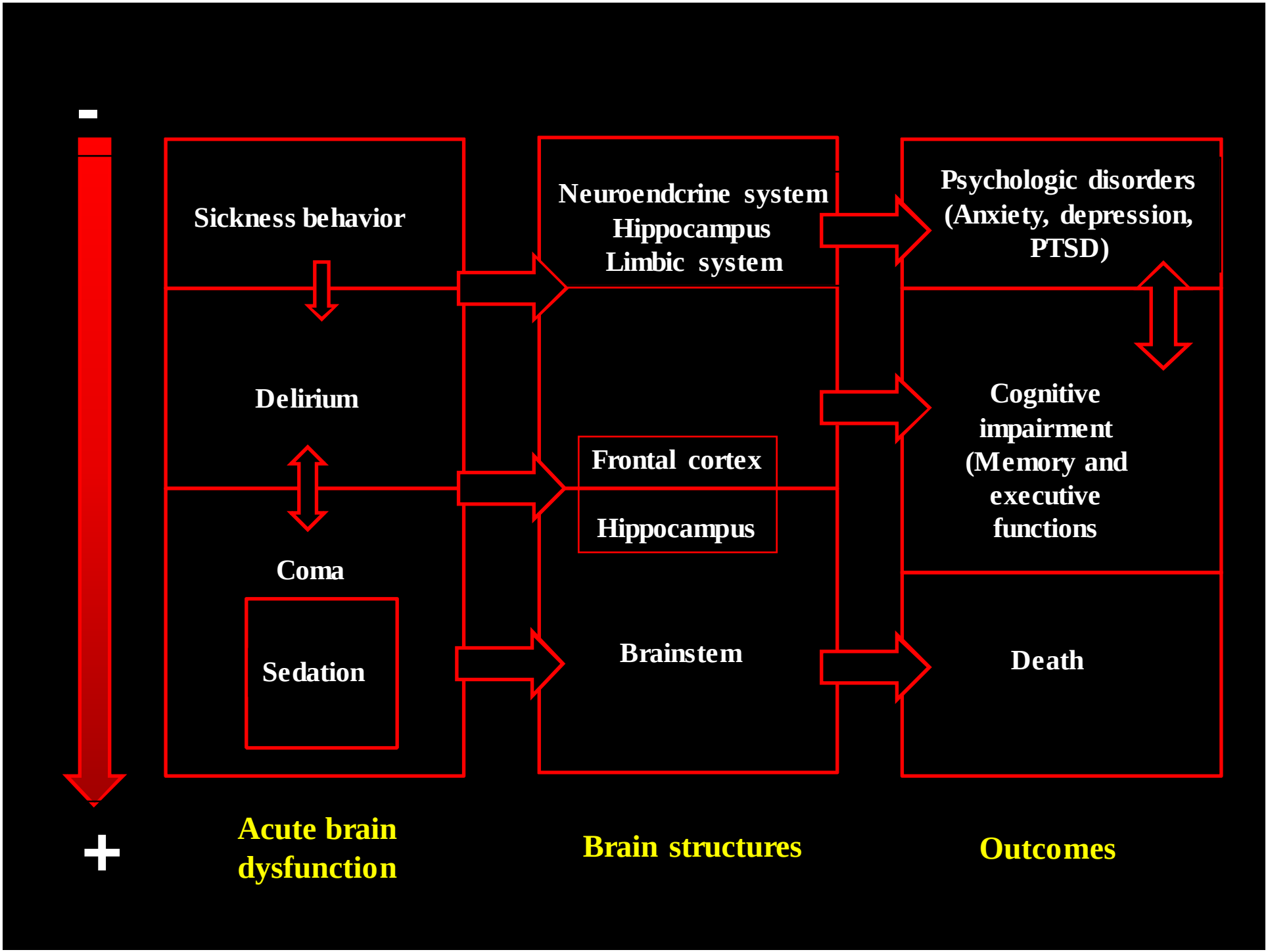
MEASUREMENTS AND MAIN RESULTS:

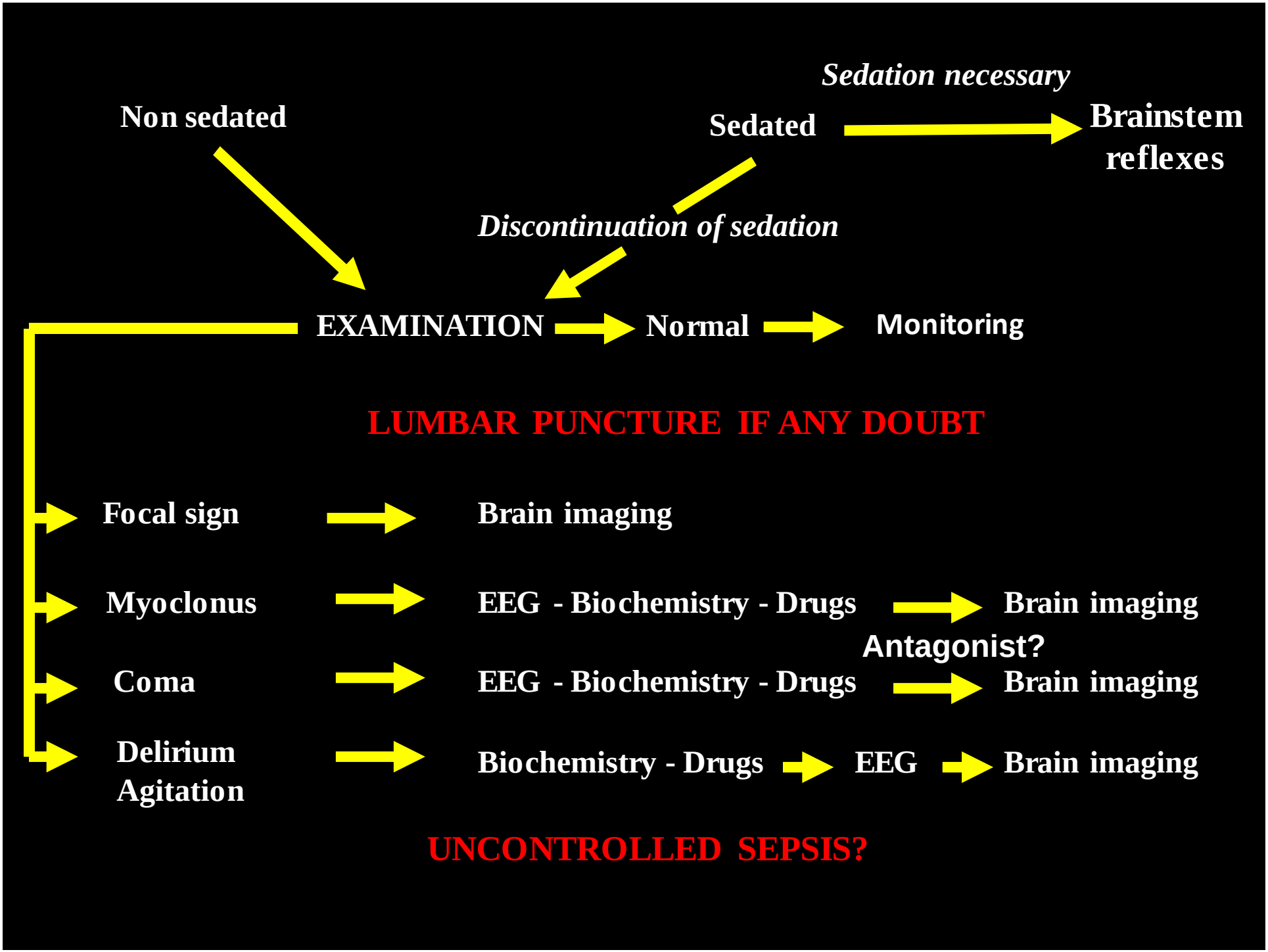
Improvements in overall Richards-Campbell Sleep Questionnaire sleep quality ratings did not reach statistical significance,

but **there were significant improvements** in daily noise ratings (mean ± SD: 65.9±26.6 vs. 60.5±26.3, p = 0.001), **incidence of delirium/coma** (odds ratio: 0.46; 95% confidence interval, 0.23-0.89; p = 0.02), and **daily delirium/coma-free status** (odds ratio: 1.64; 95% confidence interval, 1.04-2.58; p = 0.03).

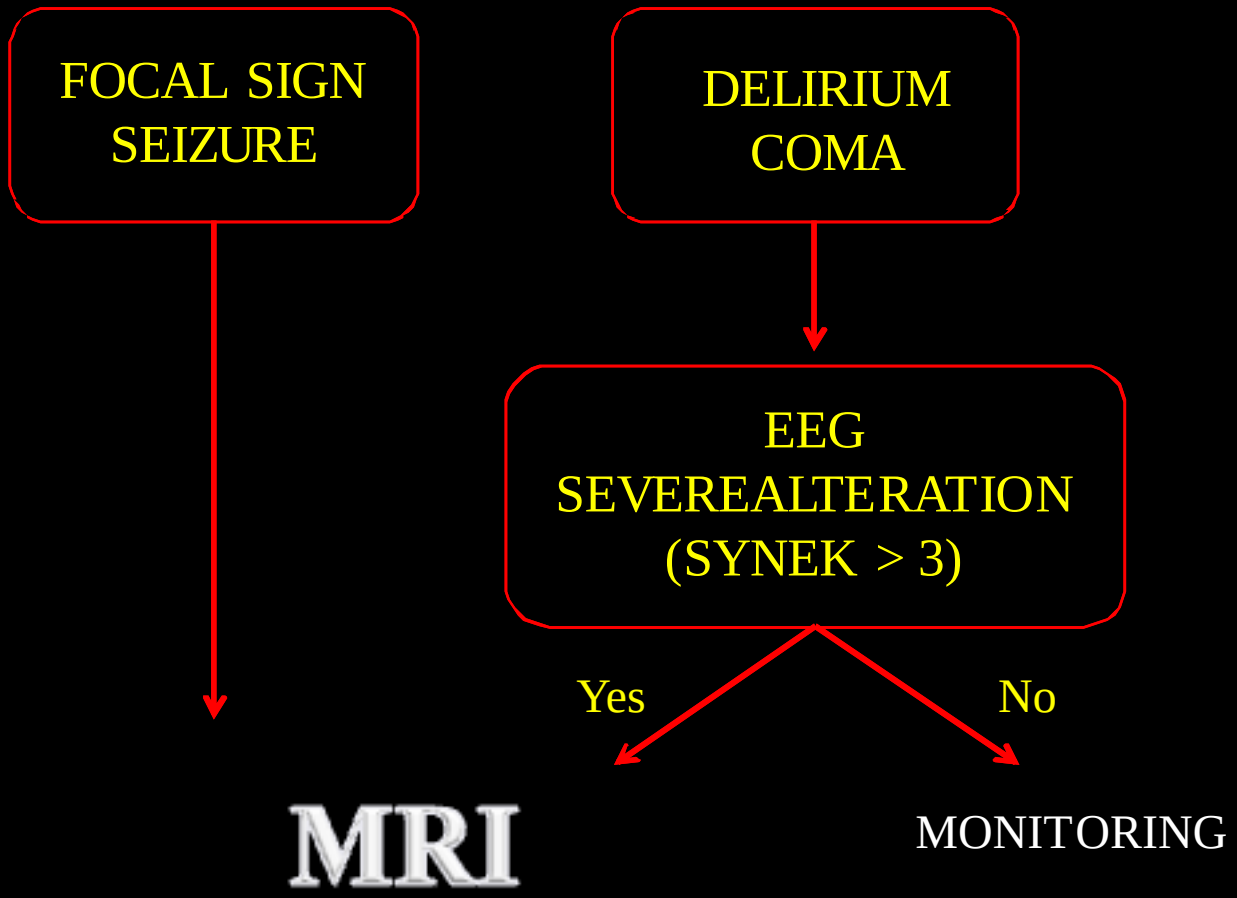
Kamdar et al – Crit Care Med - 2013

MANAGEMENT


-
+
Sickness behavior
Delirium
Coma
Sedation
Neuroendcrine system
Hippocampus
Limbic system
Frontal cortex
Hippocampus
Brainstem
Psychologic disorders
(Anxiety, depression,
PTSD)
Cognitive
impairment
(Memory and
executive
functions
Death
Acute brain
dysfunction
Brain structures
Outcomes


Sedation necessary
Non sedated
Sedated
Brainstem reflexes
Discontinuation of sedation
EXAMINATION
Normal
Monitoring
LUMBAR PUNCTURE IF ANY DOUBT
Focal sign
Brain imaging
Myoclonus
EEG - Biochemistry - Drugs
Brain imaging
Antagonist?
Coma
EEG - Biochemistry - Drugs
Brain imaging
Delirium
Agitation
Biochemistry - Drugs
EEG
Brain imaging
UNCONTROLLED SEPSIS?

MANAGEMENT


FOCAL SIGN
SEIZURE
DELIRIUM
COMA
EEG
SEVEREALTERATION
(SYNEK > 3)
Yes
No
MRI
MONITORING

TREATMENT

Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction

Radtke et al – Br J Anaesth - 2013

A total of 1277 patients of a consecutive sample were randomized (*n*=638 open, *n*=639 blinded).
In one group, the anaesthesiologists were allowed to use the bispectral index (BIS) data to guide anaesthesia
In the other group, BIS monitoring was blinded. Cognitive function was evaluated at baseline, 1 week, and 3 months after operation.

Postoperative delirium: 95 patients (16.7%) in the intervention group versus 124 patients (21.4%) in the control group (*P*=0.036).
The percentage of episodes of deep anaesthesia (BIS values <20) were independently predictive for postoperative delirium (*P*=0.006; odds ratio 1.027).

Haloperidol prophylaxis in critically ill patients with a high risk for delirium

Table 2 Differences between control group and complete intervention group

	Control group (*N* = 299)	Intervention group (*N* = 177)	Differences (*P*-value)
Predicted delirium chance	*73 ± 22*	*75 ± 19*	***0.50***
Observed delirium incidence (n,%)	225 (75%)	115 (65%)	*0.01*
Non-delirium	74 (25%)	62 (35%)	*0.38*
Delirium subtype:			
- Hyperactive	20 (7%)	6 (3%)	
- Hypoactive	81 (27%)	33 (19%)	
- Mixed	124 (41%)	76 (43%)	
Number of delirium free days without coma in 28 days	13 (3 to 27)	20 (8 to 27)	*0.003*
Re-intubation (%)	25 (8%)	15 (9%)	*0.51*
Duration mechanical ventilation in hrs	118 (39 to 250)	90 (36 to 229)	*0.24*
Unplanned removal tubes/lines (%)	58 (19%)	21 (12%)	*0.02*
- Tube	8 (3%)	4 (2%)	
- Gastric tube	26 (9%)	14 (8%)	
- CVC/arterial line	24 (8%)	1 (<1%)	
- Other	0 (0%)	2 (1%)	
Re-admission	55 (18%)	20 (11%)	*0.03*
LOS-ICU	7 (3 to 13)	6 (3 to 12)	*0.65*
LOS-in hospital	21 (12 to 41)	20 (11 to 31)	*0.16*
28-day mortality	36 (12%)	13 (7.3%)	*0.03**

Data are presented as median, interquartile range (IQR), unless mentioned otherwise. * Cox proportional hazard regression analysis adjusted for sepsis and cohort (hazard rate 0.80; 95% CI 0.66 to 0.98.

Haloperidol: 1mg/8h

Van den Boogaard et al – Crit Care - 2013

Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial

Valerie J Page, E Wesley Ely, Simon Gates, Xiao Bei Zhao, Timothy Alce, Ayumi Shintani, Jim Jackson, Gavin D Perkins, Daniel F McAuley

Methods We did this double-blind, placebo-controlled randomised trial in a general adult intensive care unit (ICU). Critically ill patients (≥18 years) needing mechanical ventilation within 72 h of admission were enrolled. Patients were randomised (by an independent nurse, in 1:1 ratio, with permuted block size of four and six, using a centralised, secure web-based randomisation service) to receive haloperidol 2·5 mg or 0·9% saline placebo intravenously every 8 h, irrespective of coma or delirium status. Study drug was discontinued on ICU discharge, once delirium-free and coma-free for 2 consecutive days, or after a maximum of 14 days of treatment, whichever came first. Delirium was assessed using the confusion assessment method for the ICU (CAM-ICU). The primary outcome was delirium-free and coma-free days, defined as the number of days in the first 14 days after randomisation during which the patient was alive without delirium and not in coma from any cause. Patients who died within the 14 day study period were recorded as having 0 days free of delirium and coma. ICU clinical and research staff and patients were masked to treatment throughout the study. Analyses were by intention to treat. This trial is registered with the International Standard Randomised Controlled Trial Registry, number ISRCTN83567338.

	Haloperidol (n=71)	Placebo (n=70)	Difference (95% CI)* or RR (95% CI)*	p value
Alive, delirium-free, and coma-free days in first 14 days	5 (0-10)	6 (0-11)	-0·48 (-2·08 to 1·21)	0·53
Days in delirium in first 14 days†	5 (2-8)	5 (1-8)	0·01 (-1·31 to 1·33)	0·99
Days in coma in first 14 days†	0 (0-2)	0·5 (0-2)	0·00 (-0·68 to 0·67)	0·99
Alive, delirium-free, and coma-free days in first 28 days	19 (0-24)	19·5 (0-25)	-0·26 (-3·72 to 3·46)	0·57
Days in delirium in first 28 days†	5 (2-10)	5 (1-9)	-0·38 (-2·37 to 1·62)	0·71
Days in coma in first 28 days†	0 (0-2)	1 (0-2)	-0·05 (-0·82 to 0·72)	0·90
Ventilator-free days in first 28 days	21 (0-25)	17 (0-25)	0·25 (-3·26 to 4·16)	0·88
Mortality at 28 days	20 (28·2%)	19 (27·1%)	RR 1·04 (0·61 to 1·77)	..
Length of critical care stay (days)‡	9·5 (5-14)	9 (5-18)	-1·45 (-5·42 to 2·52)	0·47
Length of hospital stay (days)§	18·5 (12-31)	26 (15-40)	-5·13 (-21·75 to 11·48)	0·54

Data are number (%), median (IQR), unless otherwise specified. RR=risk ratio. *CI bootstrapped. †Including patients who died within study period. ‡Excluding patients who died in ICU: n=52 for haloperidol, n=51 for placebo. §Excluding patients who died in hospital: n=42 for haloperidol, n=47 for placebo.

Table 3: Outcomes

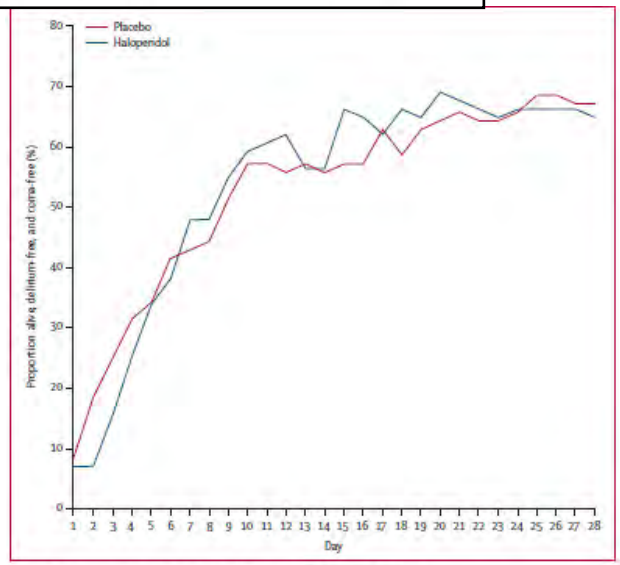


Figure 2: Proportion of study patients with resolution of delirium over time

Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial

William D Schweickert, Mark C Pohlman, Anne S Pohlman, Celerina Nigos, Amy J Pawlik, Cheryl L Esbrook, Linda Spears, Megan Miller, Mietka Franczyk, Deanna Deprizio, Gregory A Schmidt, Amy Bowman, Rhonda Barr, Kathryn E McCallister, Jesse B Hall, John P Kress

Lancet 2009; 373: 1874–82

	Intervention (n=49)	Control (n=55)	p value
Return to independent functional status at hospital discharge	29 (59%)	19 (35%)	0·02
ICU delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–7·0)	0·03
Time in ICU with delirium (%)	33% (0–58)	57% (33–69)	0·02
Hospital delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–8·0)	0·02
Hospital days with delirium (%)	28% (26)	41% (27)	0·01
Barthel Index score at hospital discharge	75 (7·5–95)	55 (0–85)	0·05
ICU-acquired paresis at hospital discharge	15 (31%)	27 (49%)	0·09
Ventilator-free days*	23·5 (7·4–25·6)	21·1 (0·0–23·8)	0·05
Duration of mechanical ventilation (days)	3·4 (2·3–7·3)	6·1 (4·0–9·6)	0·02
Duration of mechanical ventilation, survivors (days)	3·7 (2·3–7·7)	5·6 (3·4–8·4)	0·19
Duration of mechanical ventilation, non-survivors (days)	2·5 (2·4–5·5)	9·5 (5·9–14·1)	0·04
Length of stay in ICU (days)	5·9 (4·5–13·2)	7·9 (6·1–12·9)	0·08
Length of stay in hospital (days)	13·5 (8·0–23·1)	12·9 (8·9–19·8)	0·93
Hospital mortality	9 (18%)	14 (25%)	0·53

Data are n (%), median (IQR), or mean (SD). ICU=intensive care unit. *Ventilator-free days from study day 1 to day 28. Barthel Index scale 0–100, APACHE II scale 0–71.

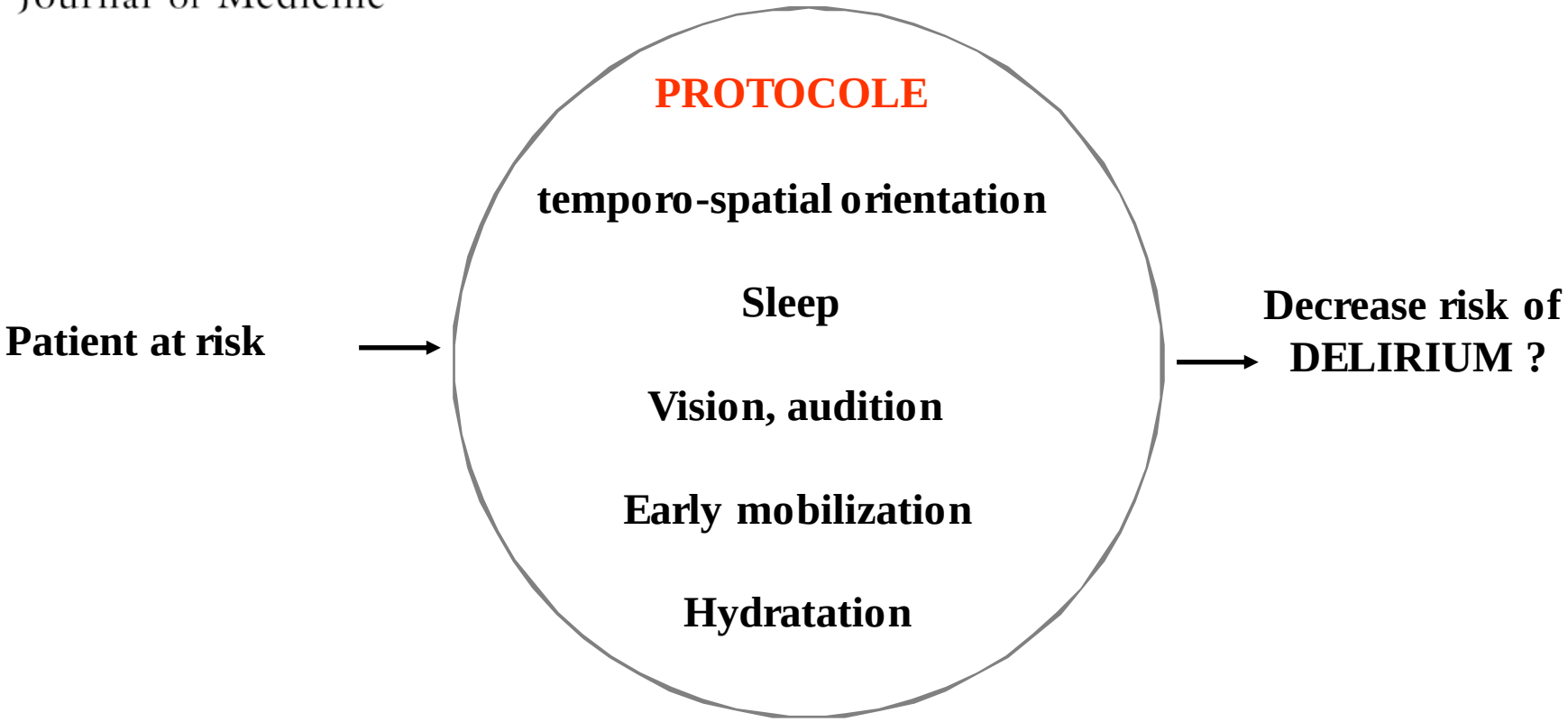
Table 3: Main outcomes according to study group

A MULTICOMPONENT INTERVENTION TO PREVENT DELIRIUM IN HOSPITALIZED OLDER PATIENTS

SHARON K. INOUYE, M.D., M.P.H., SIDNEY T. BOGARDUS, JR., M.D., PETER A. CHARPENTIER, M.P.H., LINDA LEO-SUMMERS, M.P.H., DENISE ACAMPORA, M.P.H., THEODORE R. HOLFORD, PH.D., AND LEO M. COONEY, JR., M.D.

The New England Journal of Medicine

MARCH 4, 1999



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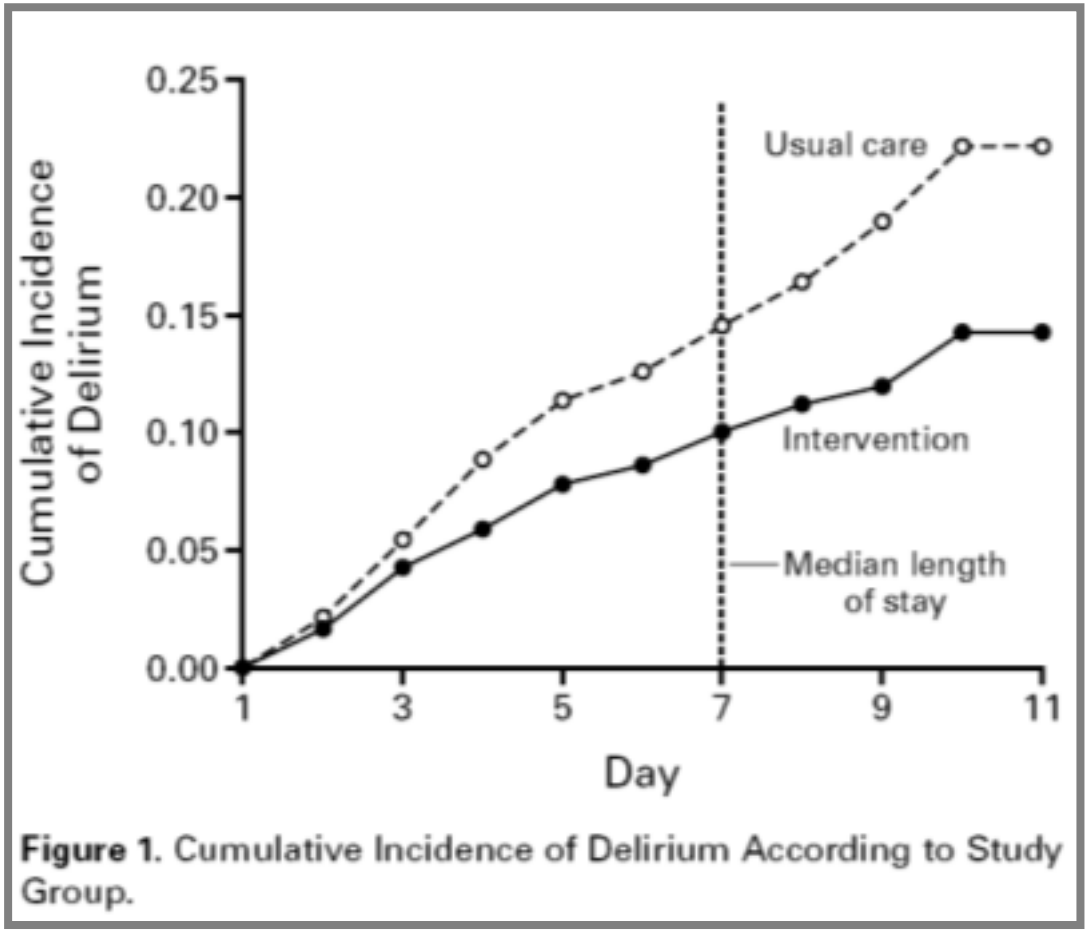
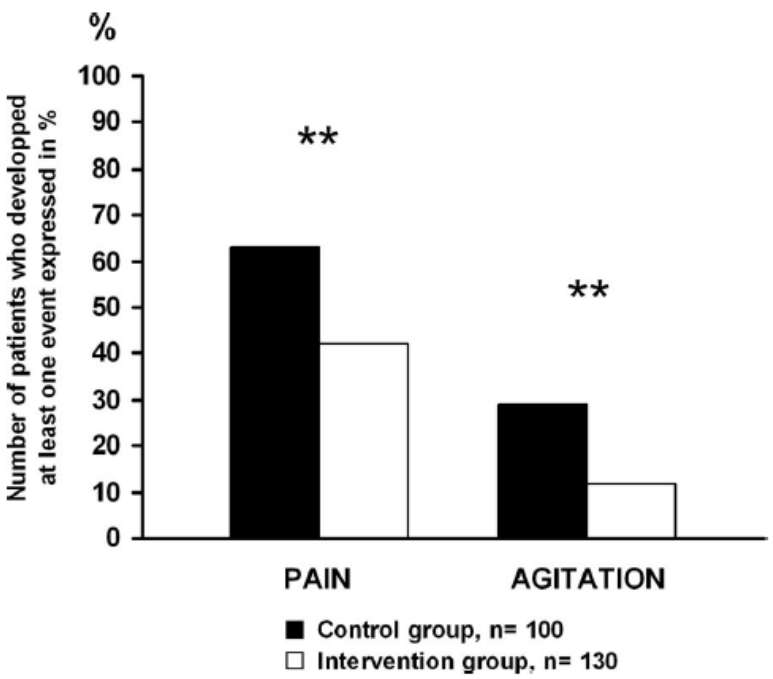
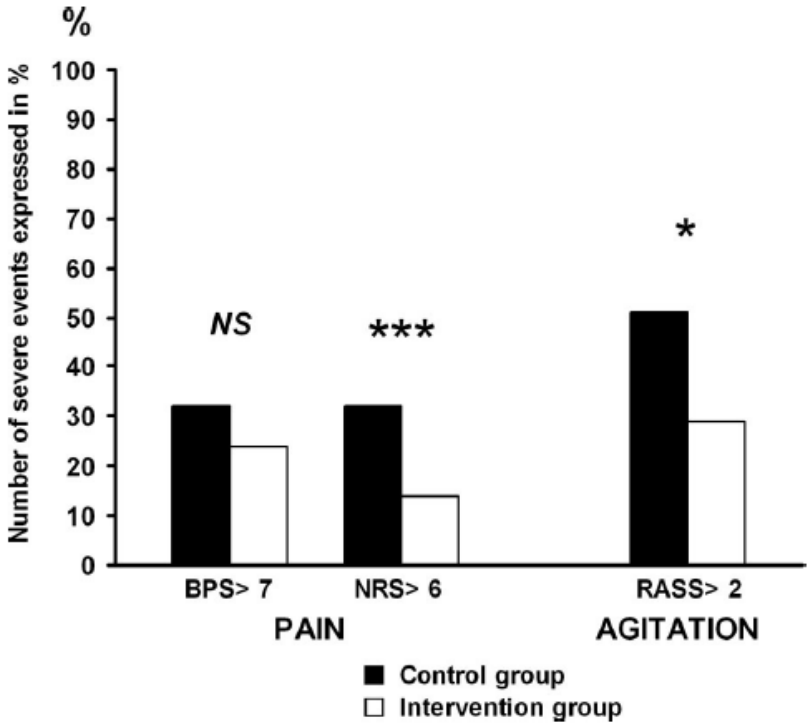


Figure 1. Cumulative Incidence of Delirium According to Study Group.

Impact of systematic evaluation of pain and agitation in an intensive care unit*

Gerald Chanques, MD; Samir Jaber, MD, PhD; Eric Barbotte, MD; Sophie Violet, RN; Mustapha Sebbane, MD; Pierre-François Perrigault, MD; Claude Mann, MD, PhD; Jean-Yves Lefrant, MD, PhD; Jean-Jacques Eledjam, MD, PhD





Effects of patient-directed music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilatory support: a randomized clinical trial.

OBJECTIVE:

To test whether listening to self-initiated patient-directed music (PDM) can reduce anxiety and sedative exposure during ventilatory support in critically ill patients.

DESIGN, SETTING, AND PATIENTS:

Randomized clinical trial that enrolled 373 patients from 12 intensive care units (ICUs).

INTERVENTIONS:

Self-initiated PDM (n = 126) with preferred selections tailored by a music therapist whenever desired while receiving ventilatory support, self-initiated use of noise-canceling headphones (NCH; n = 122), or usual care (n = 125).

RESULTS:

Patients in the PDM group had an anxiety score that was 19.5 points lower (95% CI, -32.2 to -6.8) than patients in the usual care group (P = .003).

PDM significantly reduced both measures of sedative exposure.

By the fifth study day, the PDM patients received 2 fewer sedative doses (reduction of 38%) and had a reduction of 36% in sedation intensity.

Chlan et al – JAMA 2012

SLEEP

OBJECTIVES:

To determine if a quality improvement intervention improves sleep and delirium/cognition.

DESIGN:

Observational, pre-post design.

PATIENTS:

300 medical ICU patients.

INTERVENTIONS:

This medical ICU-wide project involved a "usual care" baseline stage, followed by a quality improvement stage incorporating multifaceted sleep-promoting interventions implemented with the aid of daily reminder checklists for ICU staff.

MEASUREMENTS AND MAIN RESULTS:

Improvements in overall Richards-Campbell Sleep Questionnaire sleep quality ratings did not reach statistical significance,

but **there were significant improvements** in daily noise ratings (mean ± SD: 65.9±26.6 vs. 60.5±26.3, p = 0.001), **incidence of delirium/coma** (odds ratio: 0.46; 95% confidence interval, 0.23-0.89; p = 0.02), and **daily delirium/coma-free status** (odds ratio: 1.64; 95% confidence interval, 1.04-2.58; p = 0.03).

Kamdar et al – Crit Care Med - 2013

CONCLUSION

- **Frequent and severe complication**
- **Must be daily detected by validating scales**
- **Patients at risk must be identified**
- **Preventive strategies must be implemented**

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repair regeneration and recovery from critical illness

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Société de Réanimation de Langue Française

University of Versailles
Raymond Poincaré
Service de Réanimation
Pr Djillali Annane

Institut Pasteur
Fabrice Chrétien
Human Histopathology and Animal Models

MERCI

WHAT WAS WRONG?

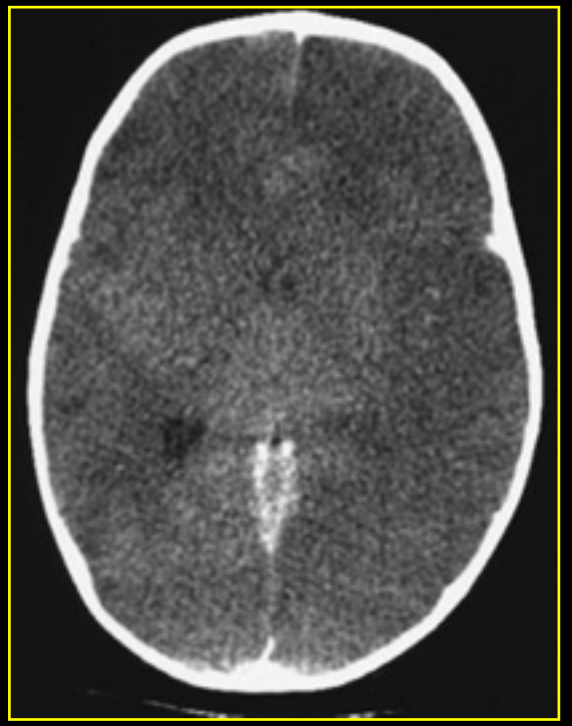
A 52 years old and alcoholic man was hospitalised in ICU for an hypoxemic community-acquired pneumonia, with blood cultures positive to S. pneumoniae. At admission, neurological examination was normal and there was no neck stiffness.

One day later, he required mechanical ventilation and developed agitation, which was treated with Haloperidol.

Because he became more and more agitated, he was heavily sedated. Agitation was ascribed to alcohol withdrawal.

A week later, while the patient was sedated, bilateral larged fixed pupils were observed.

CT scan showed diffuse brain oedema and lumbar puncture meningitis.



SEVRAGE ETHYLIQUE

By definition, the patient must have two or more of the following after cessation or reduction of alcohol use that has been heavy or prolonged:

1. **autonomic hyperactivity (sweating, tachycardia);**
2. **increased hand tremor;**
3. **insomnia;**
4. **nausea or vomiting;**
5. **transient visual, tactile, or auditory hallucinations or illusions;**
6. **psychomotor agitation; anxiety and tonic-clonic seizures.**

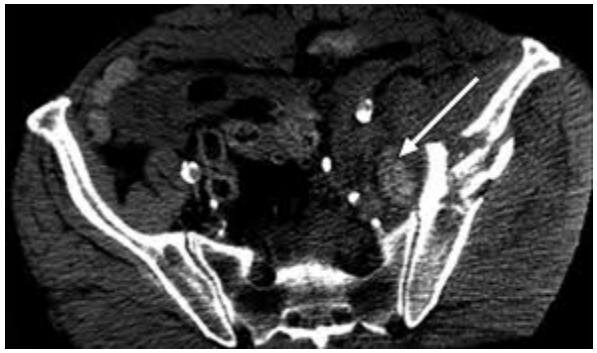
Clinical Institute Withdrawal Assessment Scale for Alcohol,

DTS is characterised by a fluctuating disturbance of consciousness and change in cognition occurring over a short period of time. It is accompanied by a further exacerbation of autonomic symptoms (sweating, nausea, palpitations and tremor) and an exacerbation of psychological symptoms including anxiety.

Treatment: BZD

CASE REPORT

- **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 vole mon enfant… »**



MULTIFACTORIAL

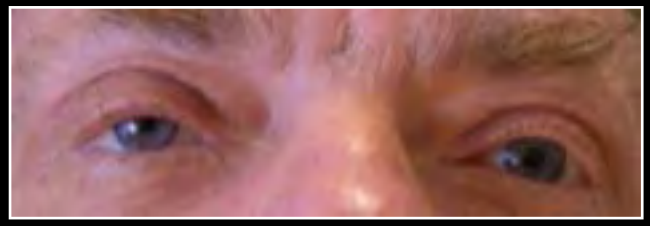
In a 55 years old septic patient:

+ hyperactive delirium

+ weakness of the right arm and slight right central facial palsy

+ Claude Bernard Horner sign

+ Oedema of the right arm



- CT scan and CSF analysis: normal

- EEG: slow cortical activity

- Biochemistry: moderate renal failure

- Blood culture : negative

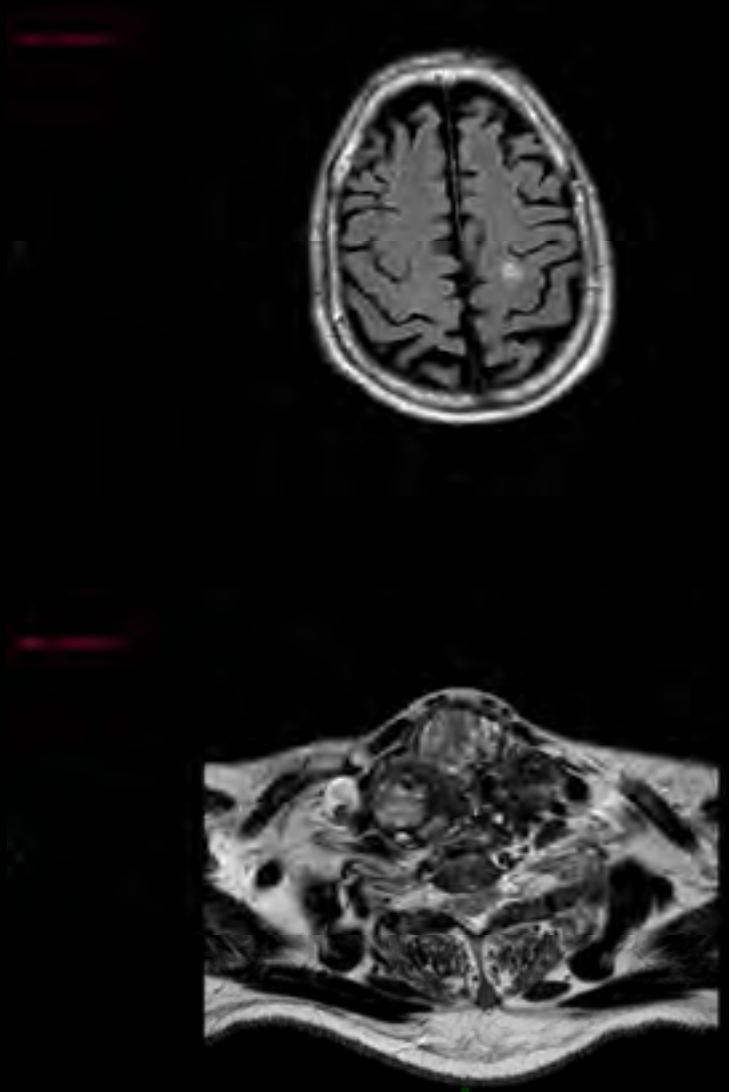
DELIRIUM WITH FOCAL SIGN IN A SEPTIC PATIENT

MULTIFACTORIAL

1. Left pre-rolandic lesion

2. Thrombosis of right jugular vein + goitre

3. Methicillin overdose



BE CAREFUL

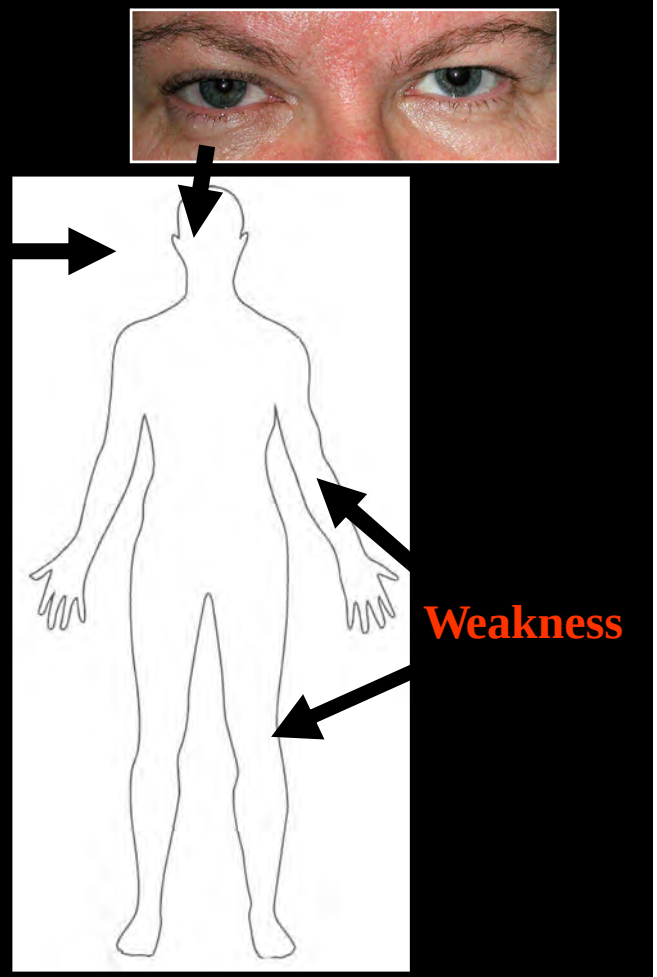
In a 65 years old man lightly sedated for a hypoxemic pneumonia:

+ no response of the left arm to painful stimuli

+ a greater hypotonia of the left arm and leg

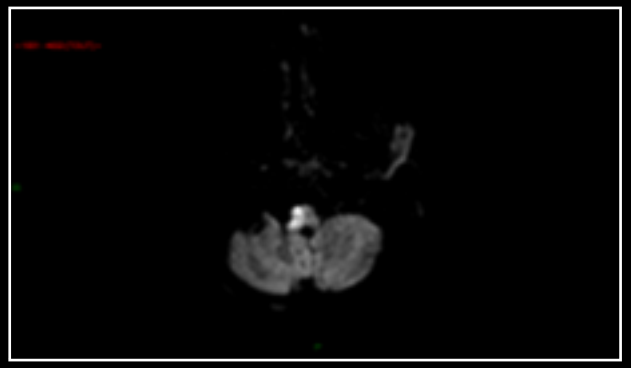
+ a decreased contraction of the right face to painful stimulation

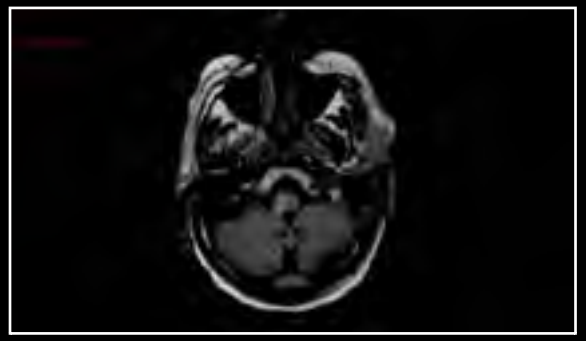
+ Claude-Bernard Horner sign



FOCAL NEUROLOGICAL SIGNS IN A CRITICALLY ILL PATIENT WITH CEREBROVASCULAR RISK FACTORS AND TREATED BY HEPARIN

BE CAREFUL

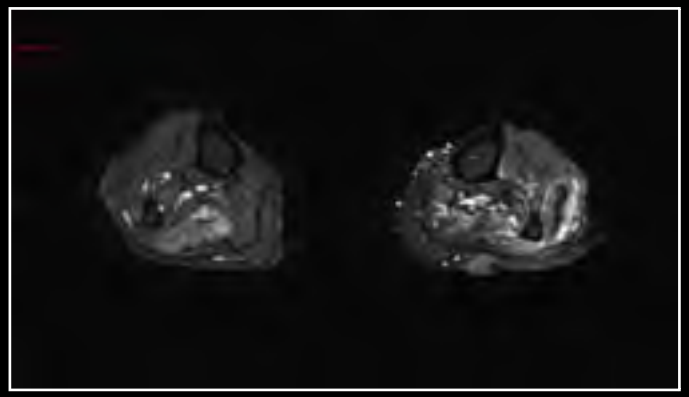




Accounts for all neurological signs

BE CAREFUL

Three days after discontinuation of sedation, the patient developed agitation and delirium. General and neurological examination was not changed. EEG was normal. Agitation and delirium was ascribed to discontinuation of sedation. Three days later, patient complained of pain of the legs and ankles that turned to be due to bacterial and ischemic myositis.



DELIRIUM WITHOUT (new) FOCAL NEUROLOGICAL SIGN IN A RECENTLY NON SEDATED PATIENT

DEVENIR

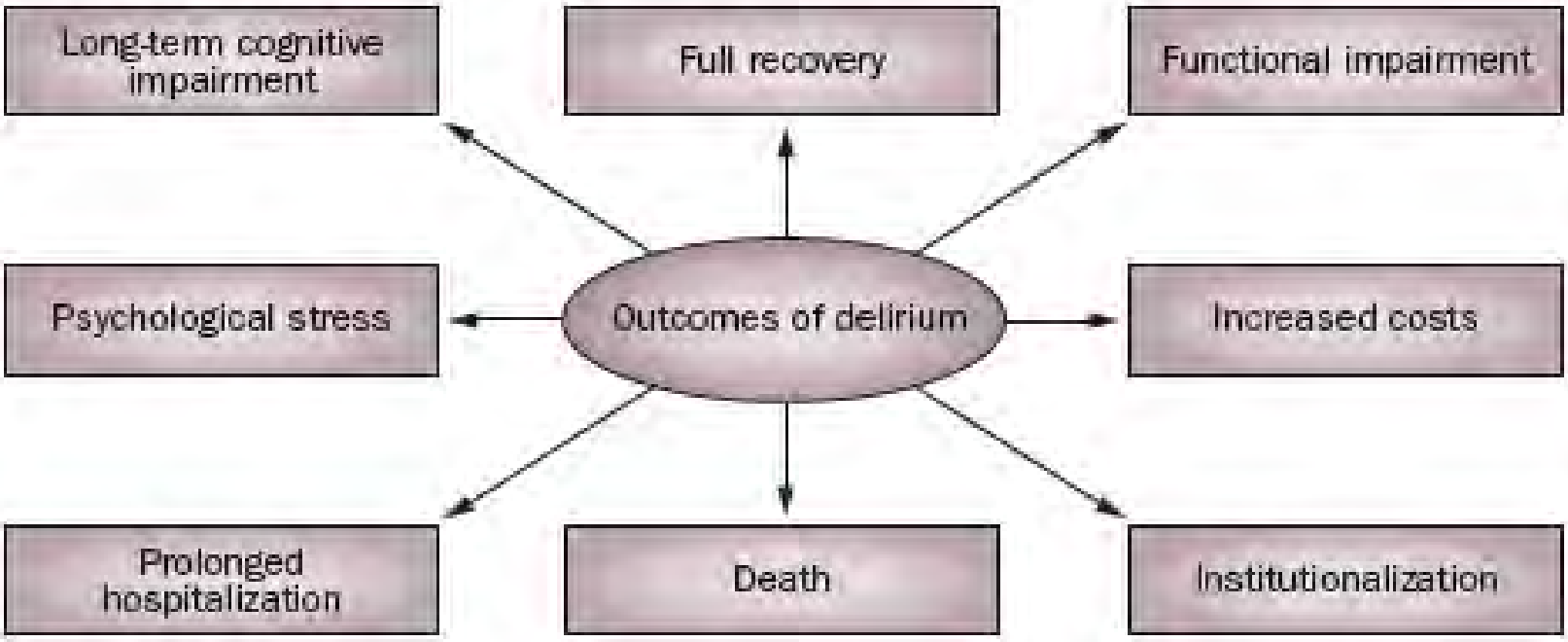


Figure 2 | Outcomes of delirium.

Pratik P. Pandharipande, MD, MSCI
Brenda T. Pun, RN, MSN, ACNP
Daniel L. Herr, MD
Mervyn Maze, MB, ChB
Timothy D. Girard, MD, MSCI
Russell R. Miller, MD, MPH
Ayumi K. Shintani, MPH, PhD
Jennifer L. Thompson, MPH
James C. Jackson, PsyD
Stephen A. Deppen, MA, MS
Renee A. Stiles, PhD
Robert S. Dittus, MD, MPH
Gordon R. Bernard, MD
E. Wesley Ely, MD, MPH

Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients

The MENDS Randomized Controlled Trial

JAMA. 2007;298(22):2644-2653

Figure 2. Delirium-Free and Coma-Free Days During Study

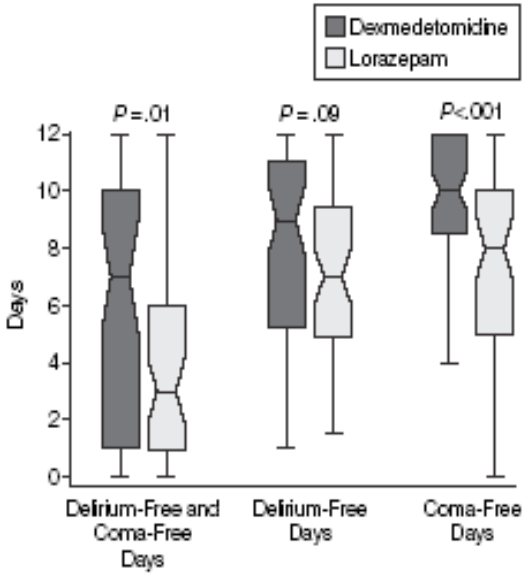


Table 2. Outcomes in Mechanically Ventilated Patients Sedated With Dexmedetomidine vs Lorazepam[a]

Outcome Variable	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*P* Value
Duration of brain organ dysfunction, d			
Delirium-free and coma-free[b]	7 (1-10)	3 (1-6)	.01
Delirium-free[b]	9 (5-11)	7 (5-10)	.09
Coma-free[b]	10 (9-12)	8 (5-10)	<.001
Delirium	2.5 (1-5)	4 (1-5)	.71
Coma	2 (0-3)	3 (2-5)	.003
Prevalence of brain organ dysfunction, No. (%)[c]			
Delirium or coma	45 (87)	50 (98)	.03
Delirium	41 (79)	42 (82)	.65
Coma	33 (63)	47 (92)	<.001
Other clinical outcomes			
Mechanical ventilator-free, d[d]	22 (0-24)	18 (0-23)	.22
Intensive care unit length of stay, d	7.5 (5-19)	9 (6-15)	.92
28-Day mortality, No. (%)	9 (17)	14 (27)	.18

SEDATION and ANALGESIA

N = 304 > 60 ans – Medical ICU

Table 5. Multivariable models for delirium duration (n = 304)

Risk Factor for Delirium Duration	Rate Ratio (95% CI)	*p* Value[b]
Model 1: Effect of use of opioids or benzodiazepines controlling for dementia, use of haloperidol, and baseline health status[a]		
Benzodiazepine or opioid use	1.64 (1.27–2.10)[c]	<0.001
Control variables		
Dementia (Informant Questionnaire on Cognitive Decline in the Elderly >3.3)	1.19 (1.07–1.33)	0.002
Haloperidol	1.35 (1.21–1.50)	<0.001
Acute Physiology and Chronic Health Evaluation II Score (minus the Glasgow Coma Scale)	1.01 (1.00–1.02)	0.02
Model 2: Modification of effect of use of opioids or benzodiazepines by dementia status: Controlling for use of haloperidol and baseline health status[a]		
Effect of benzodiazepines or opioids when dementia is absent	2.42 (1.65–3.55)	<0.001
Effect of benzodiazepines or opioids when dementia is present	1.08 (0.78–1.50)	0.64
Model 3: Modification of effect of use of haloperidol by dementia: Controlling for use of opioids or benzodiazepines and baseline health status[a]		
Effect of haloperidol when dementia is absent	1.47 (1.29–1.69)	<0.001
Effect of haloperidol when dementia is present	1.15 (0.96–1.37)	0.14

[a]The deviance divided by the degrees of freedom for the three models are respectively 0.95, 0.92, and 0.93, providing no evidence of overdispersion; [b]*p* values are calculated for the Likelihood Ratio Chi-square statistic; [c]bootstrapped results for this model coefficient yielded a slightly larger but significant confidence interval: rate ratio 1.67, 95% confidence interval (CI) 1.17, 2.27.

The use of benzodiazepines or opioids in the ICU is associated with longer duration of a first episode of delirium. But also: severity of critical ilness, dementia and use of haloperidol

Pisani et al - Crit Care Med - 2009

ORIGINAL

E. W. Ely
S. Gautam
R. Margolin
J. Francis
L. May
T. Speroff
B. Truman
R. Dittus
G. R. Bernard
S. K. Inouye

The impact of delirium in the intensive care unit on hospital length of stay

Multiple Linear Regression Model:
Predictors of Lengths of Stay in ICU and Hospital*

Variable	Length of Hospital Stay (days)		
	Beta	95% C.I.	P Value
Intercept	1.82	-	-
Duration of Delirium ≈	1.18	1.05 -1.32	0.006
APACHE II	1.01	0.98-1.03	0.61
Age	1.00	0.99 – 1.00	0.38
Gender	1.22	0.84 – 1.75	0.30
Drug Days	1.13	1.01 –1.26	0.04

Using multivariate analysis, delirium was the strongest predictor of length of stay in the hospital (P=0.006) even after adjusting for severity of illness, age, gender, race, and days of benzodiazepine and narcotic drug administration.

IDSC versus CAM-ICU

Table 3 Agreement rates between CAM-ICU and ICDSC on days 1–7 after ICU admission; *CI*, confidence interval

Days on ICU	No. of paired settings	Kappa coefficient (95% CI)
1	130	0.81 (0.78-0.84)
2	67	0.86 (0.80-0.90)
3	52	0.80 (0.76-0.84)
4	42	0.76 (0.74-0.81)
5	29	0.65 (0.59-0.71)
6	26	0.68 (0.64-0.73)
7	28	0.92 (0.88-0.96)

Kappa coefficient was determined for 1 week following the day of ICU admission (day 1)

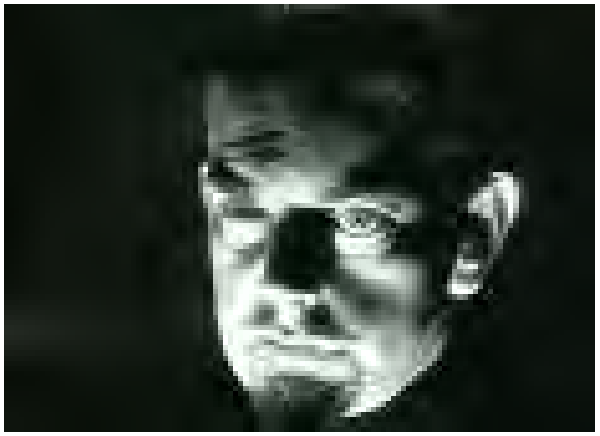


Table 4 Comparison of CAM-ICU and ICDSC delirium ratings in 374 paired observations

	ICDSC (*n*)	Negative	Positive	Total
CAM-ICU *n*	Negative	219	20	239 (64)
	Positive	15	120	135 (36)
	Total	234 (63)	140 (37)	374 (100)

Plaschke et al – ICM - 2008

Intensive Care Med (2007) 33:66–73
DOI 10.1007/s00134-006-0399-8

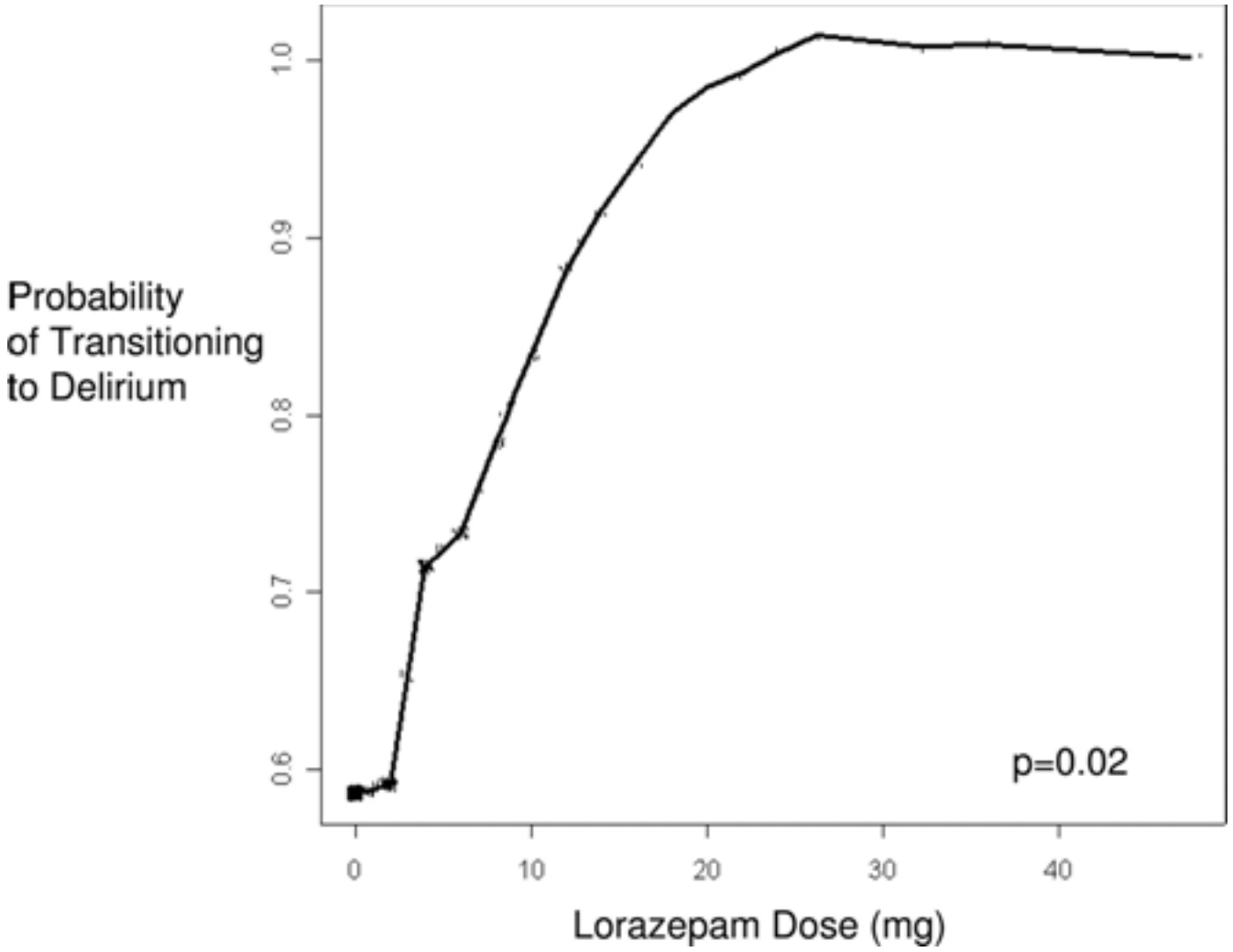
ORIGINAL

Sébastien Ouimet
Brian P. Kavanagh
Stewart B. Gottfried
Yoanna Skrobik

Incidence, risk factors and consequences of ICU delirium

Variable	*p*
Age	0.069
Medical history	
Hypertension	0.0047
Active tobacco consumption	0.0123
Alcohol consumption	0.0015
Variables on ICU admission	
APACHE II score	< 0.0001
Medication	
Epidural catheter use	0.0017
Average opiate dose	0.0096
Average benzodiazepine dose	0.0001
Average propofol dose	0.0023
Average indomethacin dose	0.044
ICU stay related factors	
Coma (all types)	< 0.0001
Anxiety	0.0824
Pain	0.0020

Coma related to sedation : Major Risk factor of DELIRIUM (OR 3.22)


Probability
of Transitioning
to Delirium
1.0
0.9
0.8
0.7
0.6
p=0.02
0
10
20
30
40
Lorazepam Dose (mg)

Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study.
Kalisvaart et al J am Geriart Soc 2005

PARTICIPANTS: **A total of 430 hip-surgery patients aged 70 and older at risk for postoperative delirium.**

INTERVENTION: **Haloperidol 1.5 mg/d or placebo was started preoperatively and continued for up to 3 days postoperatively.**

RESULTS: **The overall incidence of postoperative delirium was 15.8%.**

1. **Postoperative delirium in the haloperidol and placebo was 15.1% and 16.5%, respectively (RR=0.91, 95% CI [0.6-1.3]);**
2. **the mean highest DRS-R-98 score was 14.4+/-3.4 and 18.4+/-4.3 (mean difference 4.0, 95% CI [2.0-5.8]; P<.001);**
3. **delirium duration was 5.4 versus 11.8 days (mean difference 6.4 days, 95% CI [4.0-8.0]; P<.001); and the mean number of days in the hospital was 17.1+/-11.1 and 22.6+/-16.7, respectively (mean difference 5.5 days, 95% CI [1.4-2.3]; P<.001).**
4. **No haloperidol-related side effects were noted.**

Multivariate Model of Admission Risk Factors Associated With Delirium in the First 48 Hours of ICU Admission

patients > 60 years old

Table 2. Multivariate Model of Admission Risk Factors Associated With Delirium in the First 48 Hours of ICU Admission (MICU)

Risk Factor	Odds Ratio (95% Confidence Interval)	*P* Value
Dementia by IQCODE >3.3	6.3 (2.9-13.8)	<.001
Receipt of benzodiazepines before ICU admission	3.4 (1.6-7.0)	.001
Creatinine >2 mg/dL	2.1 (1.1-4.0)	.02
Arterial pH <7.35	2.1 (1.1-3.9)	.02

Abbreviations: ICU, intensive care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

Pisani, M. A. et al. Arch Intern Med 2007;167:1629-1634.

ARCHIVES OF INTERNAL MEDICINE

Intensive Care Med (2001) 27: 1297–1304
DOI 10.1007/s001340101017

ORIGINAL

Marc-Jacques Dubois
Nicolas Bergeron
Marc Dumont
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Delirium in an intensive care unit: a study of risk factors

Table 3 Multivariate analysis

Variable	Odds ratio	95% Confidence interval
Hypertension	2.6	1.14–5.72
Smoking history	2.2	0.94–4.94
Bilirubin level[a] (% of days with abnormal level)	1.2	1.03–1.40
Use of epidural	3.5	1.20–10.39
Morphine (mean daily dose)[b]		
0.01–7.1 mg	7.8	1.76–34.4
7.2–18.6 mg	9.2	2.17–39.0
18.7–331.6 mg	6.0	1.41–25.4

[a] Odds ratio expresses a risk increase for each 10% increased of days with abnormal laboratory value

[b] Analgesic and sedative medications were respectively transformed as parenteral morphine and lorazepam using equivalent dosage scales [14]

GENETIC: APOLIPOPROTEIN E4 POLYMORPHISMS

Table 3. Clinical outcomes (bivariate analysis)[a]

Variable	APOE4 Present (n = 12)	APOE4 Absent (n = 41)	*p* Values[b]
Days of delirium	4 (3, 4.5)	2 (1, 4)	.05
Coma days	1 (0, 4.5)	2 (0, 5)	.45
ICU length of stay	9.5 (6, 14)	7 (5, 11)	.37
Hospital length of stay	12 (8.5, 17.5)	10 (7, 15)	.53
Ventilator-free days	21.1 (15, 24)	22 (0, 26)	.72
Days on ventilator	5.5 (3.9, 8.9)	4 (2, 8)	.49
Mortality, % (n)	8.3 (1/12)	24.4 (10/41)	.42

APOE4, apolipoprotein E4; ICU, intensive care unit.

[a]All data are presented as median with interquartile ranges with the exception of mortality, which is % (n); [b]unadjusted *p* values were obtained using Wilcoxon rank-sum tests for all except for mortality, where Fisher's exact test was used.

APOE: role in amyloïdogenesis (Alzheimer disease)

Ely et al – CCM - 2007

PLASMA CORTISOL LEVELS

Table 5 Factors independently associated with delirium after CABG surgery revealed in multivariate stepwise logistic regression analysis[a]

Variable	Coefficient	Standard error	Odds ratio (95% CI)	*P* value
TMT-B[b]	0.016	0.004	1.02 (1.01 to 1.03)	< 0.0001
Creatinine concentration[b]	0.015	0.012	1.02 (0.99 to 1.04)	0.191
Dose of midazolam	0.081	0.028	1.08 (1.03 to 1.15)	0.005
Preoperative cortisol	0.005	0.002	1.005 (1.001 to 1.009)	0.025
Depression[b]	2.389	0.954	10.90 (1.68 to 70.67)	0.012
IL-2 concentration[c]	0.002	0.001	1.002 (1.001 to 1.004)	0.004
Constant	-12.964	2.725	-	< 0.0001

CI, confidence interval; TMT-B, Trial Making Test. [a]The regression model is statistically significant: $\chi^2 = 76.889$; $P < 0.001$. [b]Preoperative variable. [c]Postoperative variable.

113 post-operative patients

Kazmierski et al – Crit Care - 2013

BIOMARKERS

Table 3 Differences between delirium and nondelirium patients in inflamed and noninflamed patients

	Inflamed (n = 46)					Noninflamed patients (n = 54)				
	Delirium (n = 26)		Nondelirium (n = 20)		P value	Delirium (n = 24)		Nondelirium (n = 30)		P value
Proinflammatory cytokines										
TNF-α (pg/ml)	13	[10-16]	11	[5-18]	0.17	8	[5-13]	7	[5-11]	0.18
IL-1β (pg/ml)	3	[3-6]	4	[3-17]	0.67	3	[3-6]	3	[3-6]	0.69
IL-6 (pg/ml)	73	[38-143]	41	[21-90]	0.09	50	[29-90]	34	[22-64]	0.047[a]
IL-8 (pg/ml)	31	[24-44]	17	[9-26]	< 0.001[a]	20	[12-32]	14	[9-22]	0.001[a]
IL-17 (pg/ml)	4	[3-7]	3	[3-6]	0.22	3	[3-4]	3	[3-3]	0.63
IL-18 (pg/ml)	136	[88-187]	84	[65-132]	0.03[a]	82	[66-141]	88	[72-120]	0.54
MIF (pg/ml)	438	[294-796]	257	[157-576]	0.13	334	[214-561]	249	[179-702]	0.08
Antiinflammatory cytokines										
IL-1ra (pg/ml)	48	[27-74]	32	[18-47]	0.04[a]	24	[17-51]	16	[11-25]	0.02[a]
IL-10 (pg/ml)	23	[13-47]	13	[5-35]	0.08	28	[12-44]	22	[9-46]	0.03[a]
Chemotactic cytokines										
MCP-1 (pg/ml)	516	[295-822]	251	[199-339]	0.001[a]	268	[192-398]	233	[175-306]	0.15
Defensin										
HNP (μg/ml)	0.06	[0.03-0.13]	0.07	[0.03-0.09]	0.60	0.06	[0.04-0.10]	0.04	[0.03-0.10]	0.51
Markers of inflammation										
CRP (mg/ml)	84	[56-190]	84	[43-140]	0.40	42	[29-65]	41	[27-64]	0.44
Procalcitonin (ng/ml)	1.0	[0.23-2.0]	0.28	[0.10-0.64]	0.003[a]	0.22	[0.11-0.55]	0.12	[0.06-0.18]	0.01[a]
Stress-response hormone										
Cortisol (μmol/L)	0.59	[0.34-0.98]	0.48	[0.18-0.61]	0.06	0.46	[0.23-0.72]	0.30	[0.06-0.66]	0.06

Dosage within the 24h after onset of delirium

Van den Boogaard et al – Crit Care – 2013

AGITATION

Epidémiology

Prevalence: 52%
(Score de Ramsay)

Jaber et al – ICM - 2005

Table 5—*Characteristics of Agitation

Characteristics	Data
Onset from day of admission, d	4.4 ± 5.6
Duration, d	3.9 ± 4.1
Diurnal occurrence, No. (% of patients)	
Agitation exclusively during the day	16 (17)
Agitation exclusively during the night	6 (6)
Agitation during day and night	73 (77)
Tracheal intubation status, No. (% of patients)	
Agitation exclusively during intubated period	14 (15)
Agitation exclusively during nonintubated period	41 (43)
Agitation during both periods	40 (42)
Physical restraints, No. of patients/total (%)	43/95 (45)
Necessity of physical restraints in previously unrestrained patients	29/53 (55)
Necessity of sedatives use in patients with no previous sedation	13/27 (48)
Benzodiazepines	8/13 (61)
Opioids	4/13 (30)
Neuroleptic drugs	7/13 (54)
Obvious cause or causes of agitation in all agitated patients (pain, anxiety, shock, withdrawal)	62/95 (65)
Medical patients	35/38 (92)
Surgical patients	27/57 (47)

*Data are presented as mean ± SD unless otherwise indicated.

AGITATION

Epidémiology

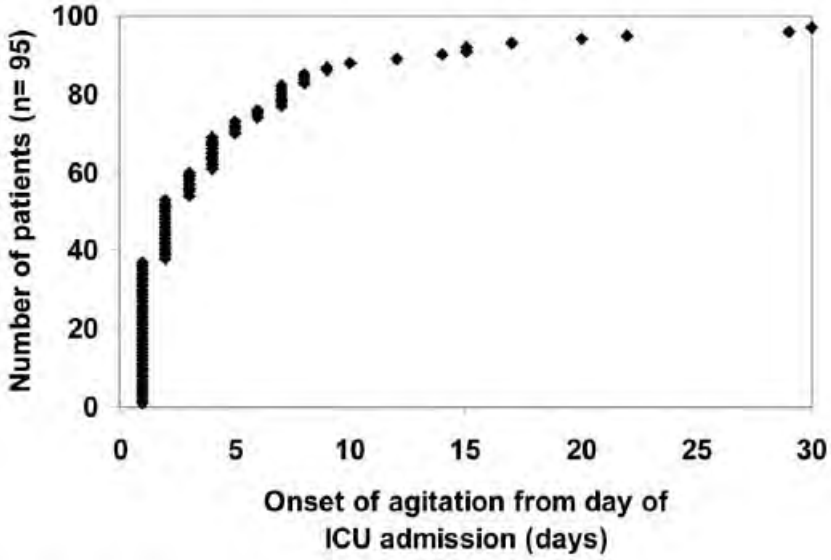


FIGURE 1. Cumulative distribution of onset of agitation from the day of admission to the ICU.

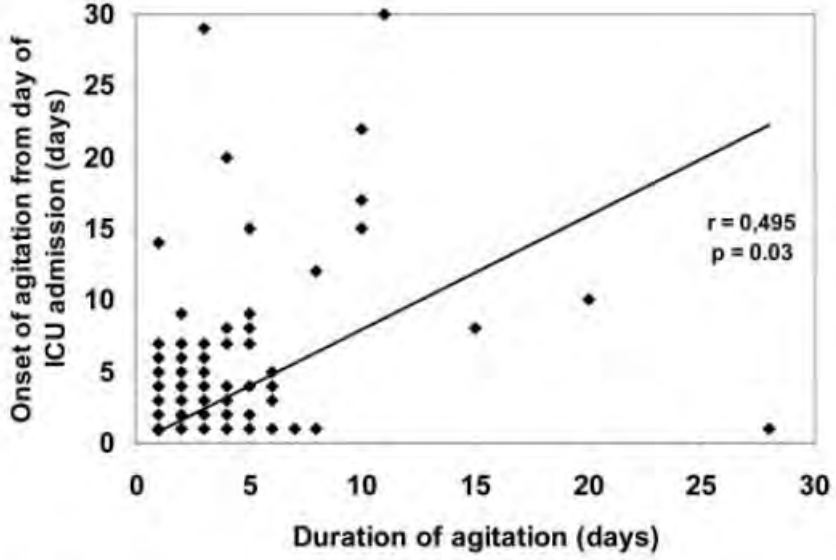


FIGURE 3. Correlation between duration of agitation and onset of agitation from the day of ICU admission.

Jaber et al – ICM - 2005

AGITATION

RISK FACTORS

Table 4—*Independent Risk Factors for the Agitation*

Predictive Risk Factors	Odds Ratio	95% CI
Age ≥ 65 yr*	2.21	0.83–5.93
Medical cause of ICU admission*	3.04	0.85–10.54
Sepsis	2.61	1.03–6.58
Alcohol abuse	3.32	1.12–10.00
Use of sedatives in 48 h before onset of agitation	4.03	1.62–10.40
Body temperature ≥ 38°	4.52	1.80–11.49
Sodium level ≤ 134 mmol/L	4.87	1.58–14.99
Sodium level ≥ 143 mmol/L	4.95	1.95–12.54
Long-termc psychoactive drug user	5.63	1.32–23.70

*These risk factors are not significant.

Jaber et al – ICM - 2005

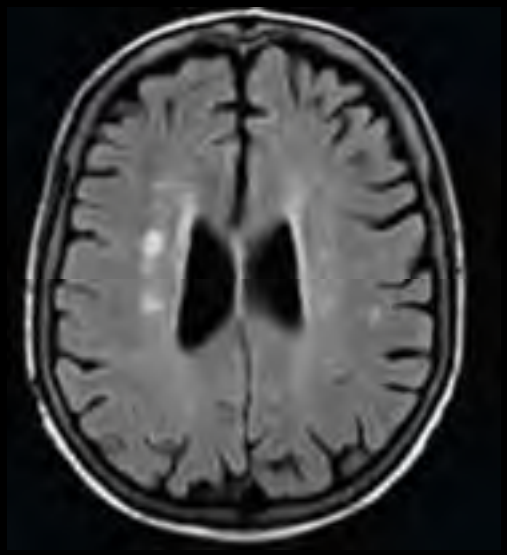
A Prospective Study of Agitation in a Medical-Surgical ICU*

Incidence, Risk Factors, and Outcomes

Samir Jaber, MD, PhD; Gérald Chanques, MD; Claire Altairac, PharmD; Mustapha Sebbane, MD; Christine Vergne, MD; Pierre-François Perrigault, MD; and Jean-Jacques Eledjam, MD, PhD

AMERICAN COLLEGE OF CHEST PHYSICIANS

Variable	Agitation (n=95)	No agitation (n=87)	*p*
SAPSII	40 ± 16	33 ± 13	<0.01
Auto-extubation	16.5%	1.7%	0.003
Desinsertion of catheter	15.9%	1.2%	0.01
Duration catheter (d)	16.6 ± 17.1	6.1 ± 5,7	0.0001
Duration of mechanical ventilation (d)	14.1 ± 18,7	3.5 ± 5,2	0.0001
Nosocomial infection (%) (Pneumonia, urinary tract, bacteremia)	33.7	6.9	<0.0001
Length of ICU stay (d)	16 ± 19	6 ± 6	0.0001



MRI IN PATIENTS WITH DELIRIUM

Of the eight patients, six (75%) demonstrated white matter hyperintensities, one (12%) had mild atrophy, and no patient had ischemic/hemorrhagic lesions.

Morandi et al – Psychiatry- 2011