NEUROUPDATE TORINO
TORINO 9-10 marzo 2017

DALLA SEDAZIONE AL COMA BARBITURICO

Nicola Latronico
University of Brescia, Italy

CONFLICTS OF INTEREST

- Angelini
- Fidia Farmaceutici
- Orionpharma
- MSD Italia

Anesthetics, Analgesics, and Sedatives

Level I and II A

• There was insufficient evidence to support a Level I or Level IIA recommendation for this topic.

Table 6-1. Quality of the Body of Evidence (Anesthetics, Analgesics, and Sedatives)

	COMPONENTS OF OVERALL QUALITY							
Topic	Number of Studies	Meta-Analysis	Number of Subjects	Class of Studies	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Prophylactic use of barbiturates[9]	1 RCT	NA	53	2	NA	Direct	Low	Low
Barbiturates as a treatment for refractory ICP[10]	1 RCT	NA	73	2	NA	Direct	Low	Low
Sedatives and analgesics[11]	1 RCT	NA	42	2	NA	Direct	Low	Low

Abbreviations: ICP=intracranial pressure, NA=not applicable, RCT=randomized controlled trial.

https://braintrauma.org/uploads/03/12/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf

Verify ICP measurement
Check calibration of monitor

Check pupils

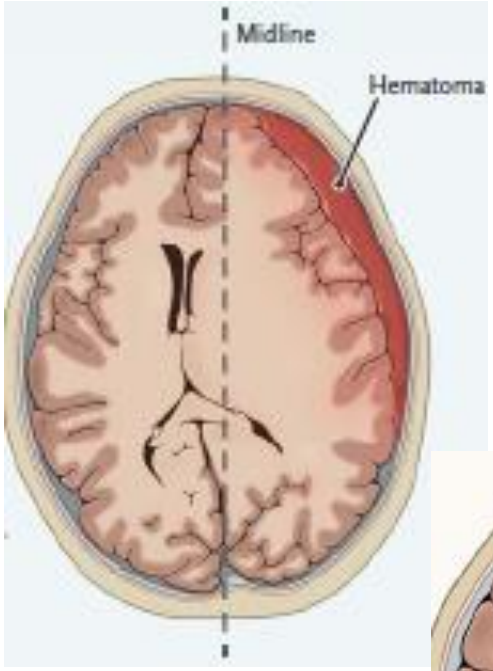
- Exclude herniation
- If herniation:
  - Perform emergency procedures to reduce ICP (tracheal intubation, ventilation, administration of hyperosmolar fluids)
  - Perform immediate diagnostics (computed tomography)
  - Perform surgical intervention when appropriate

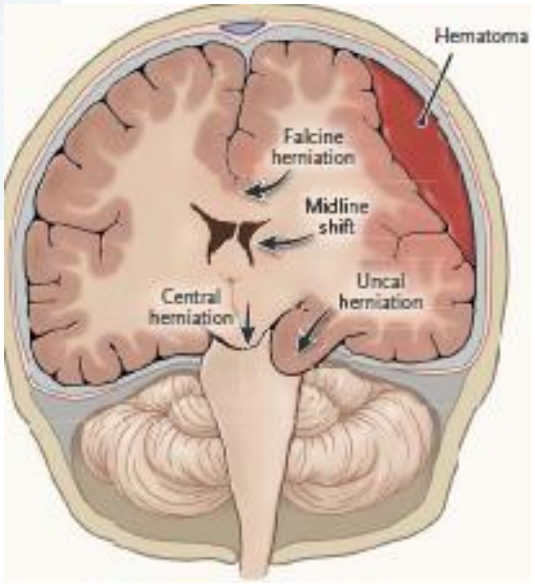
Check and treat systemic causes of increased ICP

- Vasodilatation of cerebral vessels
  - Fever
  - Seizures
  - Hypercarbia
  - Hypoxemia
  - Hypotension
- Increased venous pressure
  - Neck torsion or compression
  - Pneumothorax
  - Ventilator asynchrony
  - Increased abdominal pressure
- Increased arterial pressure
  - Pain
  - Bladder distention
- Cellular edema
  - Hyponatremia

Initiate or intensify ICP-directed treatment

- Increase sedation
- Drain CSF
- Administer hyperosmolar fluids
- Induce mild hypocarbia (hyperventilation)
- Induce metabolic suppression (barbiturates or increased sedation)
- Induce hypothermia
- Perform decompressive craniectomy





Stocchetti N, Maas AIR.
Traumatic Intracranial Hypertension.
N Engl J Med **2014**;370:2121-2130

Addenbrooke's NCCU: ICP treatment

(courtesy of Dr. Andrea Lavinio, MD, FFICM, FRCA)

ICP monitoring as clinically indicated. Primary targets:
ICP ≤ 20 mmHg and **CPP 60 to 70 mmHg**
If advanced monitoring is available, fine-tune treatment based on multimodality targets:
PRx < 0.2; **LPR < 25**; **PbtO2 ≥ 15 mmHg**; **SjO2 > 50%**

STAGE 1

1

- **Sedation:** Propofol 2-5 mg/kg/h, Fentanyl 1-4 μg/kg/h; consider Atracurium 0.5 mg/kg/h
- **Ventilation:** $SpO_2 \geq 97\%$; $PaCO_2$ 4.5-5.0 kPa (33-38 mmHg)
- **Circulation:** CVP 6 to 12 mmHg; vasopressors to maintain CPP > 60 mmHg
- **Temperature:** < 37°C (regular Paracetamol +/- ice-cold IV fluids)
- **Nursing:** 15° head up; avoid venous obstruction;
- **Nutrition:** early enteral; Insulin sliding scale (titrate to blood sugar ≤ 10 mmol/l)
- **DVT prophylaxis:** graduated stockings or pneumatic intermittent compression
- **Antiepileptics:** EEG to esclude seizures +/- institute or escalate antiepileptic therapy

ICP > 20 mmHg? Escalate to **STAGE 2,**
consider re-scan +/- **SOL evacuation**

2

- **CSF drainage:** open EVD (or consider ventricular catheter insertion)
- **Osmotic therapy:** 5% NaCl 2 ml/kg or 20% Mannitol 2 ml/kg (up to Posm ≃ 320)
- **Mild hypothermia:** Temp ≃ 35°C (daily lipids, ECG and CK if still on propofol)

ICP > 20 mmHg? Escalate to **STAGE 3,**
consider re-scan +/- **SOL evacuation**

3

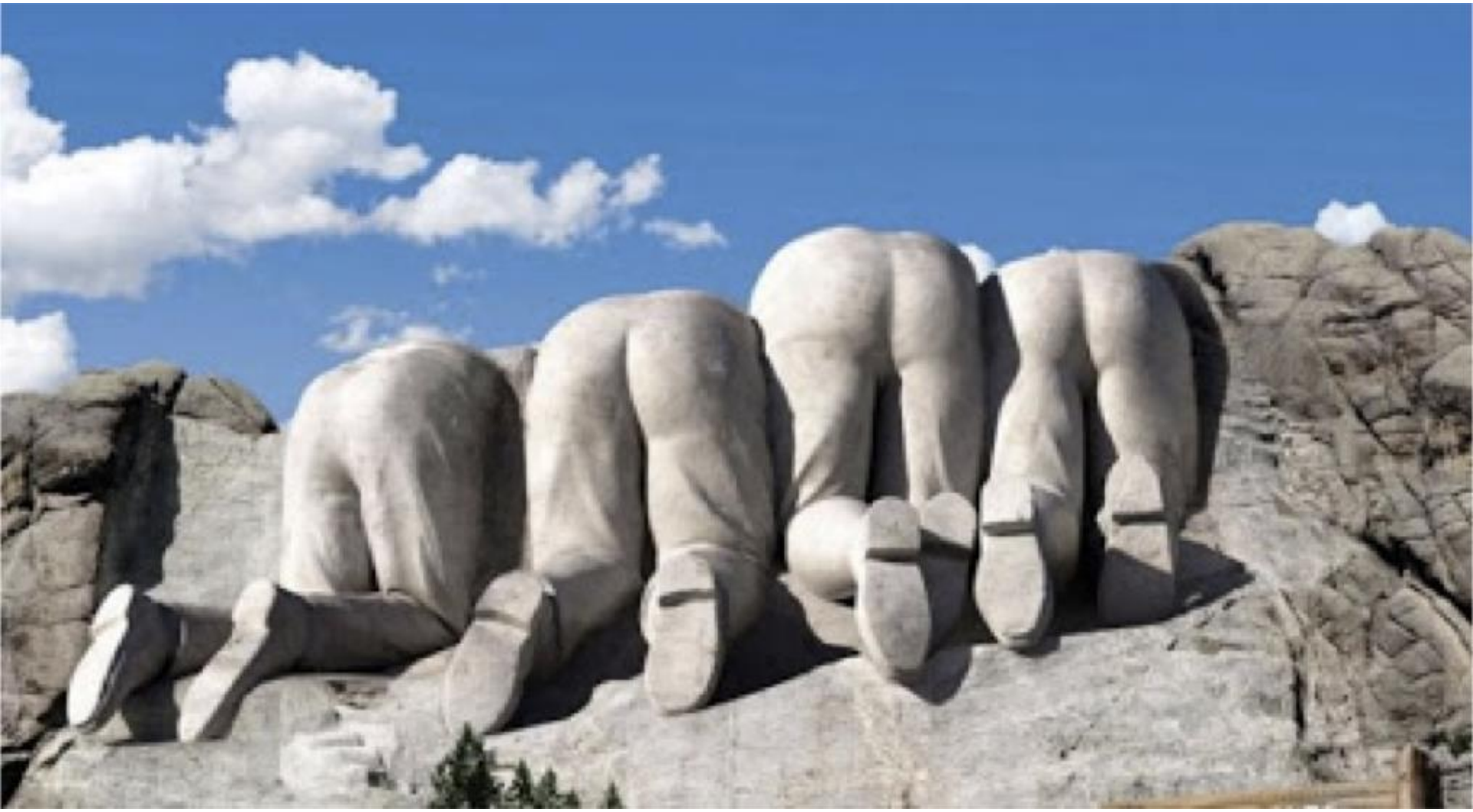
- **Moderate hypothermia:** Temp ≃ 33°C; change sedation to midazolam
- **Ventilation:** PaCO2 ≃ 4.0 kPa (30mmHg) IF SjO2 >> 50% and PbtO2 >> 15 mmHg

ICP > 20 mmHg? Escalate to **STAGE 4,**
consider re-scan +/- **decompression**

4

- **Burst suppression** Thiopentone 5 mg/kg + 3-8 mg/Kg/h (titrate to EEG S.R. ≃ 50%)
- **Surgical decompression:** bifrontal or large fronto-temporo-parietal craniectomy


KEEP
CALM
'CAUSE
THAT'S ALL
FOLKS



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DAL NON-COMA BARBITURICO ALLA NON-SEDAZIONE

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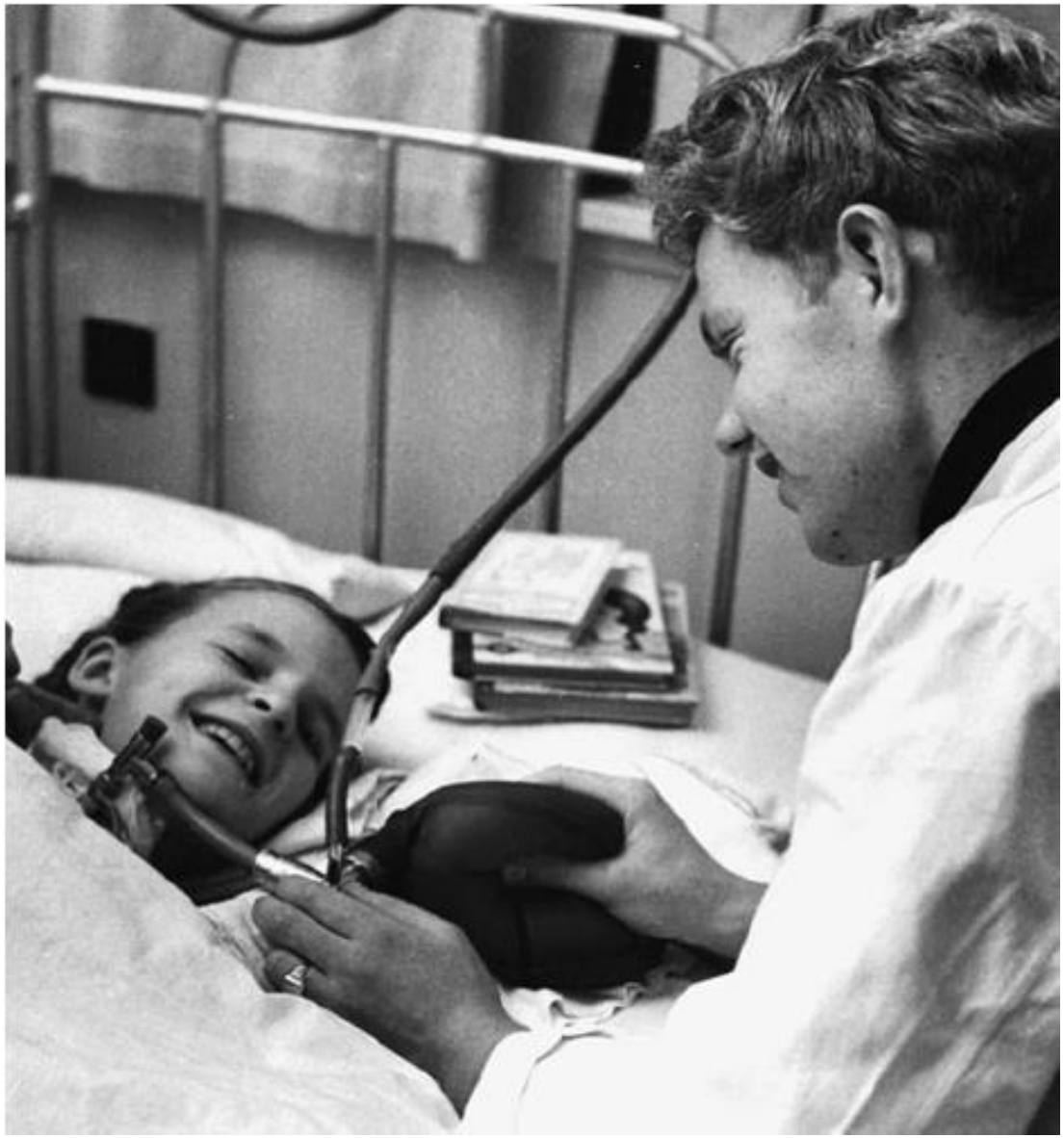


A young patient with poliomyelitis being manually ventilated by a medical student during the poliomyelitis epidemic in Copenhagen, 1953 [Source: Medical History Museum in Copenhagen].

Cited by Sénélar LR. ***Intensive Care Med*** 2011; 37:1084-1086

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

Staff education, regular sedation and analgesia quality feedback, and a sedation monitoring technology for improving sedation and analgesia quality for critically ill, mechanically ventilated patients: a cluster randomised trial

Walsh TS, et al. *Lancet Respir Med* **2016**; 4: 807–817

Introduction

Deep sedation during mechanical ventilation in the intensive care unit (ICU) is associated with longer ICU stay, more infections, and higher mortality.[1] Strategies promoting lighter sedation can improve these outcomes but increase the risk of patient agitation and discomfort. Pain and frightening memories are widely reported by ICU survivors, and are associated with longer-term psychological problems, especially post-traumatic stress.[2-4] Guidelines recommend simultaneous avoidance of deep sedation, pain, and agitation, but changing staff behaviour to improve management is challenging.[3,5] Most previous trials have used protocols or daily sedation breaks, but the effectiveness of these interventions is uncertain and probably context specific.[6,7]

A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety

Jackson DL, et al.

Crit Care **2010**; 14: R59

Systematic interventions to improve sedation practice and maintain patients at an optimal sedation level in the ICU may improve patient outcomes and optimize resource usage.

Protocol-directed sedation tended to reduce mortality; although this was only statistically significant in 2 of 13 studies, the numerical trend was for a decrease and the lack of significance could be due to underpowered studies.

Early Intensive Care Sedation Predicts Long-Term Mortality in Ventilated Critically Ill Patients

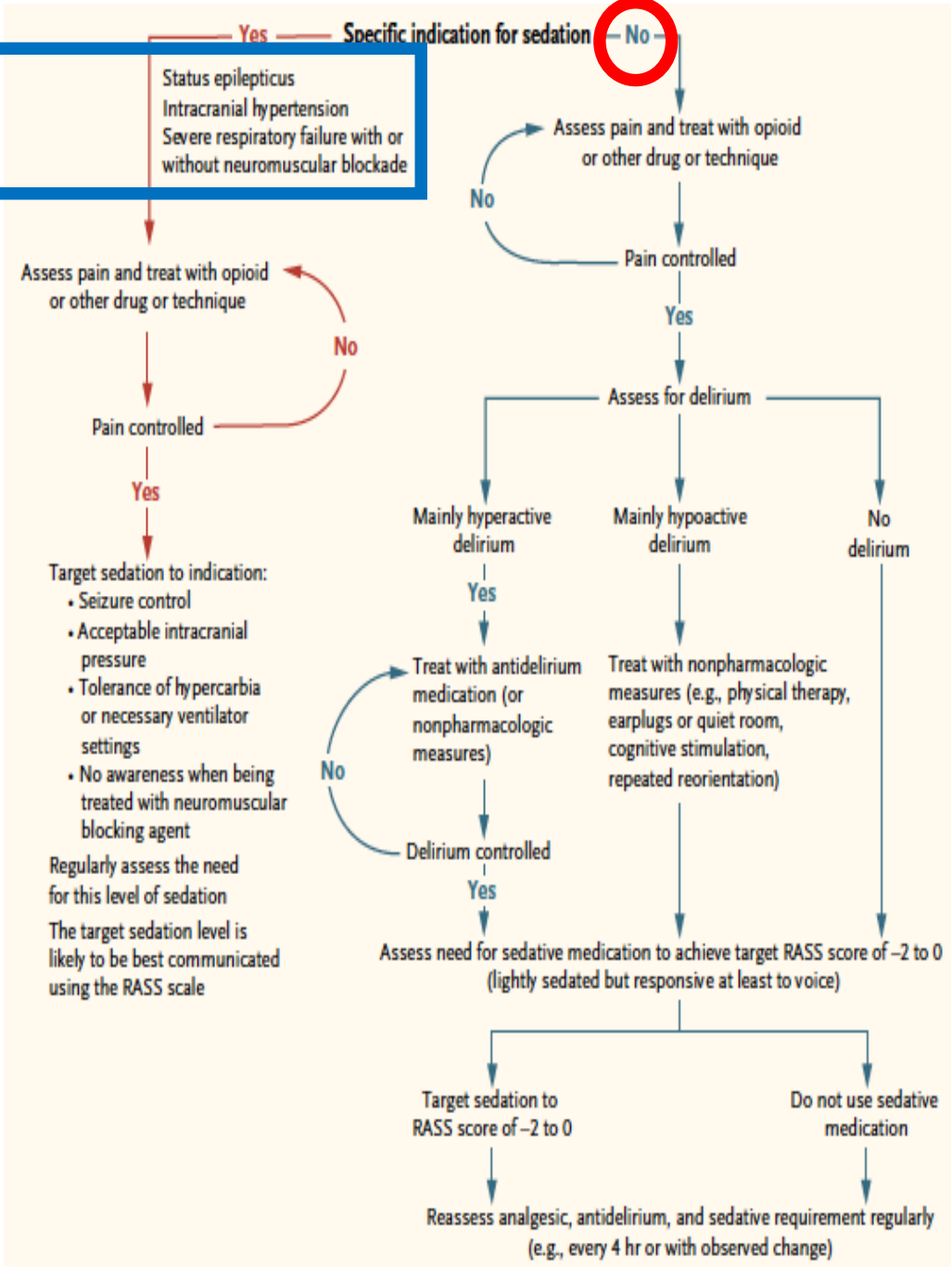
Shehabi Y, et al.

Am J Resp Crit Care Med **2013**; 186:724-731

Early deep sedation was an independent predictor of time to extubation (HR 0.90; 95% CI 0.87–0.94; P <0.001), hospital death (HR, 1.11; 95% CI 1.02–1.20; P= 0.01), and 180-day mortality (HR, 1.08; 95% CI 1.01–1.16; P= 0.026).

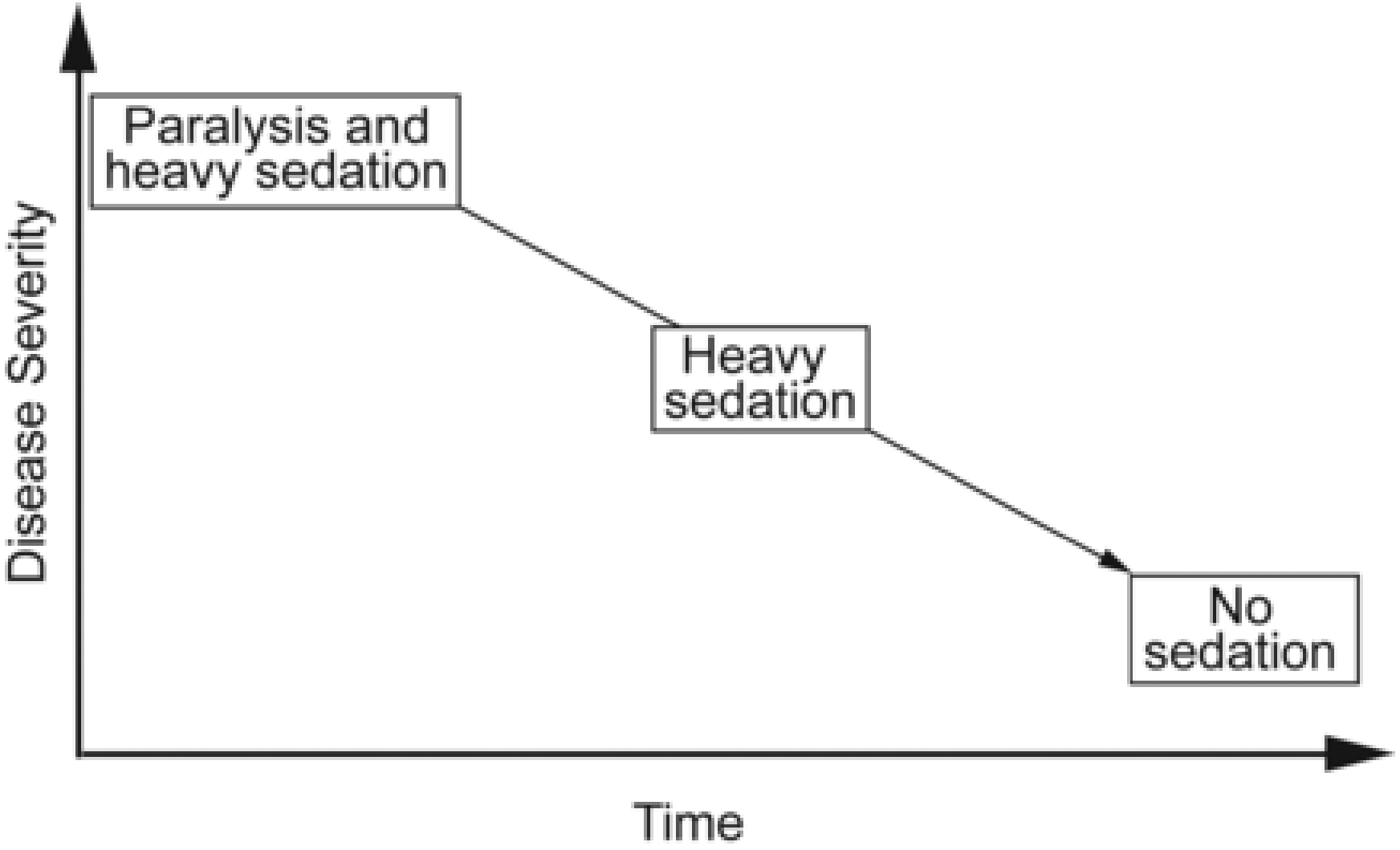
Targeted Temperature Management
Paroxysmal sympathetic activity

Oddo M, et al. Critical Care **2016**; 20:128



Reade MC, Finfer S. Sedation and Delirium in the Intensive Care Unit. *NEJM* **2014**;370:444-54.

Reconciling the Apparent Paradox of Benefits of Both Minimal Sedation and Heavy Sedation (With Paralysis)

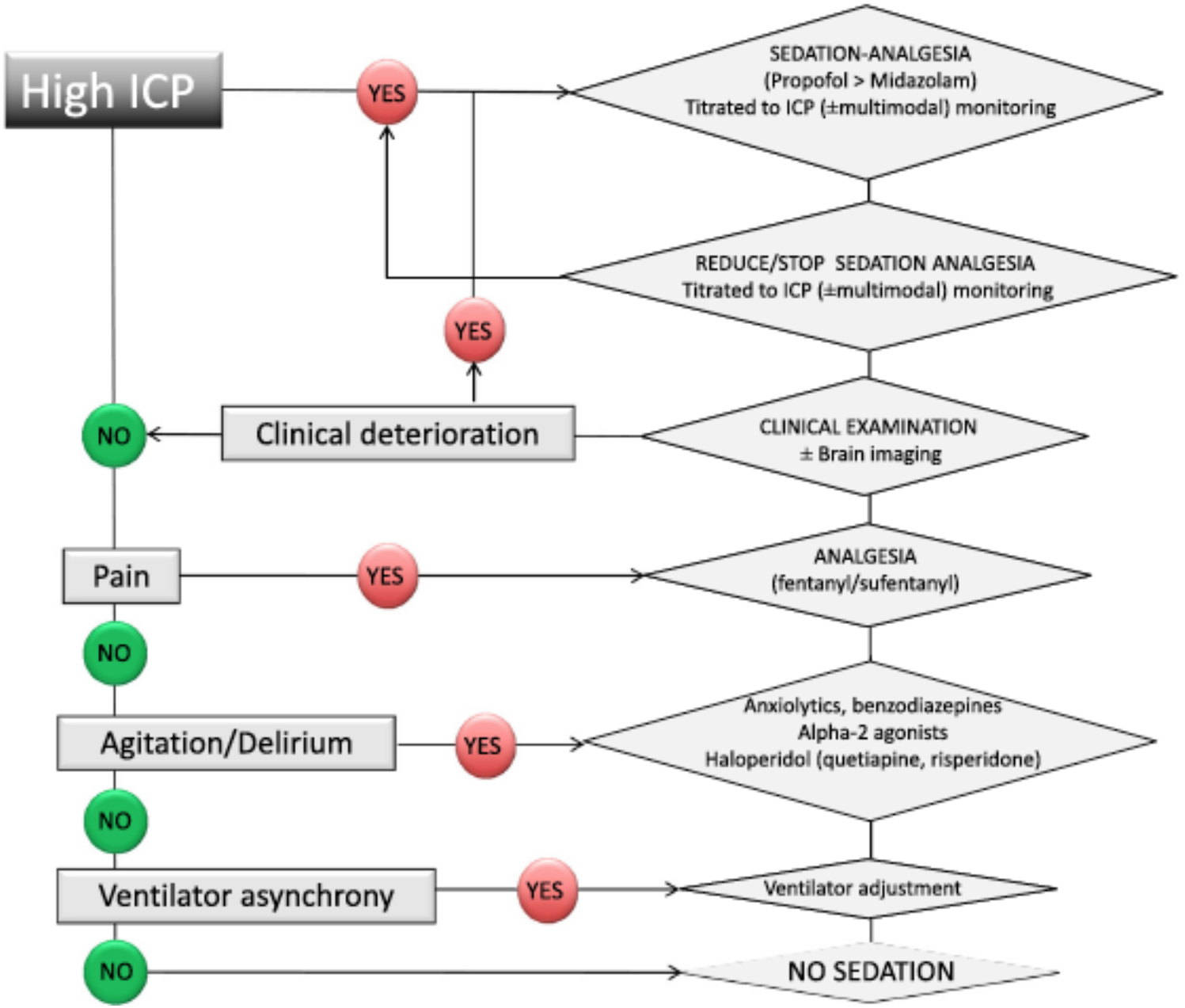


Piriyapatsom A, et al. *Resp Care* **2013**; 58(6):1024-1037

Optimizing sedation in patients with acute brain injury

Oddo M, et al.
Crit Care **2016**; 20: 128

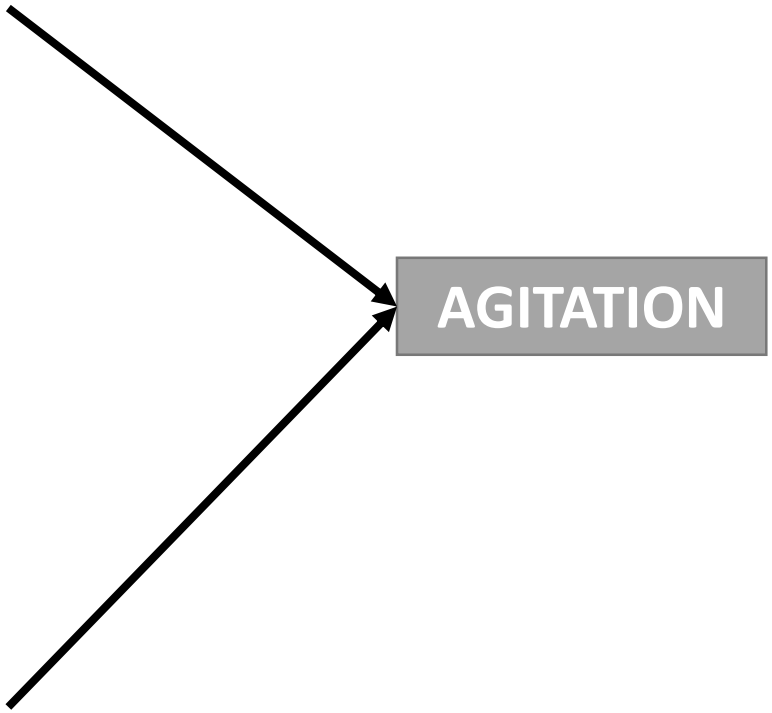
We suggest a pragmatic approach for the use of sedation-analgesia in the NICU, focusing on some practical aspects, including optimal titration and management of sedation withdrawal according to ABI severity.



Oddo M, et al. *Critical Care* **2016**; 20:128

1. Status epilepticus
2. Intracranial hypertension
3. Severe respiratory failure w/wt NMBA
4. Targeted Temperature Management
5. Paroxysmal sympathetic activity
6. Pain
7. Decreased Cerebral Perfusion
8. Severe Hypoxaemia, Sepsis
9. High Temperature
10. Electrolyte Imbalance
11. Sleep Disturbances
12. Deliriogenic Medications
13. Motor hyperactivity
14. Cough
15. Tracheal suctioning
16. Patient-ventilator dissynchrony
17. Shivering
18. Transportation
19. ***Agitation***

SEDATION



- Reade MC, et al. NEJM **2014**; 370:444
- Oddo M, et al. Critical Care **2016**; 20:128
- Vincent JL, et al. Intensive Care Med **2016**;42:962
- Oddo M, Steiner LA. Sedation and analgesia in the neurocritical care unit. In: Smith M, Kofke WA, Citerio G, editors. Oxford textbook of neurocritical care. Oxford: Oxford University Press; **2016**

The 3C Rules

Calm
Comfortable
Cooperative

-1 < RASS <0

SHORT TERM SEDATION MAY BE REQUIRED WHILE YOU CORRECT THE CAUSE

Vincent JL, et al. *Intensive Care Med* **2016** Jun;42(6):962-971

Indication	First-line sedative	First-line analgesic	Alternatives
'Standard' sedation, no ICP elevation	Propofol Midazolam	Fentanyl Morphine	Sufentanil Remifentanil
Elevated ICP	Propofol Midazolam	Fentanyl Morphine	Sufentanil Remifentanil
Targeted temperature management	Propofol Midazolam	Fentanyl Morphine	Sufentanil Remifentanil
Status epilepticus	Propofol Midazolam	Fentanyl Morphine	Sufentanil Remifentanil
Liver dysfunction	Propofol	Fentanyl Sufentanil Remifentanil	
Renal dysfunction	Propofol	Remifentanil	
Haemodynamic instability	Midazolam	Fentanyl	Ketamine
Agitation, delirium	α2-agonists	Fentanyl Morphine	Antipsychotics

Oddo M, et al. *Critical Care* **2016**; 20:128

The 3C Rules

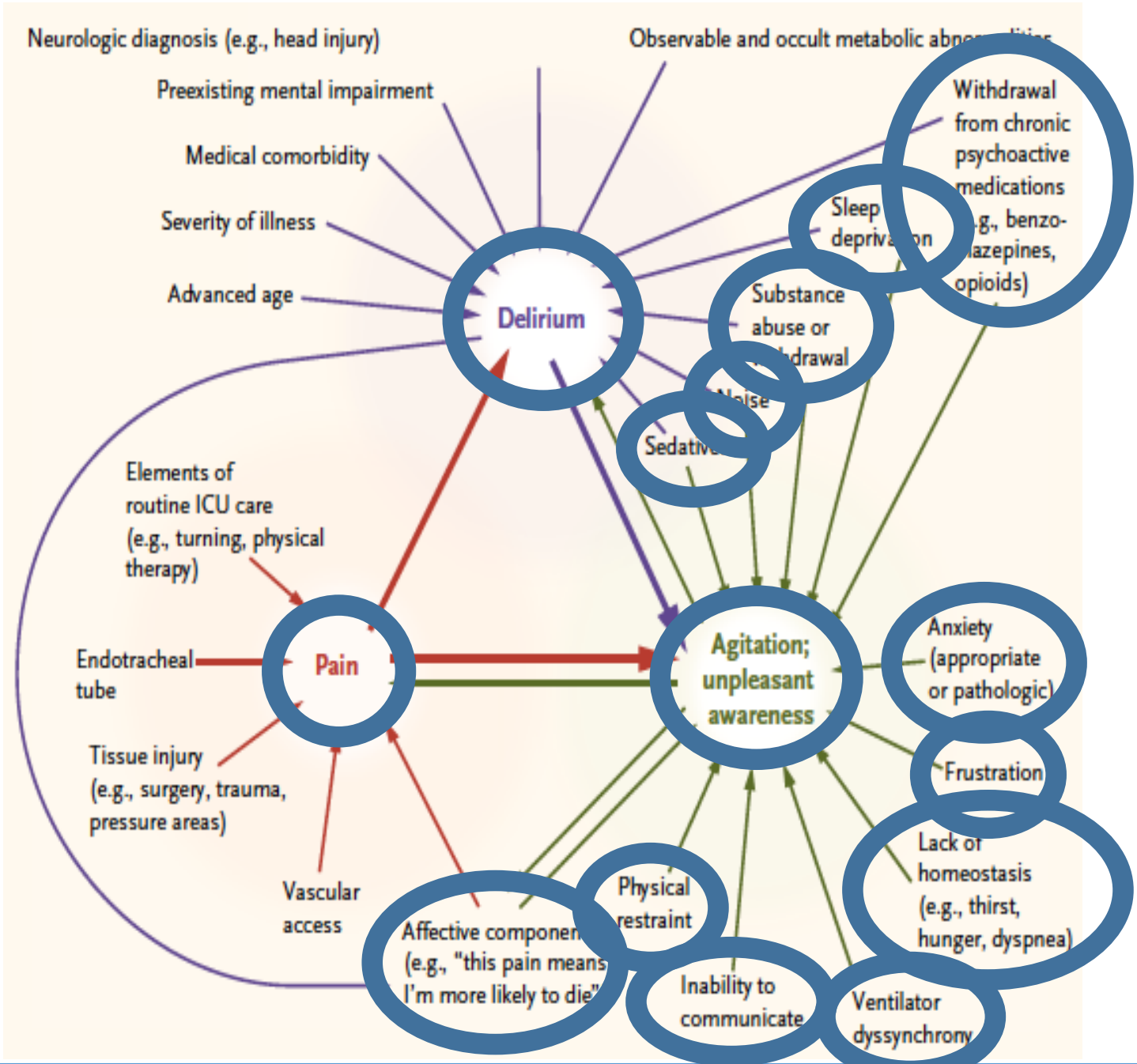
Calm
Comfortable
Cooperative

-1 < RASS <0

ASK YOURSELF WHY

SHORT TERM SEDATION MAY BE REQUIRED WHILE YOU CORRECT THE CAUSE

Vincent JL, et al. *Intensive Care Med* **2016** Jun;42(6):962-971



Reade MC, Finfer S. Sedation and Delirium in the Intensive Care Unit. *NEJM* **2014**;370:444-54.

Critical Care and the Brain

Tasker RC, Menon DK

JAMA **2016** 315(8):749-750

Critical care is always about the brain. This statement Is obvious when the primary problem is neurologic emergencies.

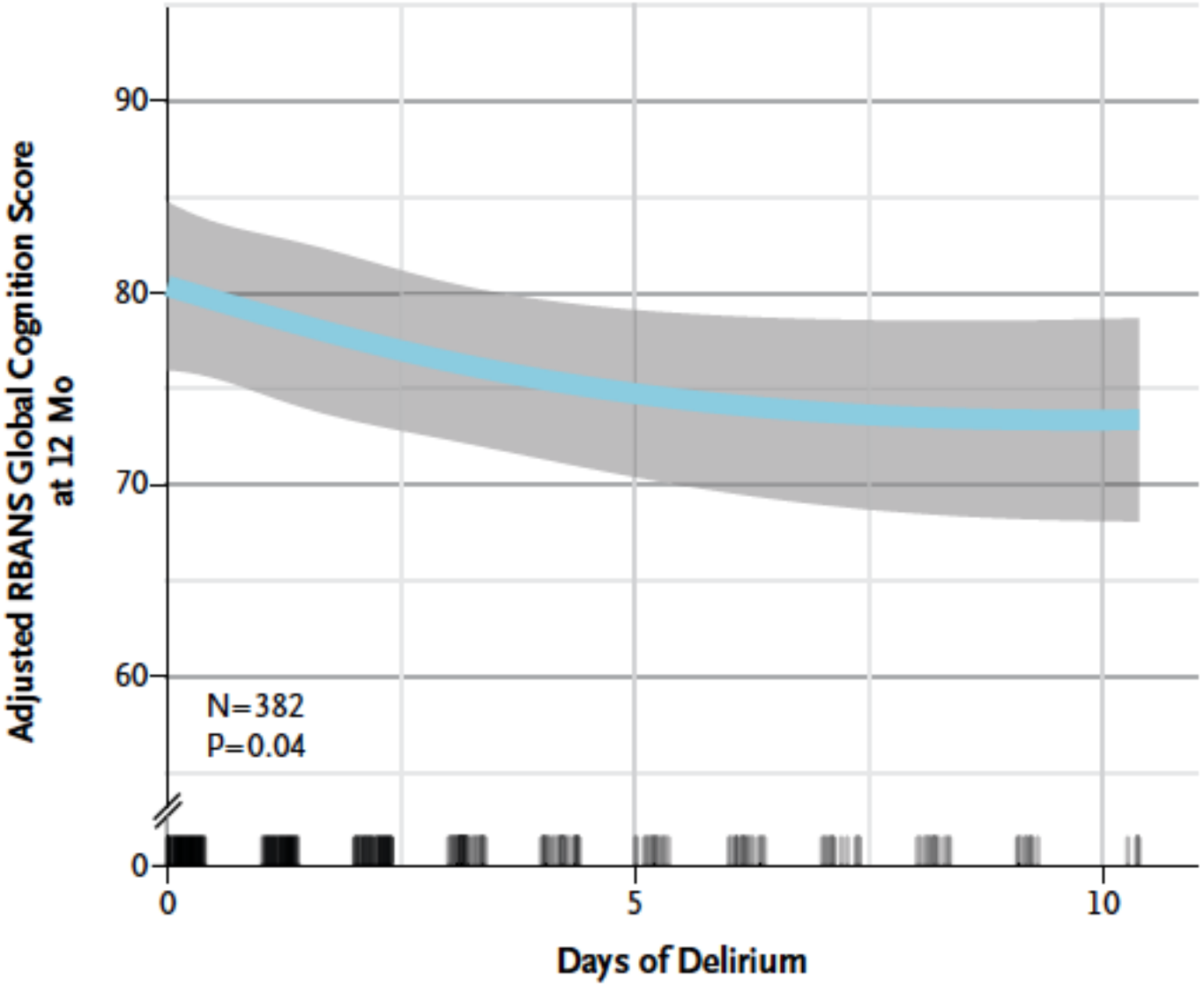
However, even when the primary pathology necessitating ICU treatment lies outside the brain, the eventual aim of care is preserving cerebral function.

Long-Term Cognitive Impairment after Critical Illness

Pandharipande PP, et al.
N Engl J Med **2013**; 369: 1306-1316

At 3 months, 40% of the patients had global cognition scores that were similar to scores for patients with **moderate TBI** and 26% had scores similar to scores for patients with **mild Alzheimer's disease**.

Deficits occurred in both older and younger patients and persisted at 1 year (34% and 24%, respectively).



Pandharipande PP, et al. *N Engl J Med* **2013**; 369: 1306-1316

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Rhodes A, et al.

Intensive Care Med **2017** Mar;43(3):304-377

We recommend that continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration end points.

Limiting the use of sedation in critically ill ventilated patients reduces the duration of mechanical ventilation and ICU and hospital LOS, and allows earlier mobilization.

BUNDLES

E PLURIBUS UNUM

ABCDEF bundle

Assess, Prevent, and Manage Pain

Both Spontaneous Awakening Trials and Spontaneous Breathing Trials

Choice of Analgesia and Sedation

Delirium: Assess, Prevent and Manage

Early Mobility and Exercise

Family Engagement and Empowerment

2014

ICU DELIRIUM www.icudelirium.org

The Surgical Optimal Mobility Score predictsmortality and length of stay in an Italian population of medical, surgical, and neurologic intensive care unit patients

Piva S, et al.
J Crit Care **2015**; 30: 1251–1257

- Adverse event rate was excellent also **in acutely ill neurologic patients**, of whom 1/3 could sit up in bed, stand, or ambulate during the ICU stay, indicating that early mobilization can be safely implemented in this category of patients, provided that cerebral and systemic physiology are stabilized.

- SOMS improvement was independently associated with lower hospital mortality (OR 0.07; 95% CI 0.01-0.42)

Early, Goal-directed Mobilization in the Surgical Intensive Care Unit. A Randomized Controlled Trial

Schaller S, Anstey M, Blobner M, Edrich T, Grabitz SD, Gradwohl-Matis I, Heim M, Houle T, Kurth T, Latronico N, Lee J, Meyer MJ, Peponis T, Talmor D, Velmahos GC, Waak K, Walz MJ, Zafonte R, Eikermann M,
for the *International Early SOMS-guided Mobilization Research Initiative*

Lancet **2016**; 388: 1377-1388

Early, goal-directed mobilisation improved patient mobilisation throughout SICU admission, shortened **patient length of stay** in the SICU, and improved **patients' functional mobility** at hospital discharge.

QoL at 3 months was not different.


RESPIRONICS

CONCLUSIONS (1)

- Are there indications for continuous sedation? If none, treat pain, do not sedate or sedate minimally.
- The concept of severity.
- Why are pts agitated? There are many conditions causing agitation: ***give them a name***!
- Mobilize the patient ASAP.

” Ma qual è infine quella forza che ricerca le cose occulte, … quella di **chi per primo diede il nome a tutte le cose**, opera di somma sapienza, secondo Pitagora, o di chi radunò gli uomini che vivevano isolati e li chiamò a vita sociale, o di chi fissò in pochi segni alfabetici i suoni della voce che sembravano infiniti, o di chi notò dei pianeti le orbite, le anticipazioni e le soste?

Tutti grandi uomini, come anche i precedenti che introdussero il raccolto dei cereali, l’uso dei vestiti, l’abitazione in dimore separate, un tenore superiore di vita, mezzi di difesa contro le fiere: e noi, divenuti per opera loro mansueti e civili, passammo da forme di arte necessarie a forme più raffinate.

Marco Tullio Cicerone. *Opere Politiche e Filosofiche. Discussioni Tusculane*. Leonardo Ferrero, Nevio Zorzetti, Nino Marinone (Eds). Libro I 25, 62. UTET, Torino. ISBN: 978-88-418-9003-5

CONCLUSIONS(2)

- Mobilize the patient ASAP.

THANK YOU