

Sedazione, miorisoluzione e monitoraggio



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Disclosure of interests:



... none !

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Endorsement SIAARTI, Aniarti, AAROI-EMAC

To be
or not to be,
that is the question.

William Shakespeare, 1564-1616



To be, or not to be, that is the question:

Essere, o non essere, questo è il dilemma:

whether 'tis nobler in the mind to suffer

se sia più nobile nella mente soffrire

the slings and arrows of outrageous fortune,

i colpi di fionda e i dardi dell'oltraggiosa fortuna

or to take arms against a sea of troubles,

o prendere le armi contro un mare di affanni

and by opposing end them? To die, to sleep...

e, contrastandoli, porre loro fine? Morire, dormire...

ORIGINAL ARTICLE

Long-Term Cognitive Impairment after Critical Illness

P.P. Pandharipande, T.D. Girard, J.C. Jackson, A. Morandi, J.L. Thompson,
B.T. Pun, N.E. Brummel, C.G. Hughes, E.E. Vasilevskis, A.K. Shintani,
K.G. Moons, S.K. Geevarghese, A. Canonico, R.O. Hopkins, G.R. Bernard,
R.S. Dittus, and E.W. Ely, for the BRAIN-ICU Study Investigators*

ABSTRACT

BACKGROUND

Survivors of critical illness often have a prolonged and disabling form of cognitive impairment that remains inadequately characterized.

METHODS

We enrolled adults with respiratory failure or shock in the medical or surgical intensive care unit (ICU), evaluated them for in-hospital delirium, and assessed global cognition and executive function 3 and 12 months after discharge with the use of the Repeatable Battery for the Assessment of Neuropsychological Status (population age-adjusted mean [\pm SD] score, 100 \pm 15, with lower values indicating worse global cognition) and the Trail Making Test, Part B (population age-, sex-, and education-adjusted mean score, 50 \pm 10, with lower scores indicating worse executive function). Associations of the duration of delirium and the use of sedative or analgesic agents with the outcomes were assessed with the use of linear regression, with adjustment for potential confounders.

The authors' full names, degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Pandharipande at 1211 21st Ave. S, MAB Ste. 526, Nashville, TN 37212, or at pratik.pandharipande@vanderbilt.edu.

*The Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) Study Investigators are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2013;369:1306-16.

DOI: 10.1056/NEJMoa1301372

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RBANS Global Cognition Score

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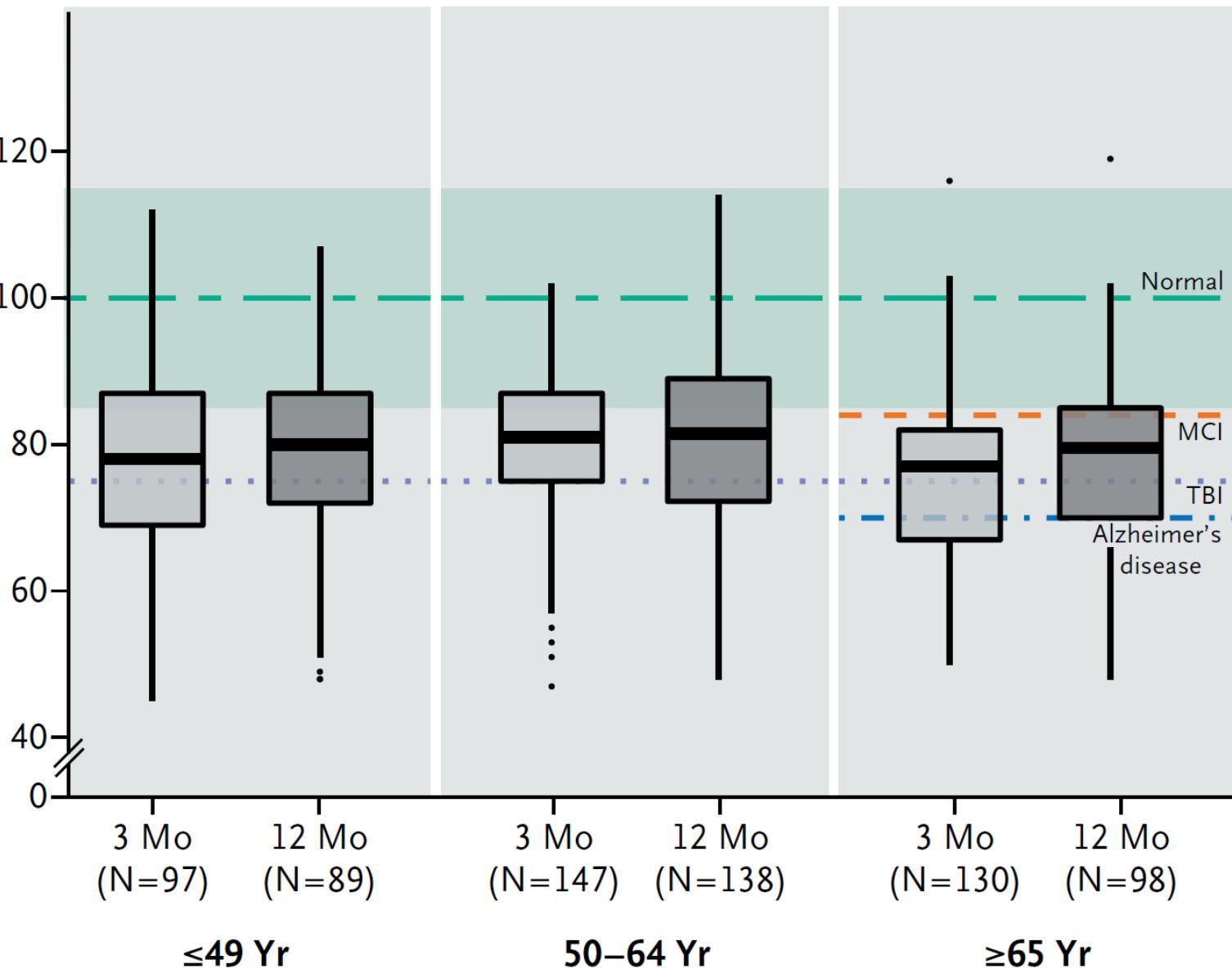
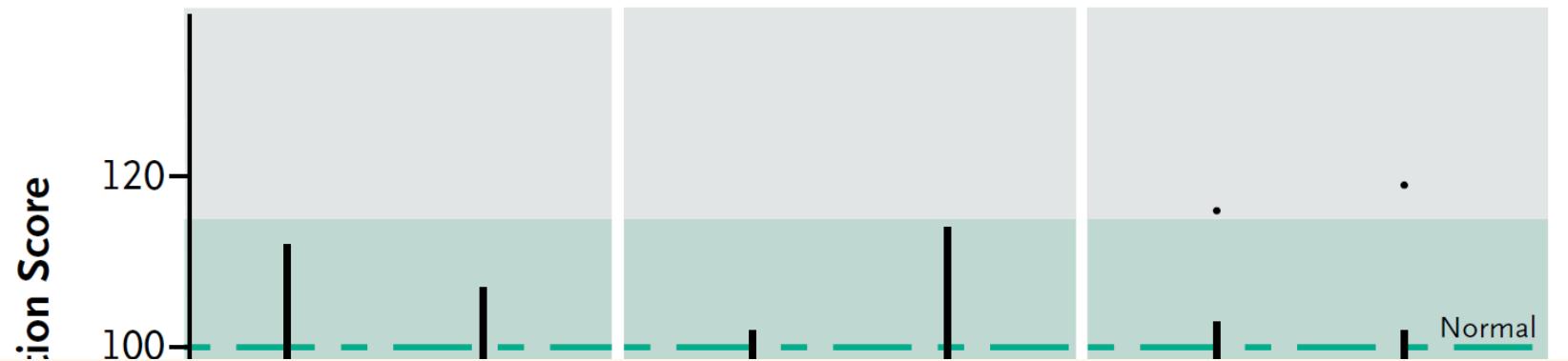


Figure 1. Global Cognition Scores in Survivors of Critical Illness.



Use of sedative or analgesic agent in ICU — no. (%)

Benzodiazepine	509 (62)	274 (59)
Propofol	425 (52)	256 (55)
Dexmedetomidine	105 (13)	63 (13)
Opiate	641 (78)	362 (78)

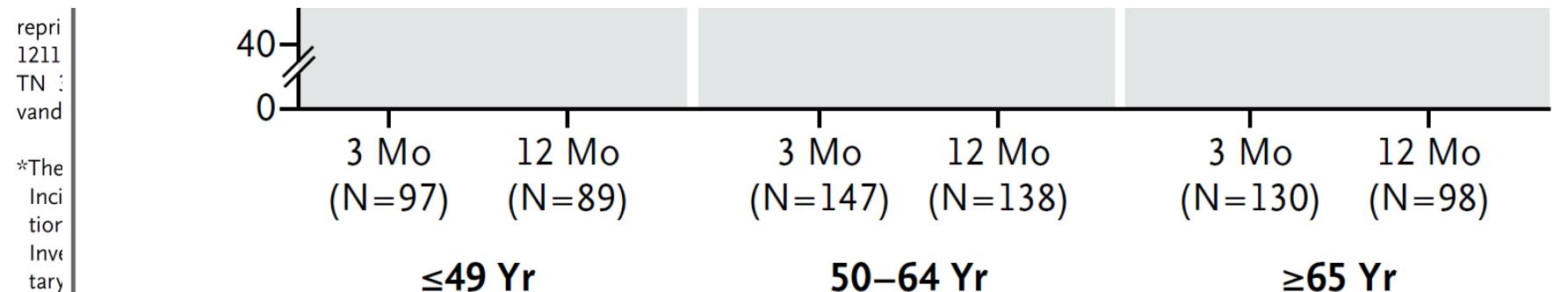


Figure 1. Global Cognition Scores in Survivors of Critical Illness.

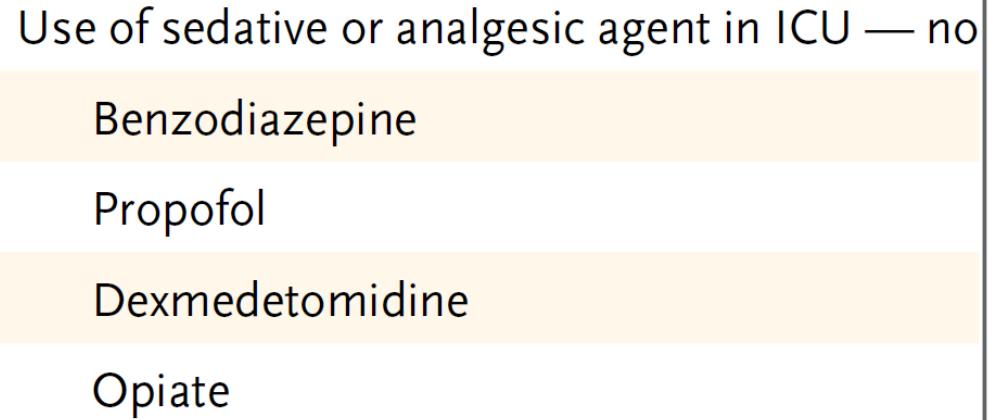


Figure 1. Global Cognition Scores

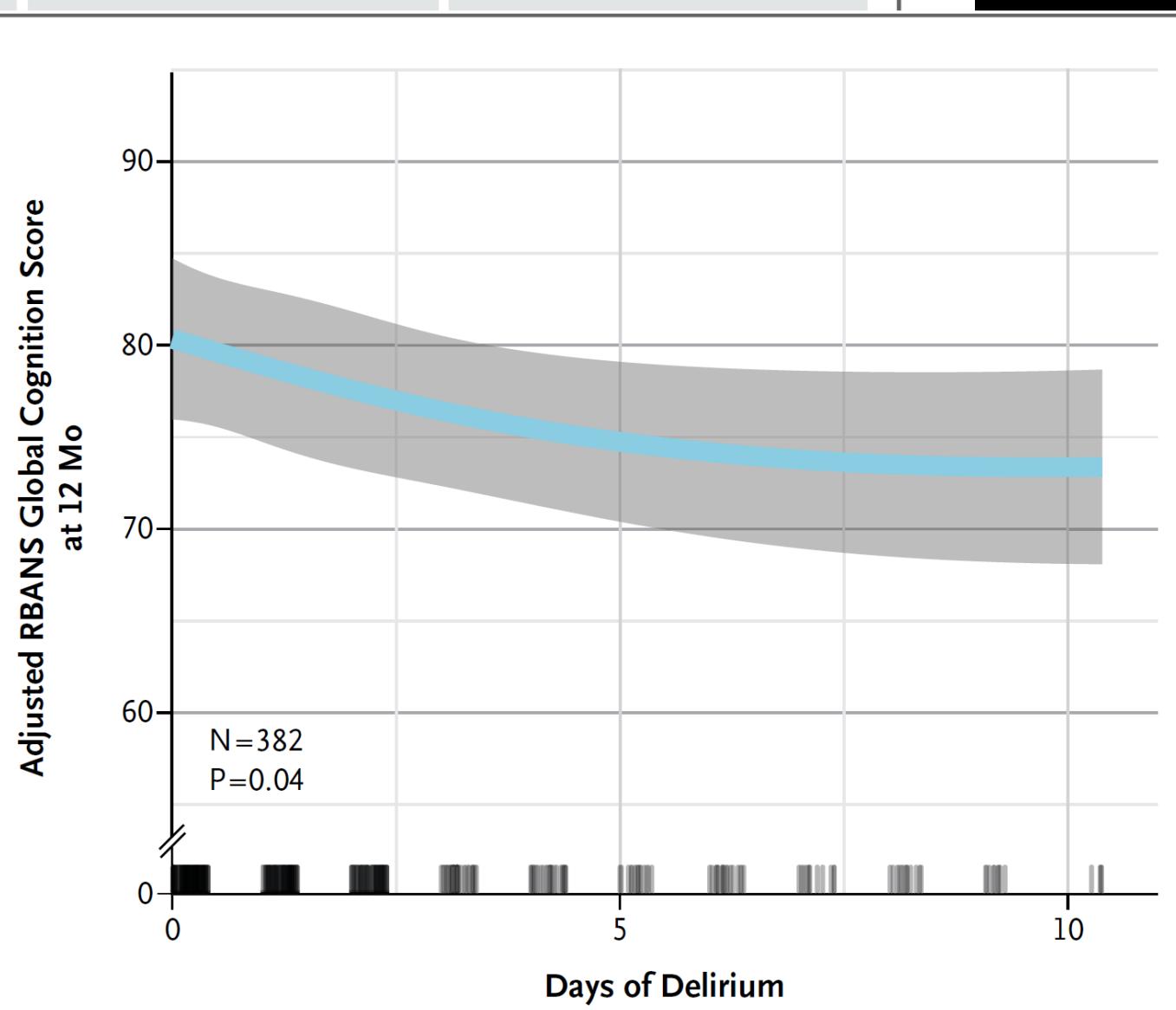


Figure 2. Duration of Delirium and Global Cognition Score at 12 Months.

Il compito della Terapia Intensiva

Mantenere gli
equilibri vitali...

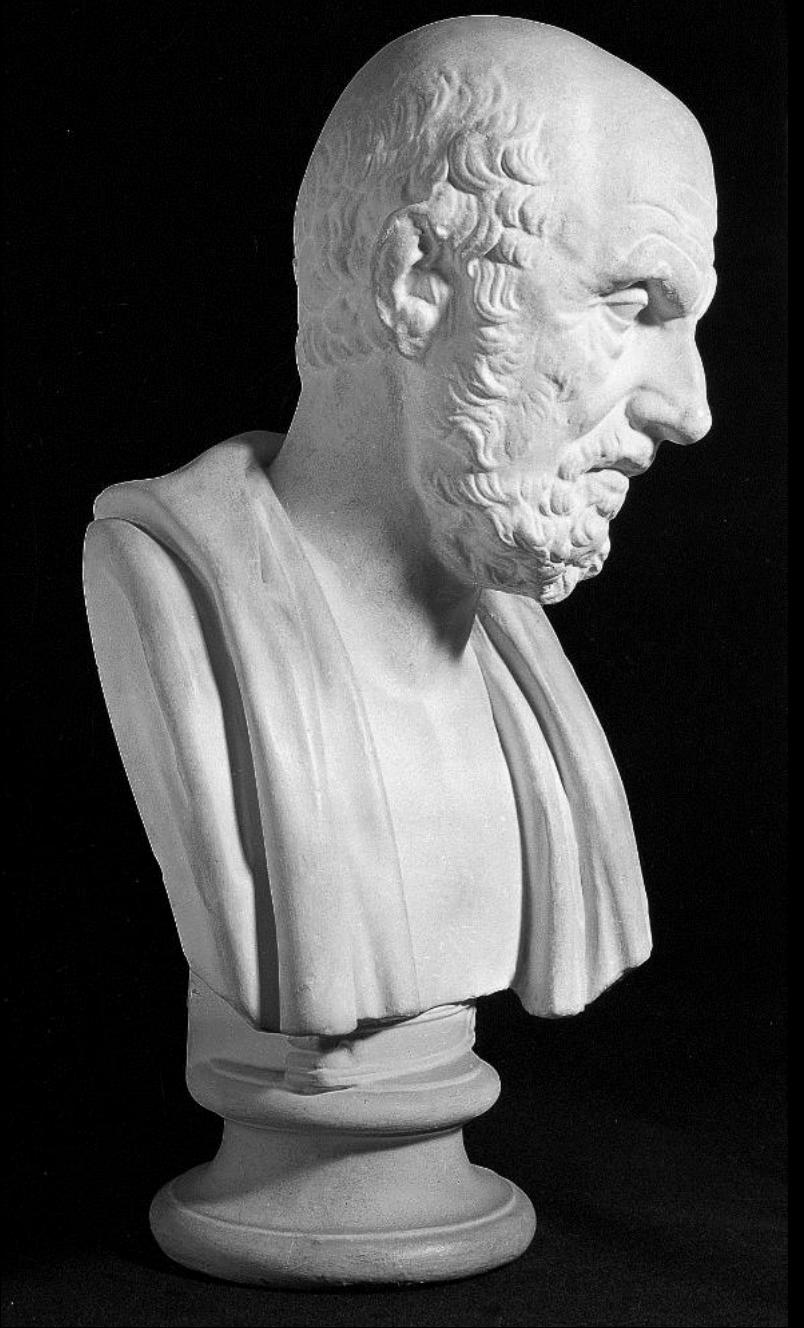


Il compito della Terapia Intensiva

Mantenere gli
equilibri vitali...



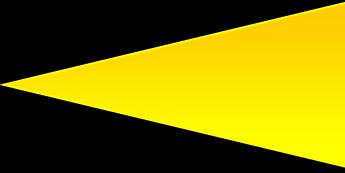
...per poi
stare meglio !



Divinum est
sedare dolorem.

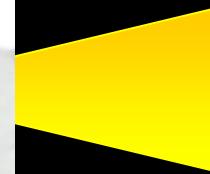
Ippocrate, 460-377 a.C.

Perché effettuare analgo-sedazione in Terapia Intensiva? E' davvero necessaria?

- Confort ottimale per paziente
- Riduzione della “risposta di stress” 
- Riduzione complicanze cardiache e respiratorie
- Aiuto nelle procedure diagnostiche/terapeutiche
- Diminuzione di sintomi di agitazione e delirium

Perché effettuare analgo-sedazione in Terapia Intensiva? E' davvero necessaria?

- Cognitiva
- Riduzione del dolore
- Riduzione della ansia
- Aiuto alla respirazione
- Diminuzione di sintomi di agitazione



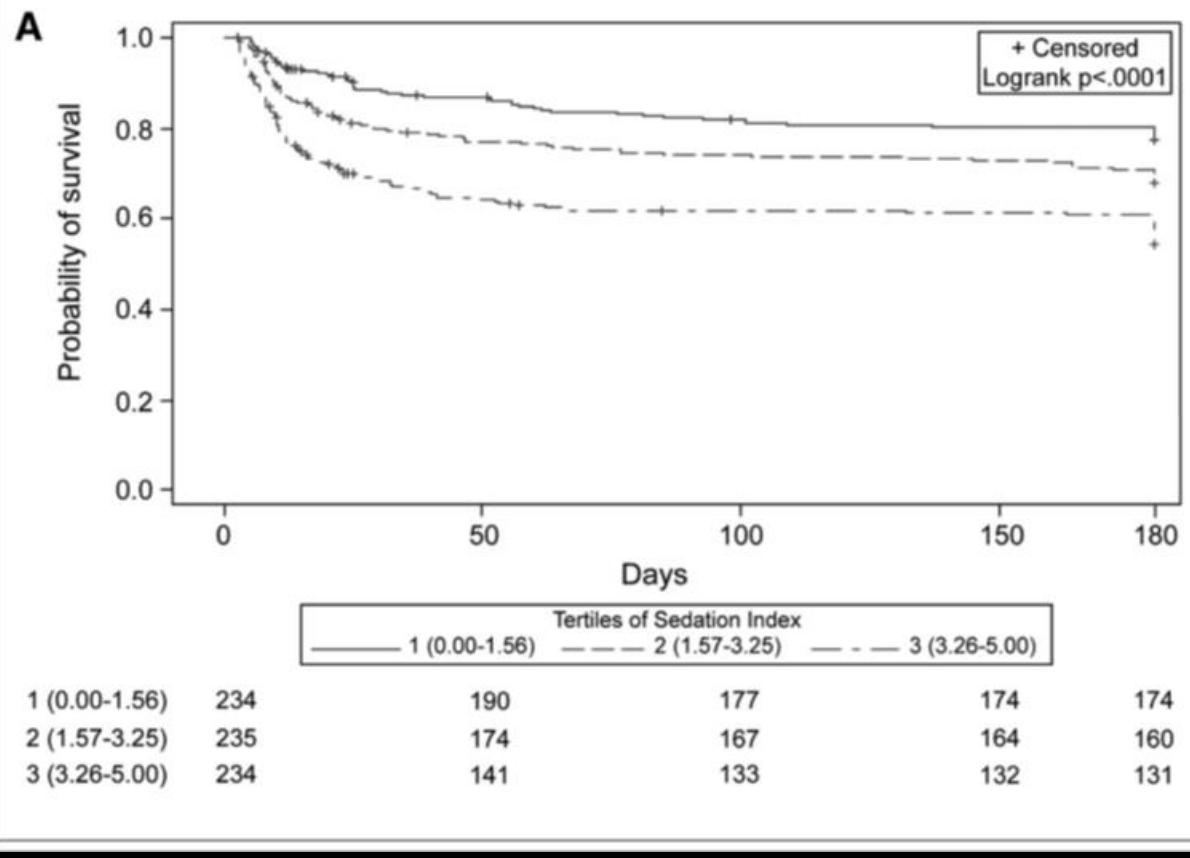
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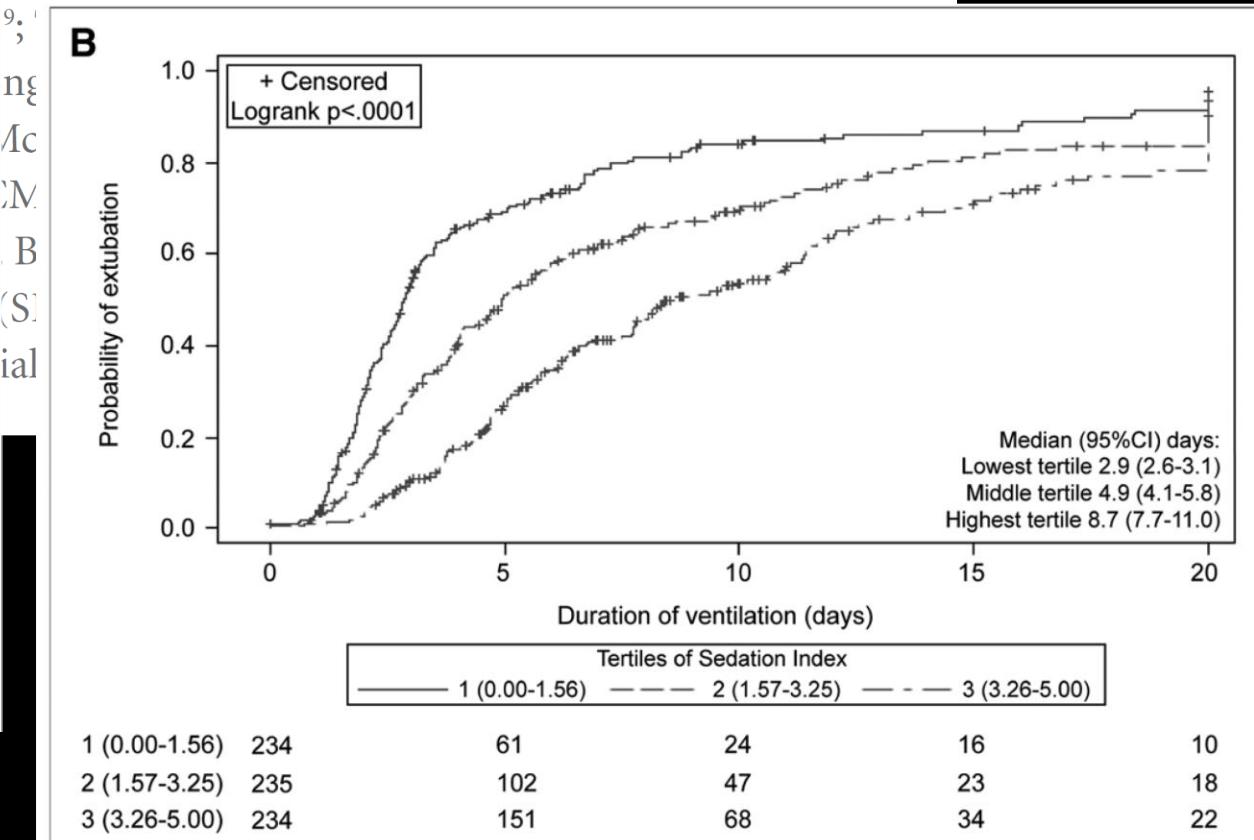
Sedation Intensity in the First 48 Hours of Mechanical Ventilation and 180-Day Mortality: A Multinational Prospective Longitudinal Cohort Study

Yahya Shehabi, PhD, FCICM, FANZCA, EMBA^{1,2}; Rinaldo Bellomo, MD (Hons), FRACP, FCICM^{3,4,5}; Suhaini Kadiman, MD, M.MED⁶; Lian Kah Ti, MBBS, Mmed⁷; Belinda Howe, RN, BN⁸; Michael C. Reade, MBBS, MPH, Dphil, FCICM⁹; Tien Meng Khoo, MBBS, MRCP, EDIC¹⁰; Anita Alias, MD, MMed(Anaesth)¹¹; Yu-Lin Wong, FANZCA, MMed (ICM)¹²; Amartya Mukhopadhyay, FRCP, MPH⁷; Colin McArthur, MBChB, FANZCA, FCICM¹³; Ian Seppelt, MBBS, BSc (Med), FANZCA, FCICM¹⁴; Steven A. Webb, MPH, PhD, FCICM^{8,15}; Maja Green, PhD, MSc, BSc (Hons)¹; Michael J. Bailey, PhD, MSc (statistics), BSc (Hons)^{1,8}; for the Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group

Sedation Intensity in the First 48 Hours of Mechanical Ventilation and 180-Day Mortality: A Multinational Prospective Longitudinal Cohort Study



^{1,2}; Rinaldo Bellomo, MD (Hons), FRACP, FCICM^{3,4,5};
MBBS, Mmed⁷; Belinda Howe, RN, BN⁸;



Paziente ideale



Paziente ideale

(secondo gli infermieri della Rianimazione di Cambridge)

- Sedato.
- Curarizzato.
- Catetere vescicale.
- Colostomia terminale.
- Peso < 50 kg.
- Figlio unico, orfano, single, senza amici.



Effetti collaterali di analgesici e sedativi...

- Sепси
- Ipotensione, bradicardia, disturbi cardiaci
- Insufficienza respiratoria
- Ileo
- Ristagno venoso, trombosi venosa profonda
- Svezzamento ritardato dalla ventilazione meccanica
- Permanenza prolungata in T.I.
- Aumento costi
- Impossibilità valutazione alterazioni SNC



Quali «strategie sedative» nella storia recente delle TI?

- '80: I pazienti devono adattarsi ai macchinari
 - *Sedazione profonda e immobilità!*

Quali «strategie sedative» nella storia recente delle TI?

- '80: I pazienti devono adattarsi ai macchinari
 - *Sedazione profonda e immobilità!*
- '90: I macchinari devono adattarsi ai pazienti, ma i ricordi della T.I. sono spaventosi e angoscianti!
 - *No mio-rilassanti, ancora sedazione profonda*

Quali «strategie sedative» nella storia recente delle TI?

- '80: I pazienti devono adattarsi ai macchinari
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- '90: I macchinari devono adattarsi ai pazienti, ma i ricordi della T.I. sono spaventosi e angoscianti!
 - *No mio-rilassanti, ancora sedazione profonda*
- 2000: Sedazione guidata da protocolli
 - *Interruzione giornaliera*
 - *Sedazione basata sull'analgesia*

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



Thomas Strøm, Torben Martinussen, Palle Toft

Summary

Background Standard treatment of critically ill patients undergoing mechanical ventilation is continuous sedation. Daily interruption of sedation has a beneficial effect, and in the general intensive care unit of Odense University Hospital, Denmark, standard practice is a protocol of no sedation. We aimed to establish whether duration of mechanical ventilation could be reduced with a protocol of no sedation versus daily interruption of sedation.

Lancet 2010; 375: 475–80

Published Online

January 29, 2010

DOI:10.1016/S0140-

6736(09)62072-9

See [Comment](#) page 436

Department of Anesthesia and Intensive Care Medicine, Odense University Hospital (T Strøm MD, Prof P Toft DMSc), and Department of Biostatistics, Faculty of Health Sciences (Prof T Martinussen PhD), University of Southern Denmark, Denmark

Methods Of 428 patients assessed for eligibility, we enrolled 140 critically ill adult patients who were undergoing mechanical ventilation and were expected to need ventilation for more than 24 h. Patients were randomly assigned in a 1:1 ratio (unblinded) to receive: no sedation ($n=70$ patients); or sedation (20 mg/mL propofol for 48 h, 1 mg/mL midazolam thereafter) with daily interruption until awake ($n=70$, control group). Both groups were treated with bolus doses of morphine (2·5 or 5 mg). The primary outcome was the number of days without mechanical ventilation in a 28-day period, and we also recorded the length of stay in the intensive care unit (from admission to 28 days) and in hospital (from admission to 90 days). Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00466492.

Strom T, *Lancet*, 2010

- 2010: No sedation strategy ?!?!?

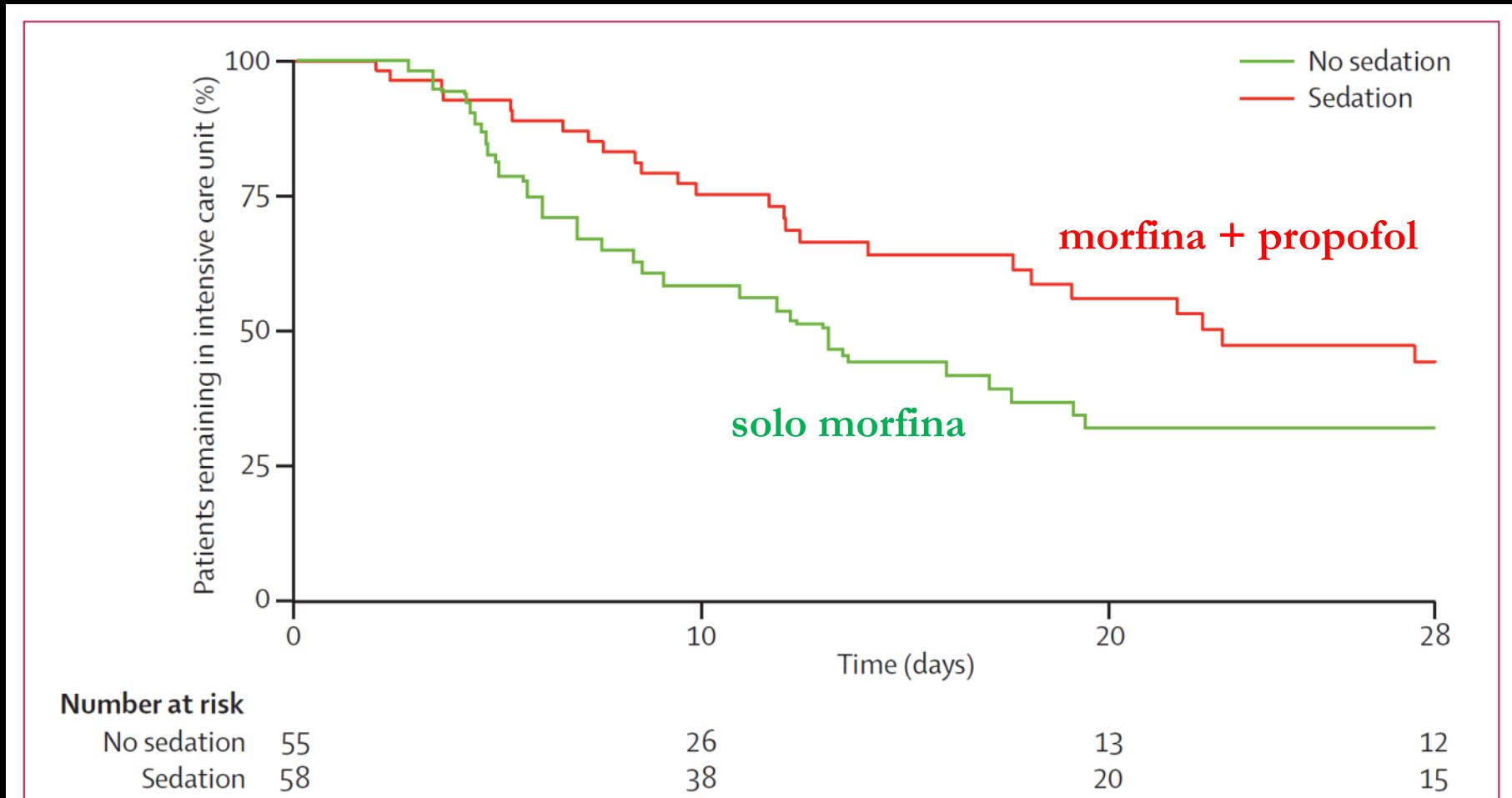
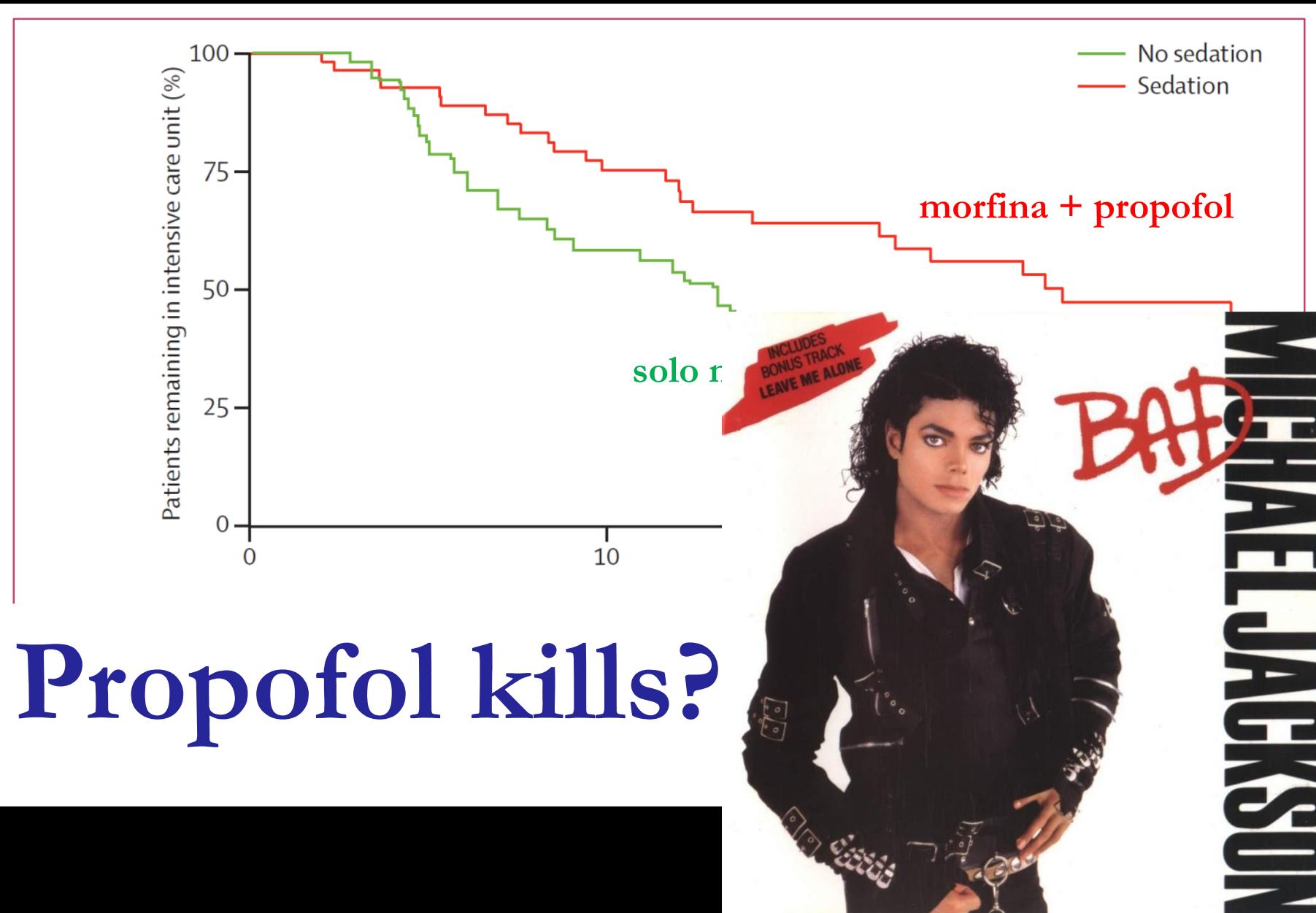
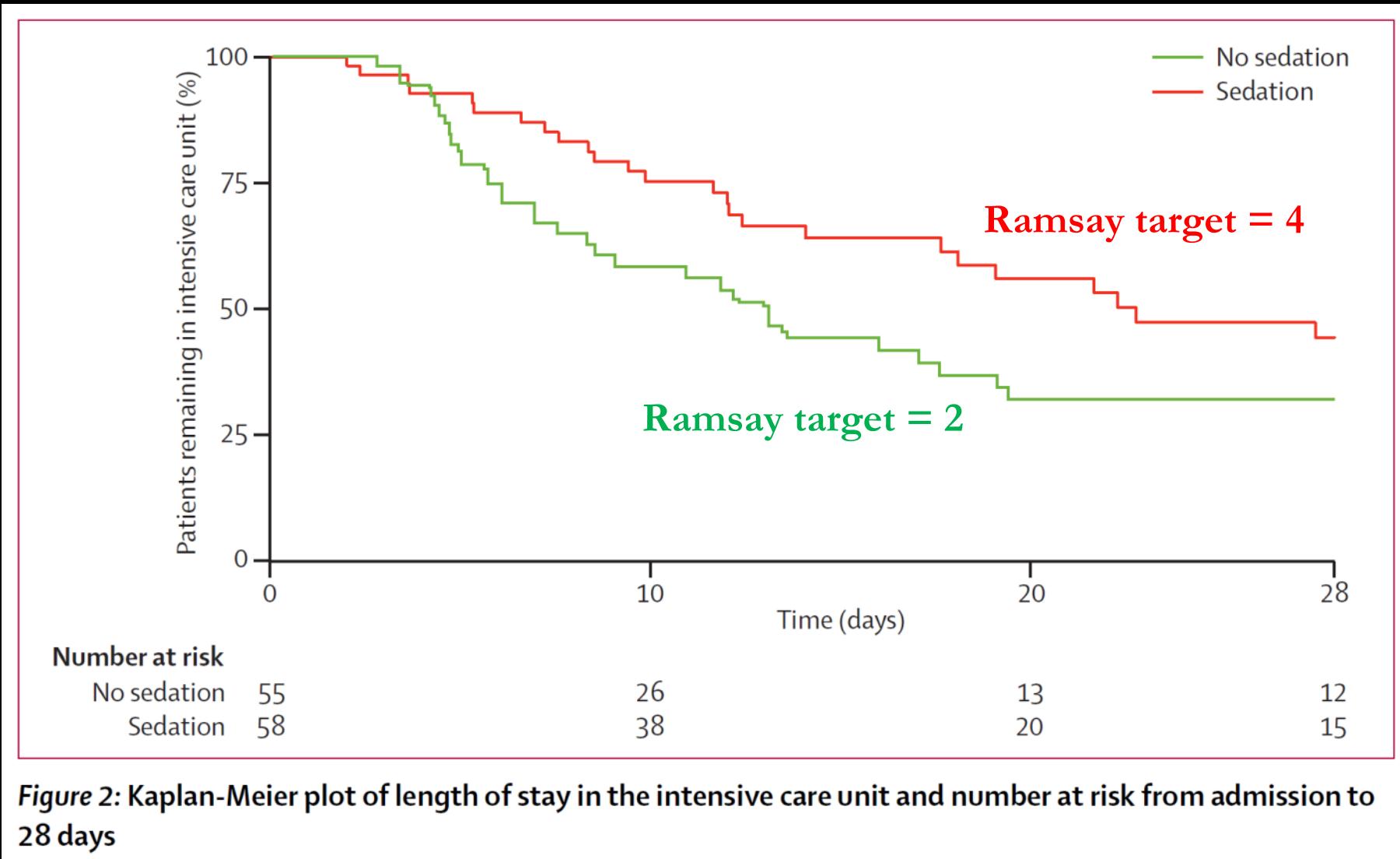


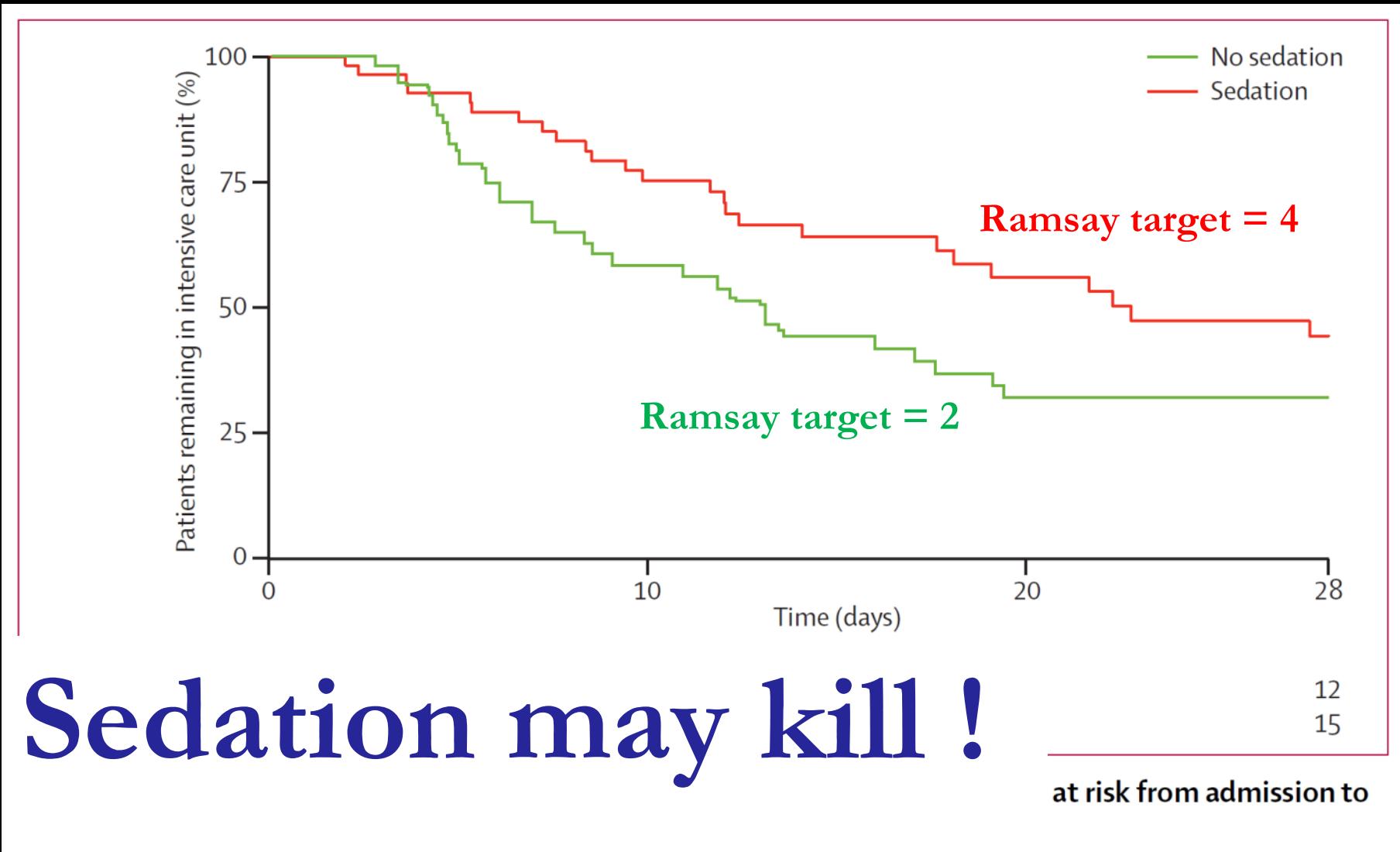
Figure 2: Kaplan-Meier plot of length of stay in the intensive care unit and number at risk from admission to 28 days

Strom T, *Lancet*, 2010





Strom T, *Lancet*, 2010



Strom T, *Lancet*, 2010

Ma siamo disposti a desiderare
che i nostri pazienti critici
Siano mantenuti ad un livello di
“sedazione leggera»?

(cioè RASS fra -1 e 0)

STUDY PROTOCOL

Open Access

Non-sedation versus sedation with a daily wake-up trial in critically ill patients receiving mechanical ventilation (NONSEDA Trial): study protocol for a randomised controlled trial

Palle Toft^{1*}, Hanne Tanghus Olsen², Helene Korvenius Jørgensen³, Thomas Strøm¹, Helle Lykkeskov Nibro⁴, Jacob Oxlund⁵, Karl-Andre Wian⁶, Lars Marius Ytrebø⁷, Bjørn Anders Kroken⁷ and Michelle Chew⁸

Ma siamo disposti a desiderare
che i nostri pazienti critici
siano “il più svegli possibile”... ? ! ? !



ORIGINAL ARTICLE

Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients

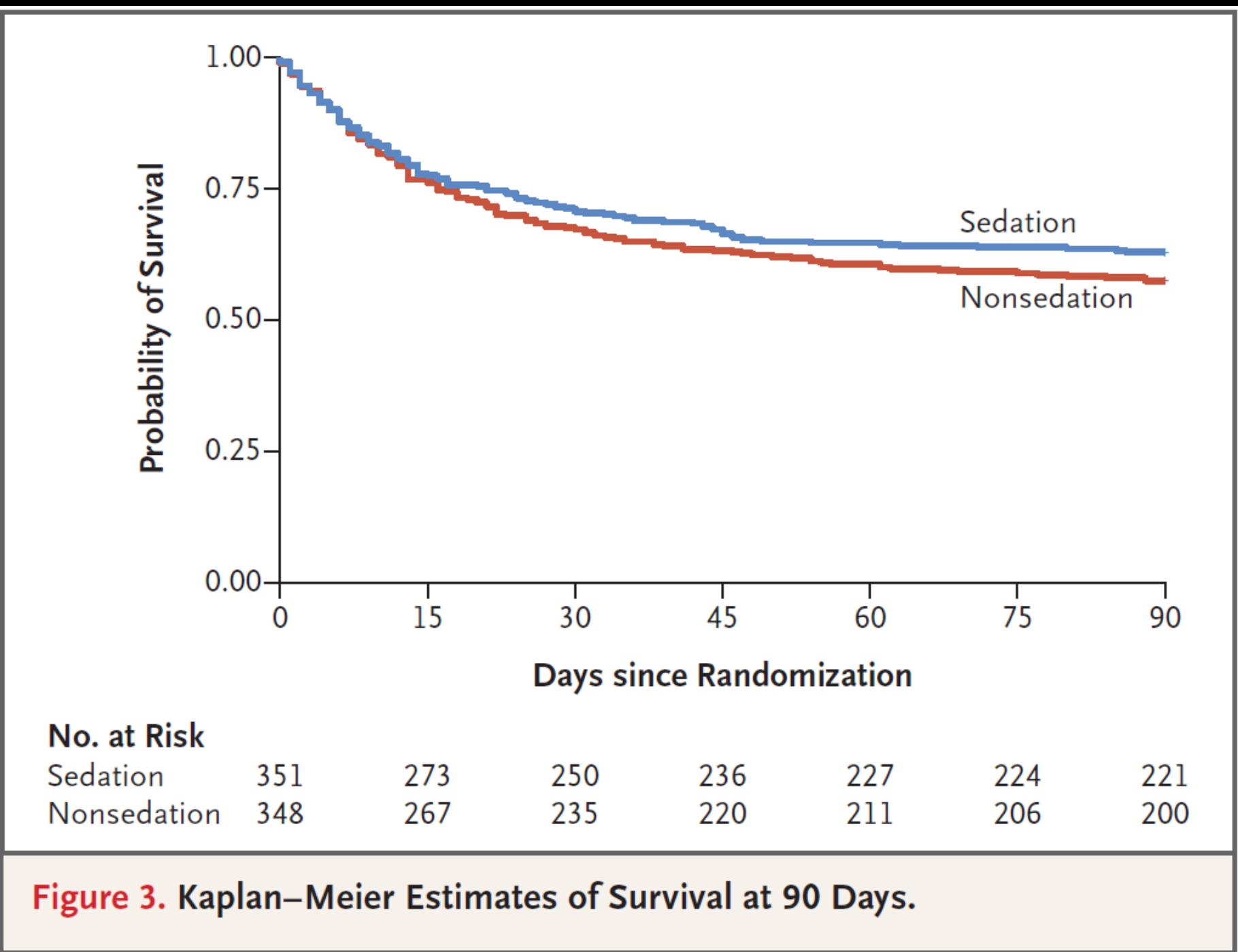
Hanne T. Olsen, M.D., Helene K. Nedergaard, M.D., Ph.D.,
Thomas Strøm, M.D., Ph.D., Jakob Oxlund, M.D., Karl-Andre Wian, M.D.,
Lars M. Ytrebø, M.D., Ph.D., Bjørn A. Kroken, M.D., Michelle Chew, M.D., Ph.D.,
Serkan Korkmaz, Jørgen T. Lauridsen, M.Sc., and Palle Toft, M.D., D.M.Sc.

ABSTRACT

BACKGROUND

In critically ill, mechanically ventilated patients, daily interruption of sedation has been shown to reduce the time on ventilation and the length of stay in the intensive care unit (ICU). Data on whether a plan of no sedation, as compared with a plan of light sedation, has an effect on mortality are lacking.

From the Departments of Anesthesiology and Intensive Care, Odense University Hospital–Svendborg Hospital, Svendborg (H.T.O.), the Departments of Clinical Research (H.T.O., H.K.N., T.S., J.O., P.T.)



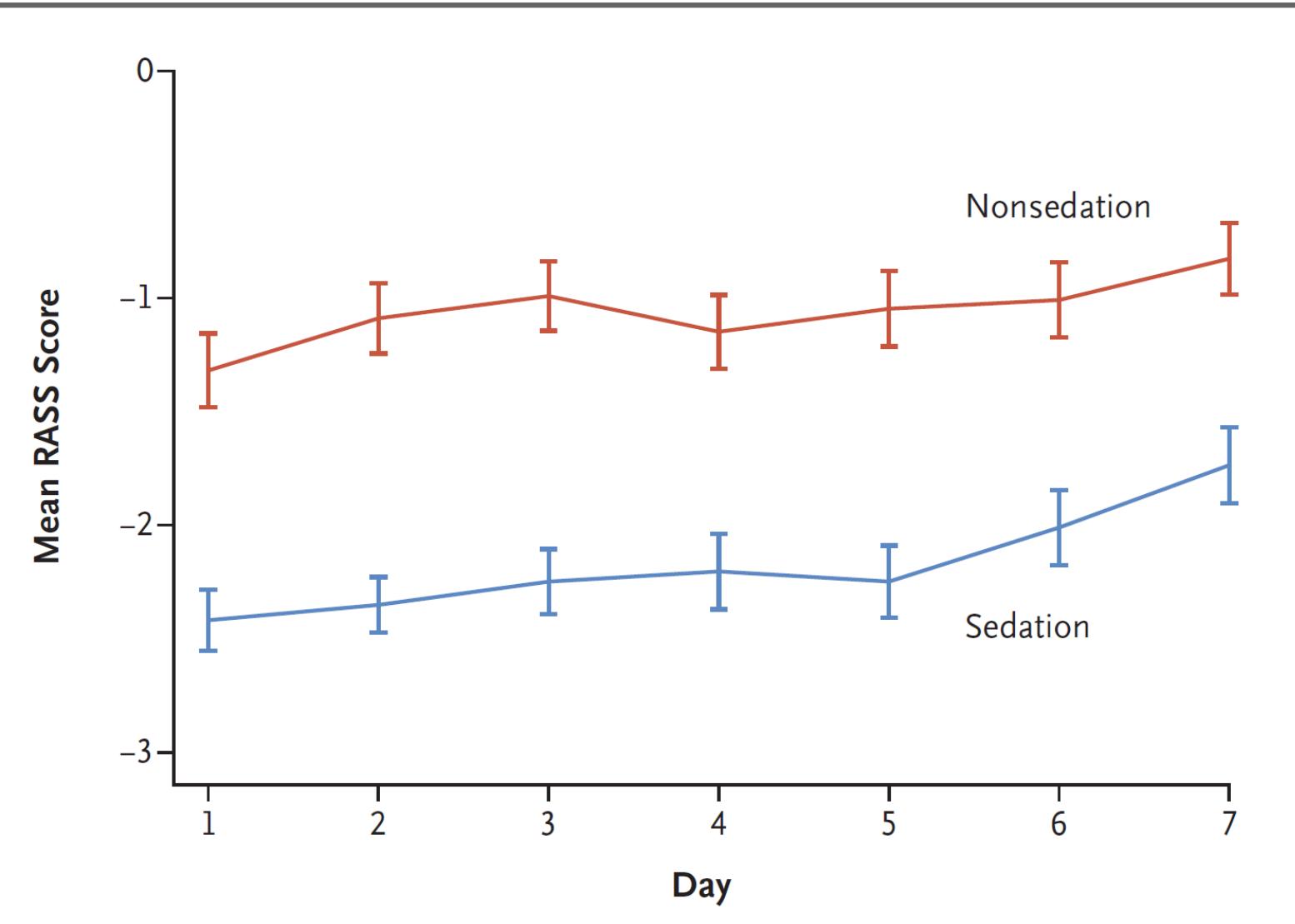
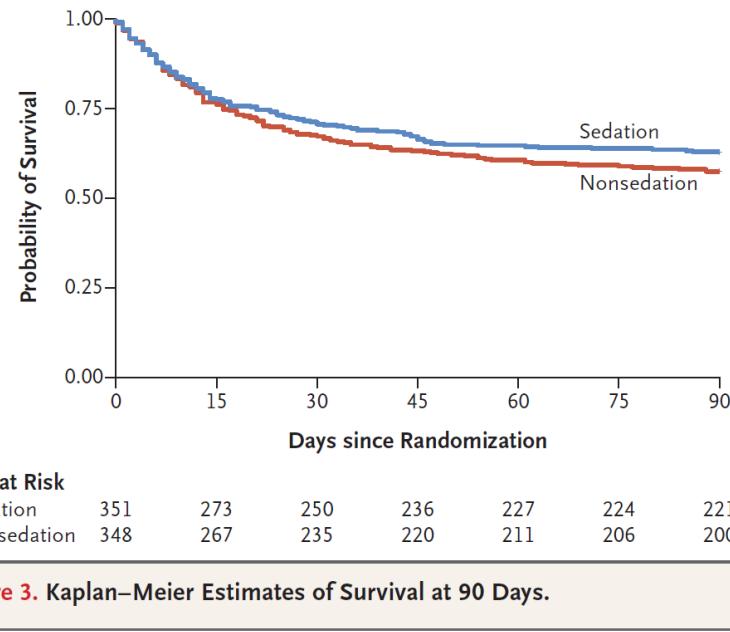
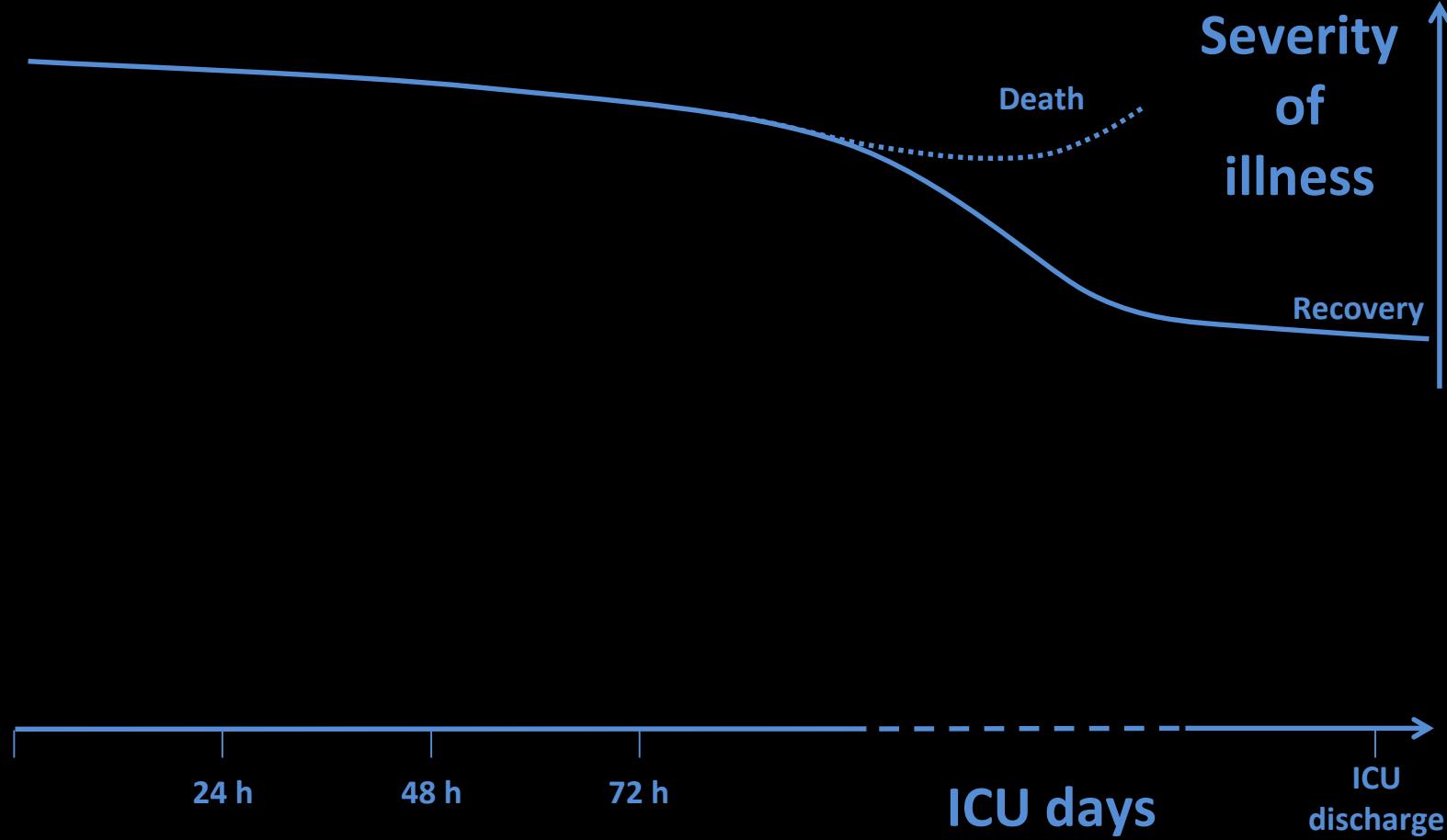
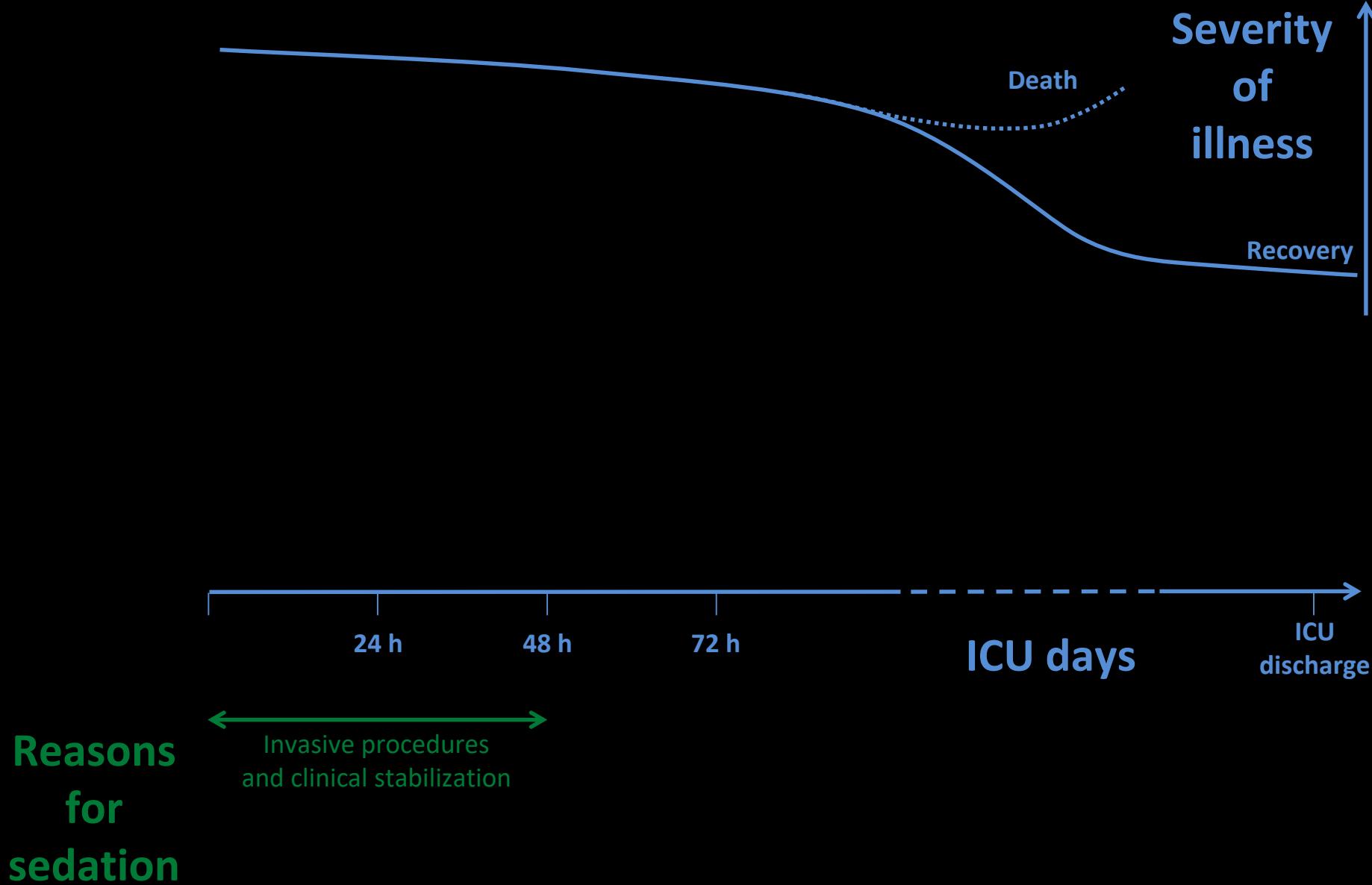


Figure 2. RASS Score during the First 7 Days of the Trial.

RASS denotes Richmond Agitation and Sedation Scale, on which scores range from -5 (unresponsive) to +4 (combative).

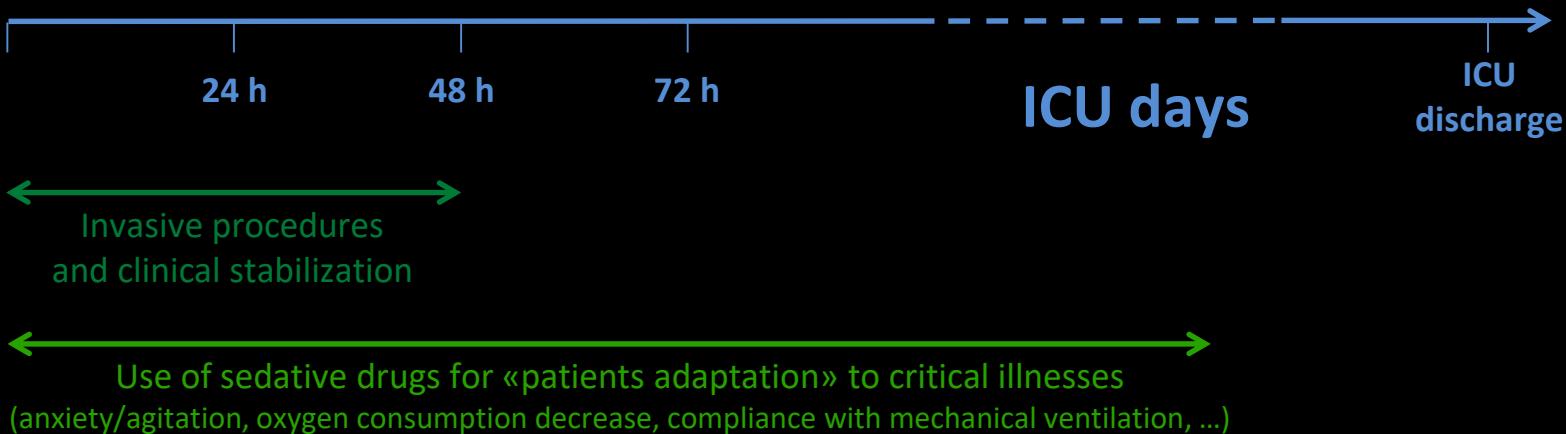


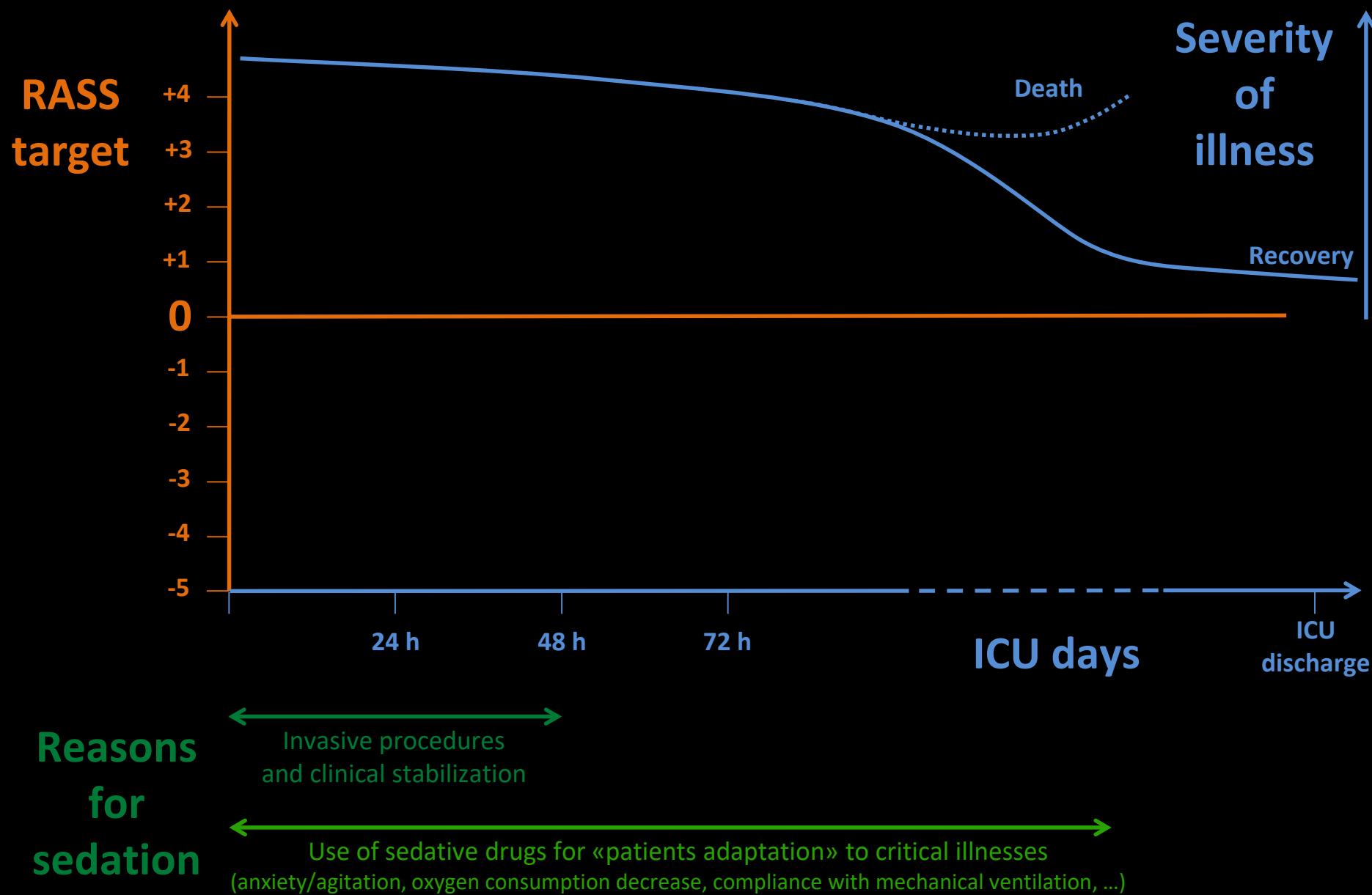


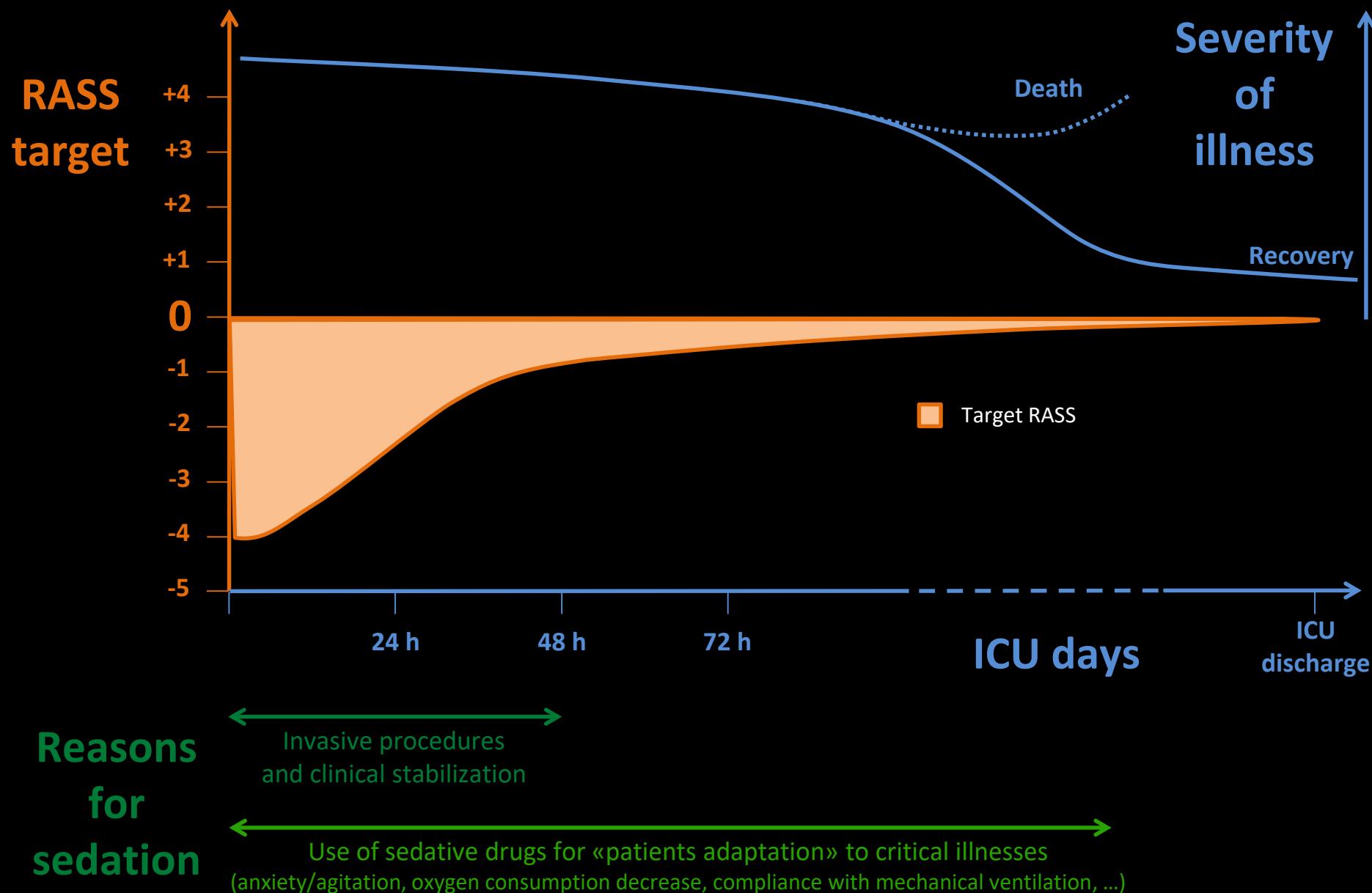


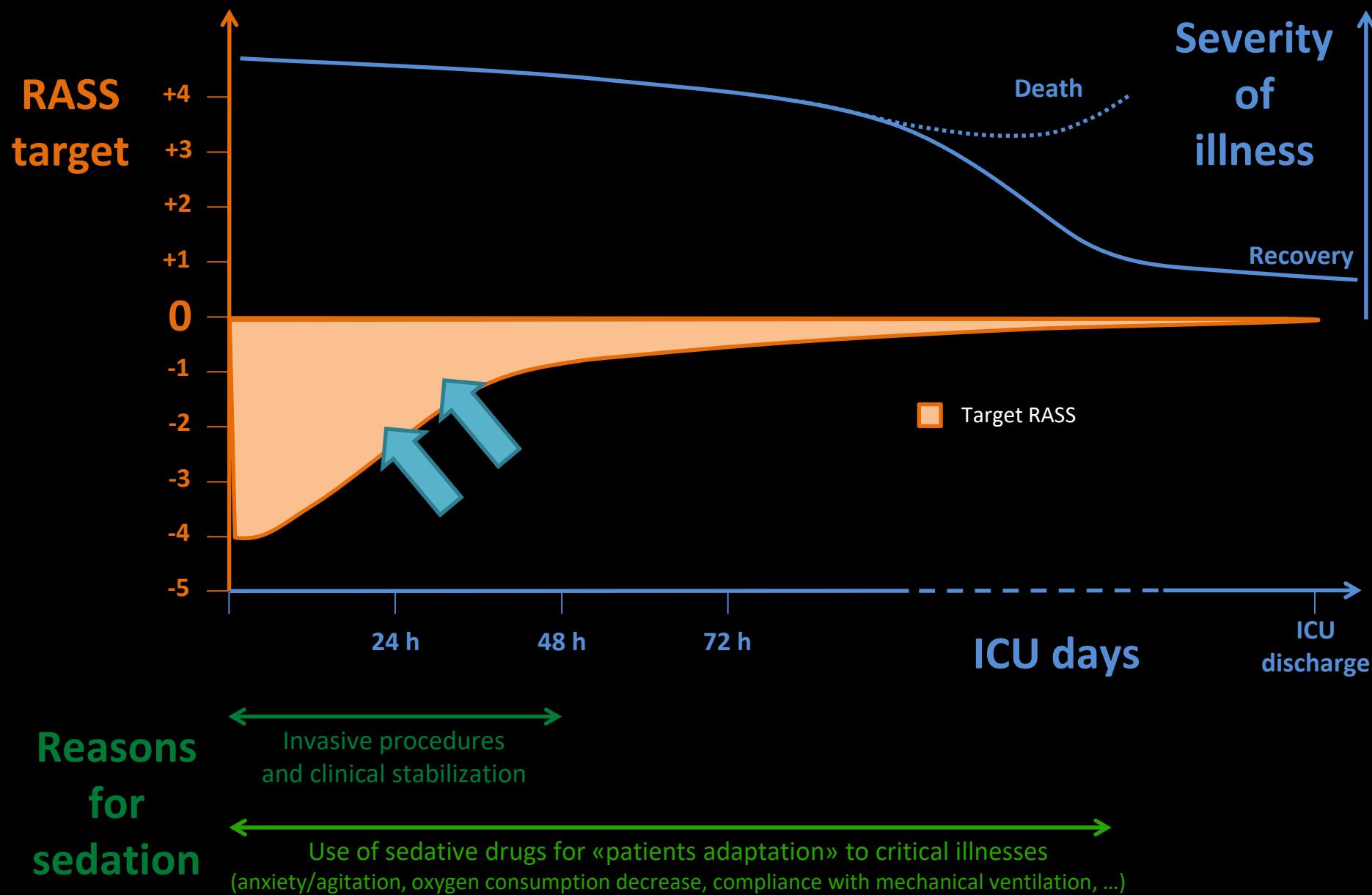


Reasons for sedation









Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?



Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?

Coma

St. Dolore

St. Verbale

Soporoso

Tranquillo

Agitato

Scala di Ramsay

Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?

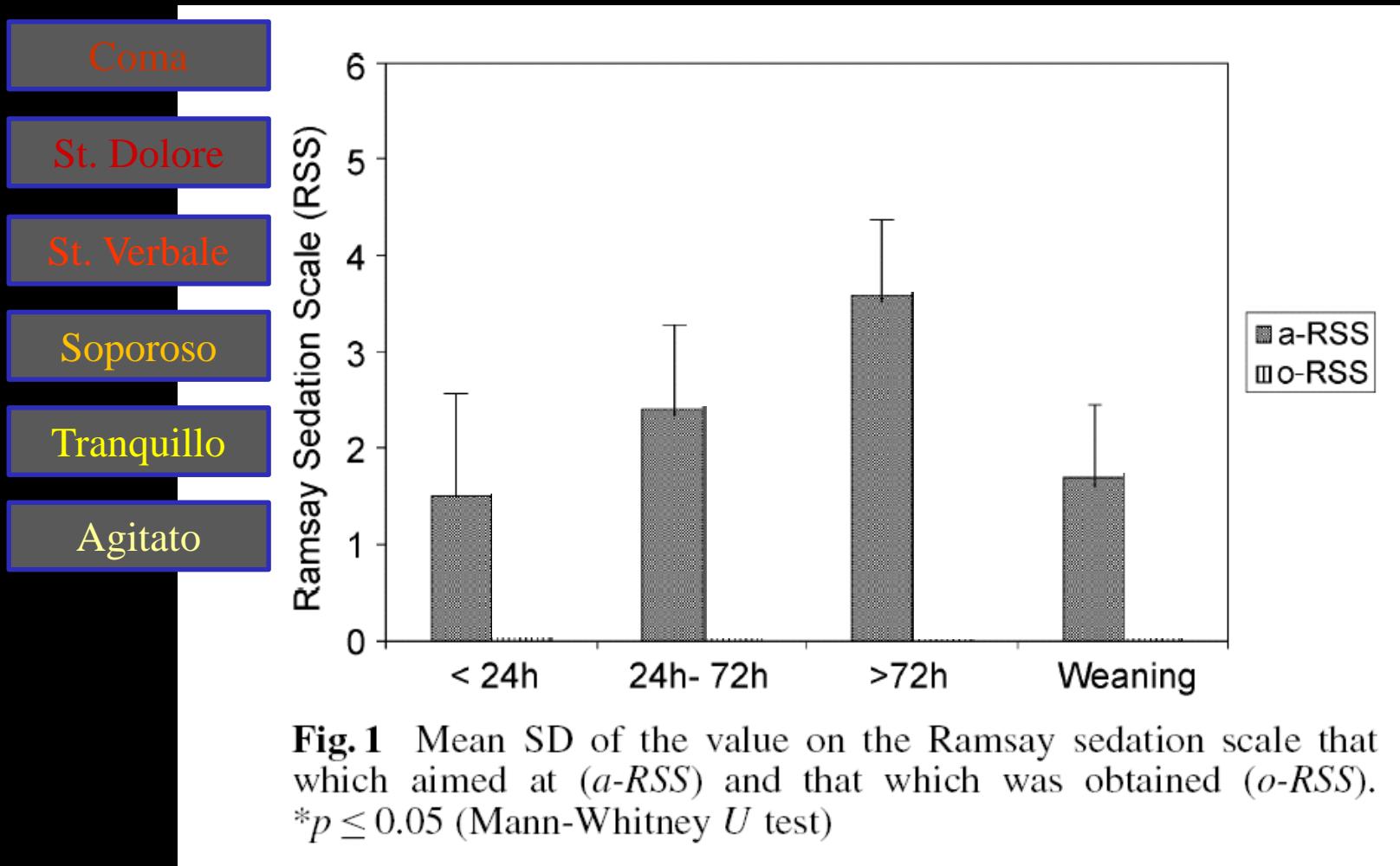
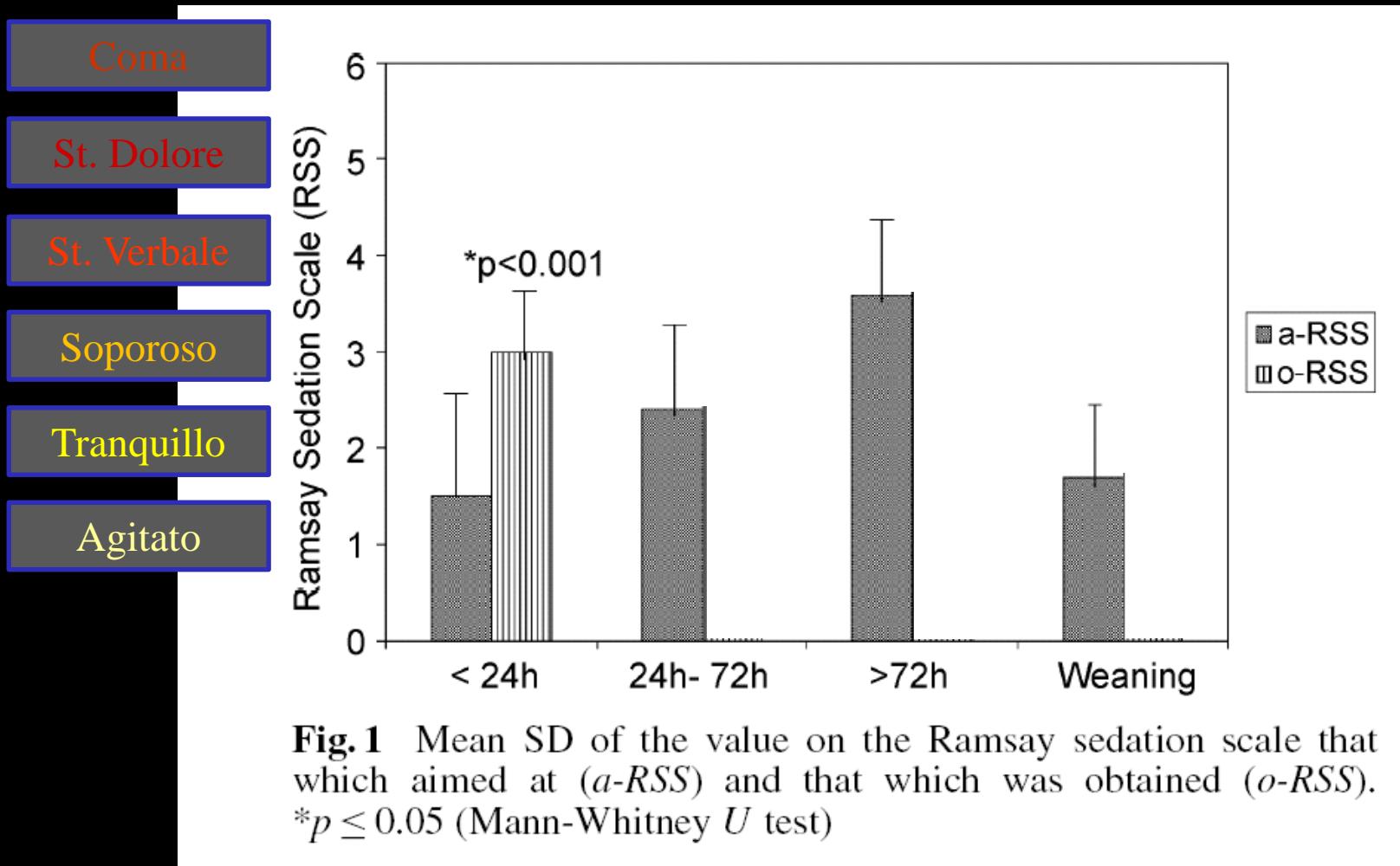


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (a-RSS) and that which was obtained (o-RSS).
* $p \leq 0.05$ (Mann-Whitney U test)

Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?



Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?

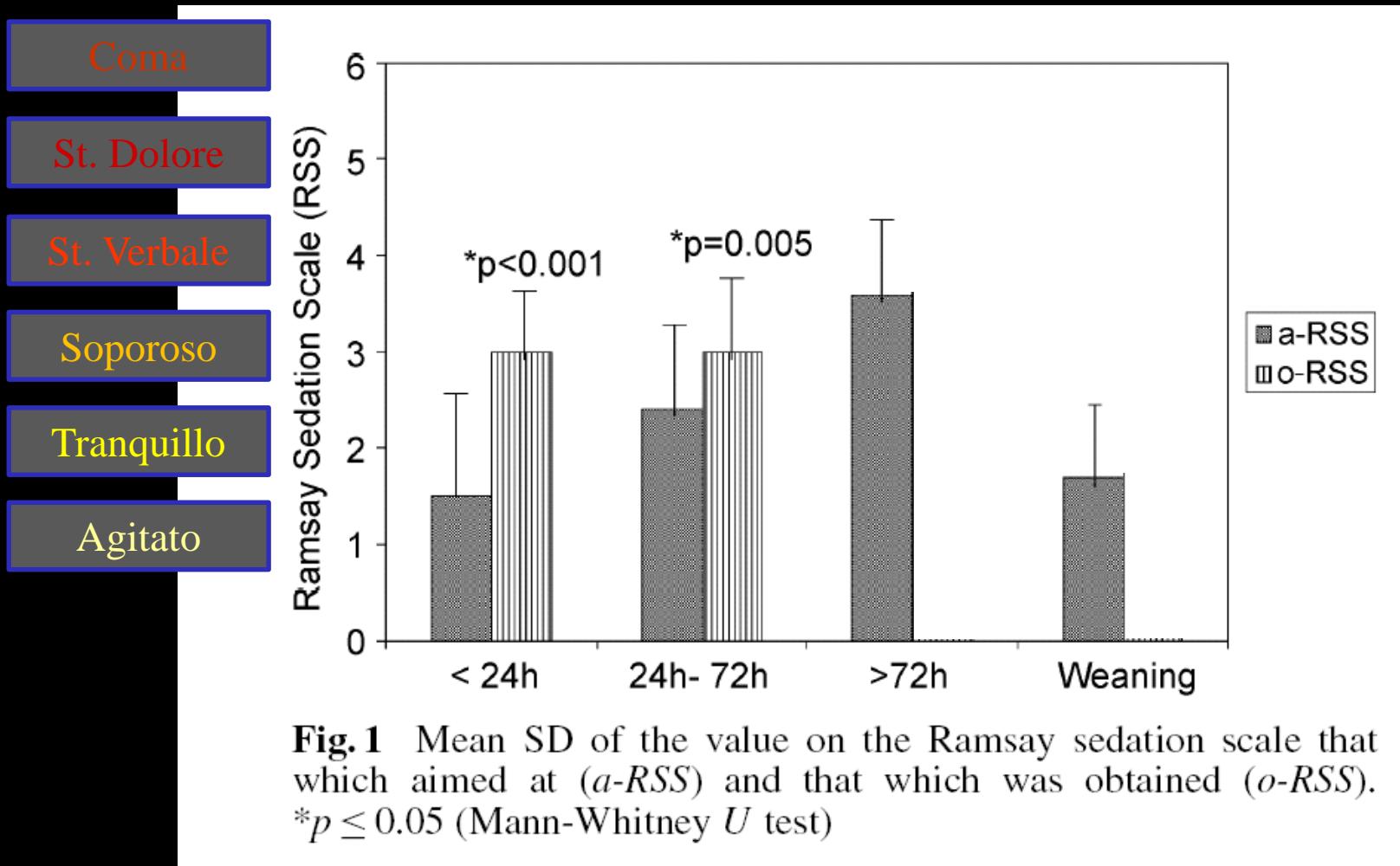
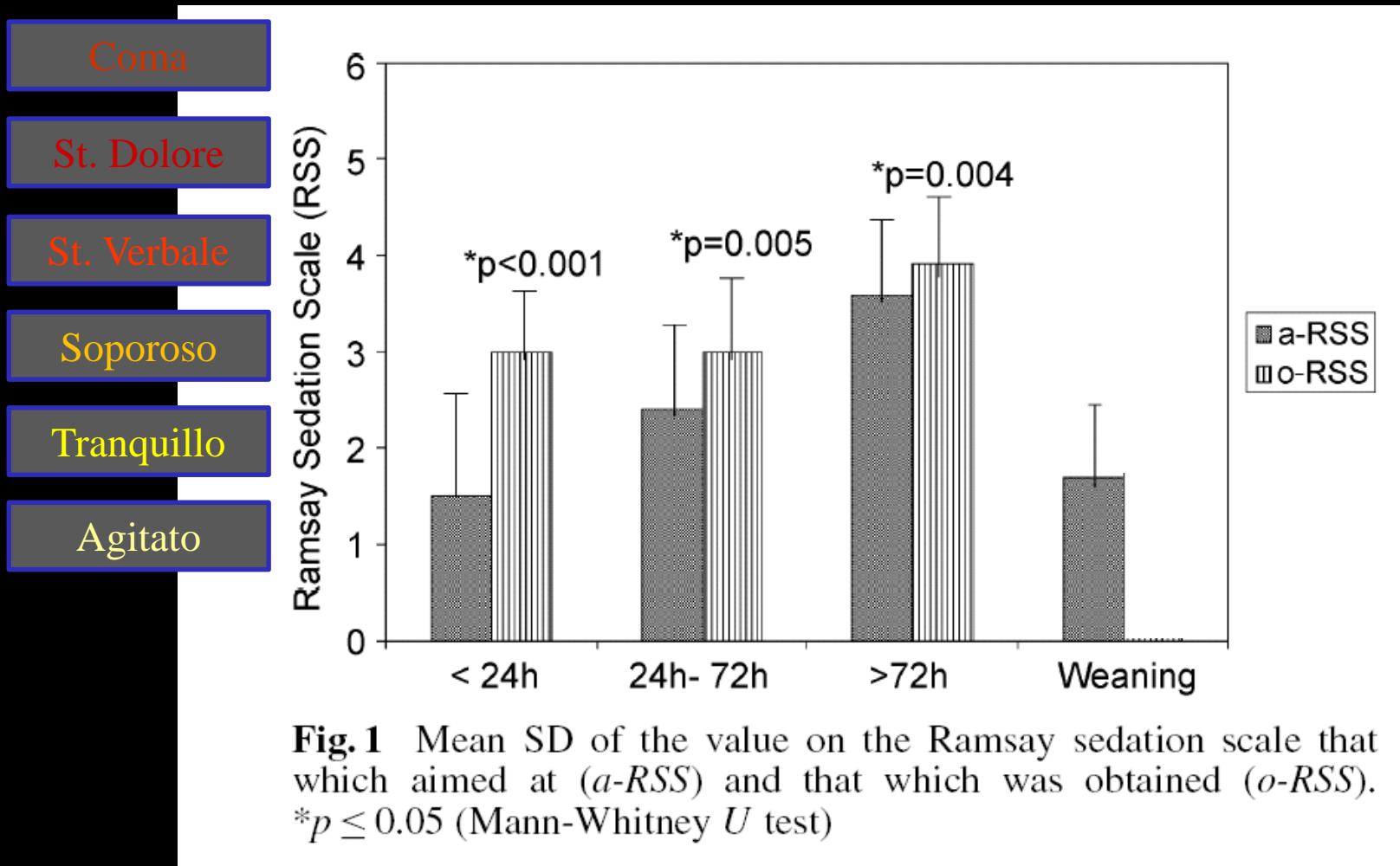


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a*-RSS) and that which was obtained (*o*-RSS).
 $*p \leq 0.05$ (Mann-Whitney *U* test)

Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?



Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?

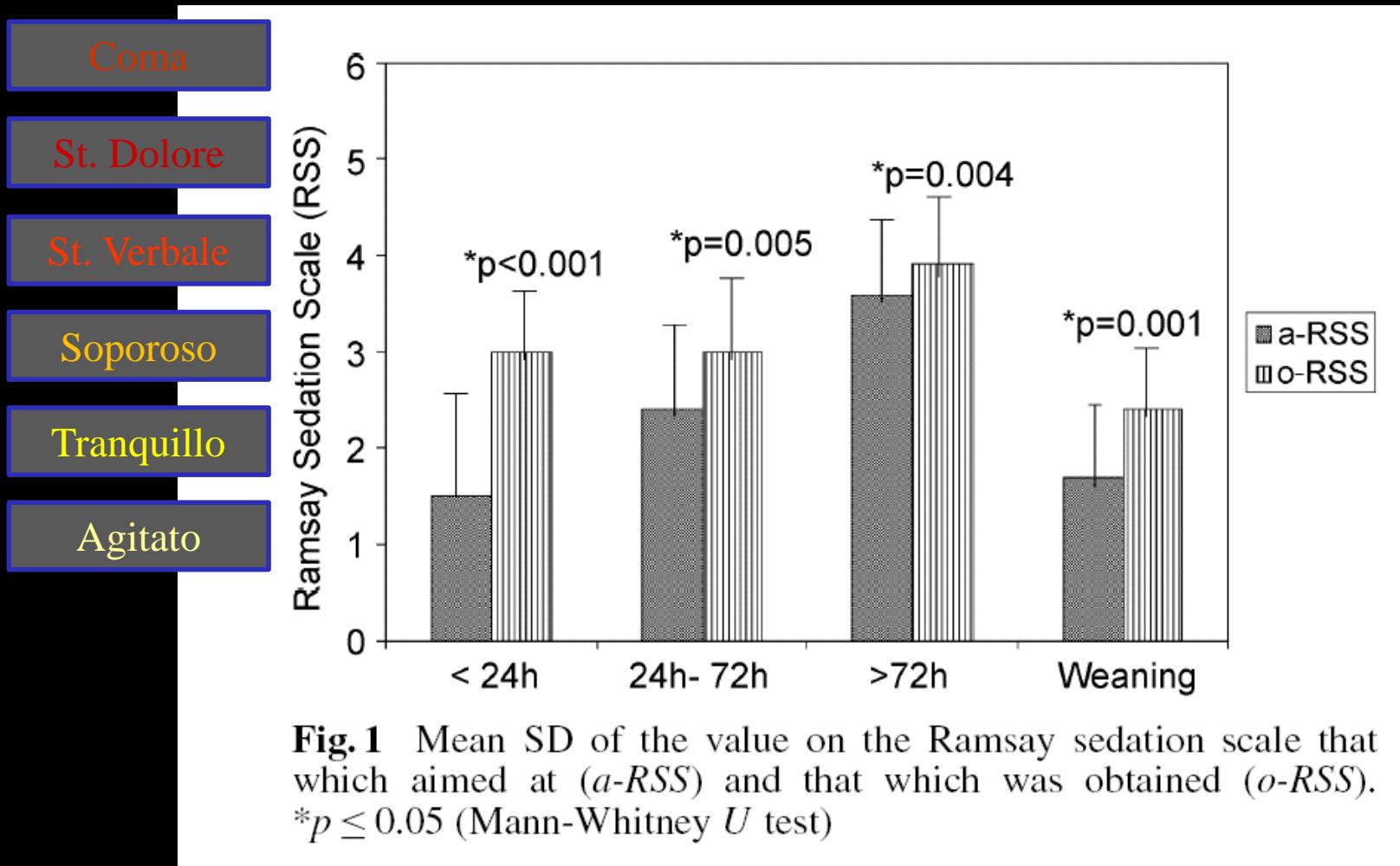


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (a-RSS) and that which was obtained (o-RSS).
* $p \leq 0.05$ (Mann-Whitney U test)



OPEN ACCESS

This is the original (English) version.
The translated (German) version starts at p. 16.

Review Article

Evidence and consensus-based German guidelines for the management of analgesia, sedation and delirium in intensive care – short version

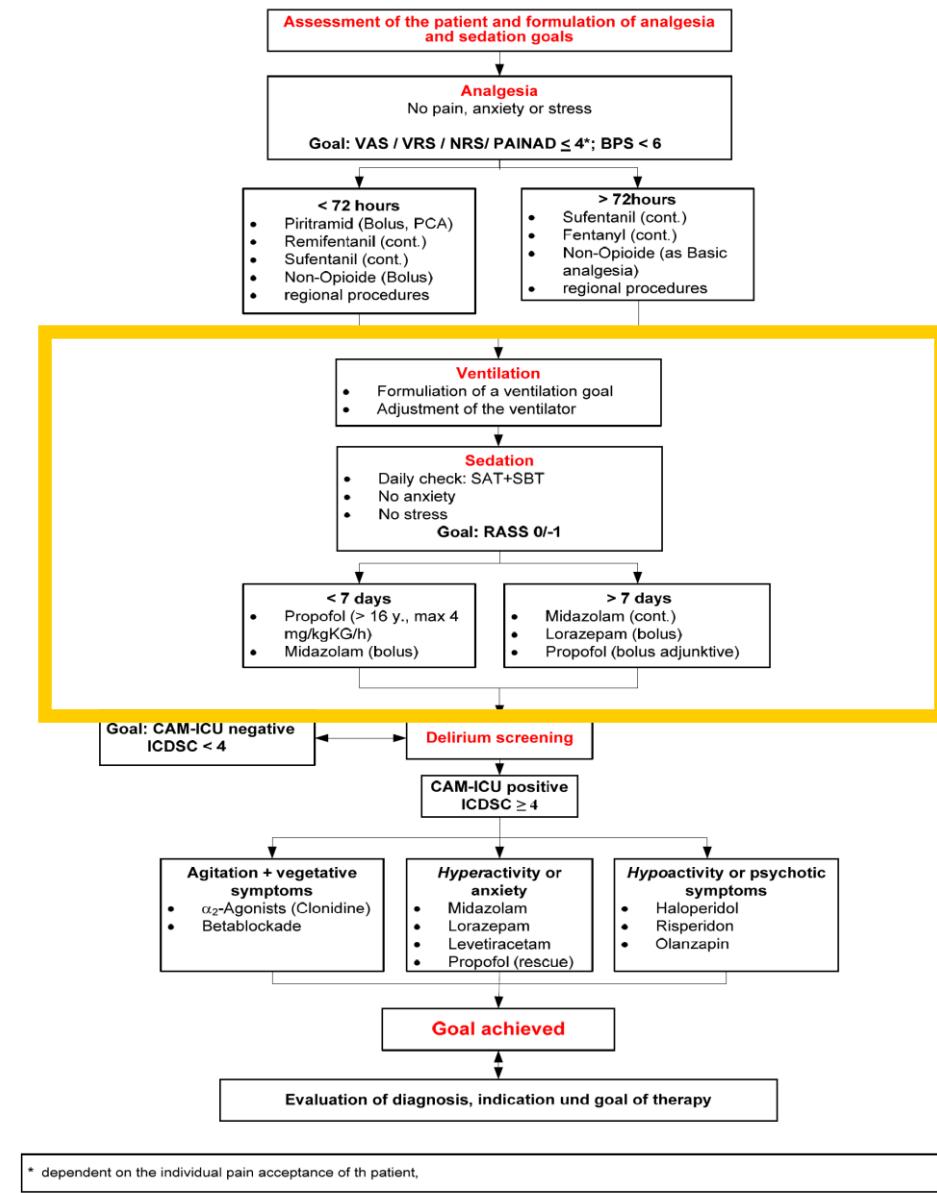
Abstract

Targeted monitoring of analgesia, sedation and delirium, as well as their appropriate management in critically ill patients is a standard of

Jörg Martin¹

Martin J, *Ger Med Sci*, 2010

2. Overall-scheme for analgesia, sedation and delirium treatment in adults



RASS: Richmond Agitation Sedation Scale (-5 to +4)

VAS: Visual Analogue Scala, VRS: Verbale Rating Scala, NRS: Numeric Rating Scale (0-10)

BPS: Behavioral Pain Scale (3-12), PAINAD: Pain Assessment in Advanced Dementia (0-10)

CAM-ICU: Confusion Assessment Method for the ICU (positive/negative)

ICDSC: Intensive Care Delirium Screening Checklist (0-8)



Ventilation

- Formulation of a ventilation goal
- Adjustment of the ventilator

Sedation

- Daily check: SAT+SBT
- No anxiety
- No stress

Goal: RASS 0/-1

< 7 days

- Propofol (> 16 y., max 4 mg/kgKG/h)
- Midazolam (bolus)

> 7 days

- Midazolam (cont.)
- Lorazepam (bolus)
- Propofol (bolus adjunktive)



Intensive Care Medicine

OPEN ACCESS

This is the original (English) version.
The translated (German) version starts at p. 22.

Guideline

Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) – short version

Abstract

In 2010, under the guidance of the DGAI (German Society of Anaesthesiology and Intensive Care Medicine) and DIVI (German Interdisciplinary Association for Intensive Care and Emergency Medicine), twelve German medical societies published the “Evidence- and Consensus-based

DAS-Taskforce 2015:
Ralf Baron¹
Andreas Binder¹

Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) – short version

Abstract

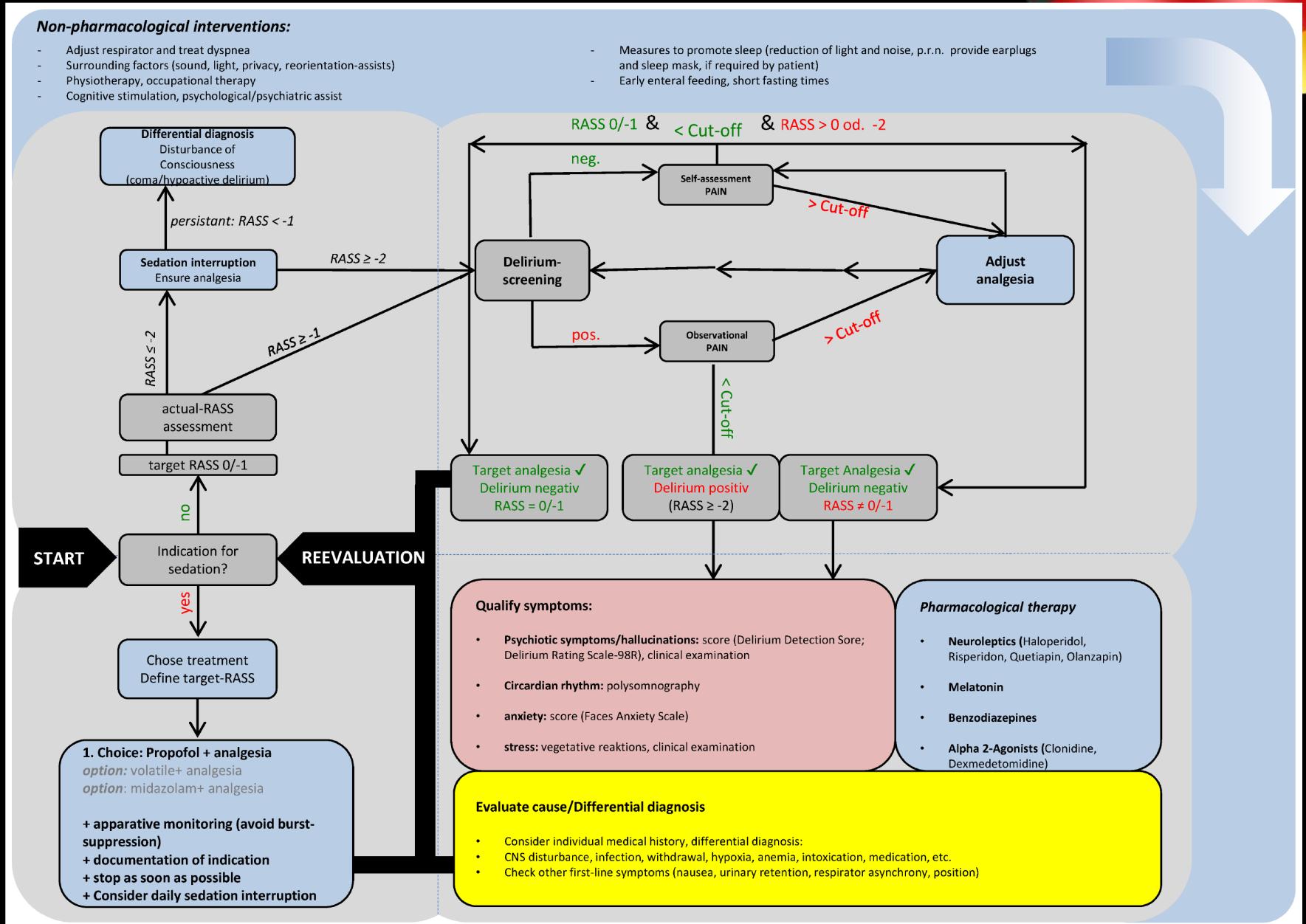
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DAS-Taskforce 2015:
Ralf Baron¹
Andreas Binder¹

Baron J, *Ger Med Sci*, 2015



- 17 società scientifiche - 49 voting members
- 284 references
- 147 raccomandazioni (72 A – 51 B – 24 Ø)



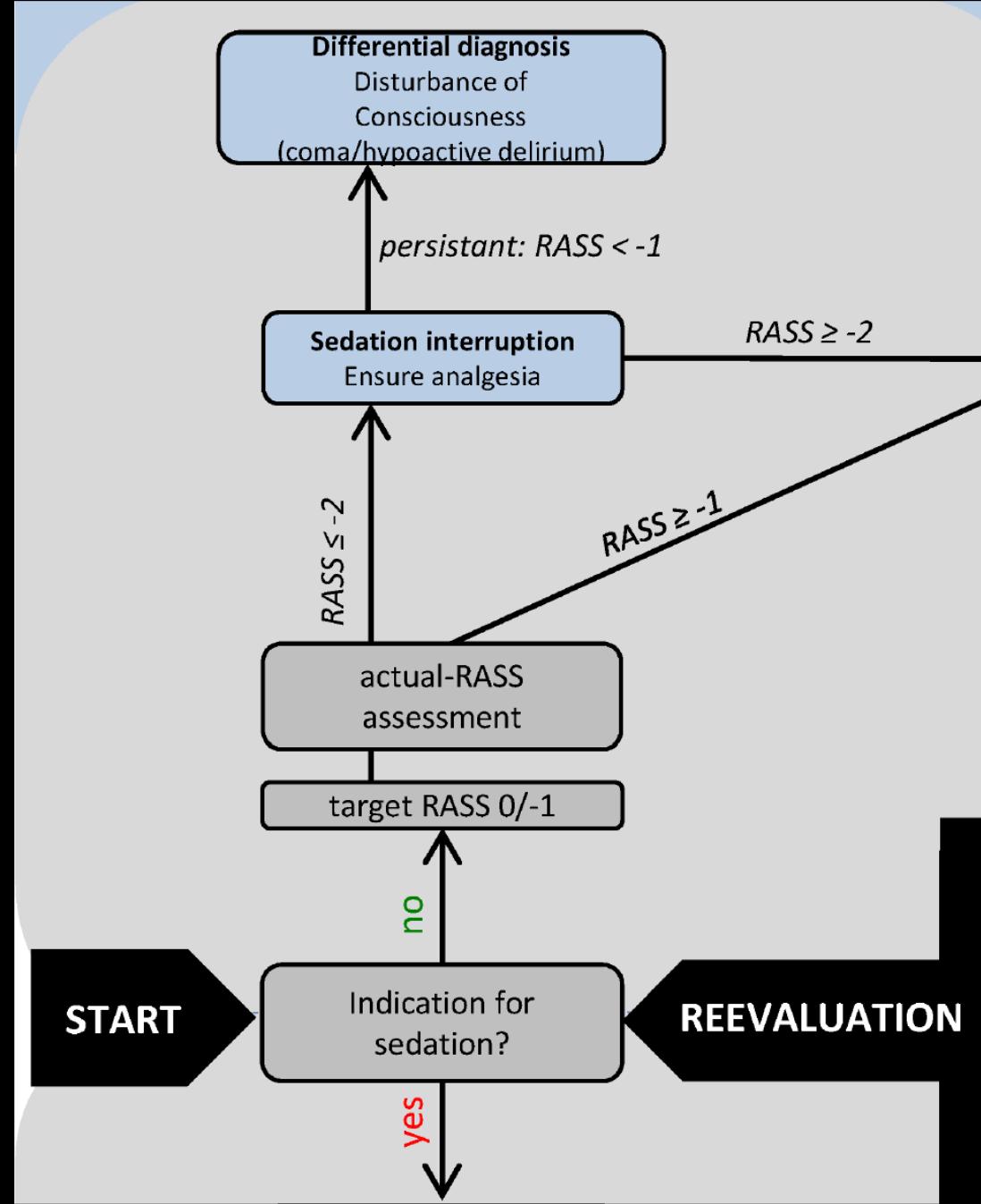
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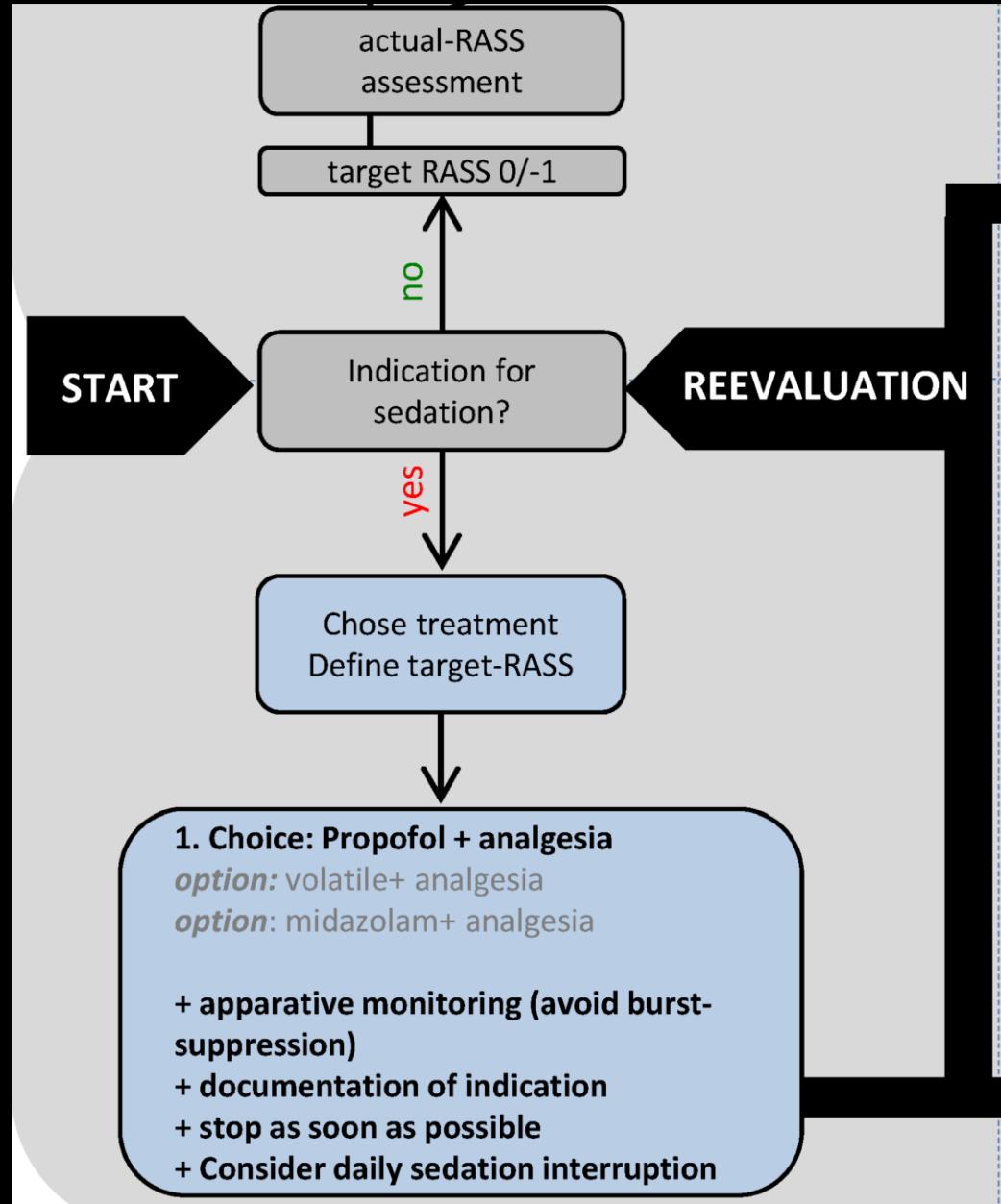
Non-pharmacological interventions:

- Adjust respirator and treat dyspnea
- Surrounding factors (sound, light, privacy, reorientation-assists)
- Physiotherapy, occupational therapy
- Cognitive stimulation, psychological/psychiatric assist
- Measures to promote sleep (reduction of light and noise,
p.r.n. provide earplugs and sleep mask, if required by patient)
- Early enteral feeding, short fasting times

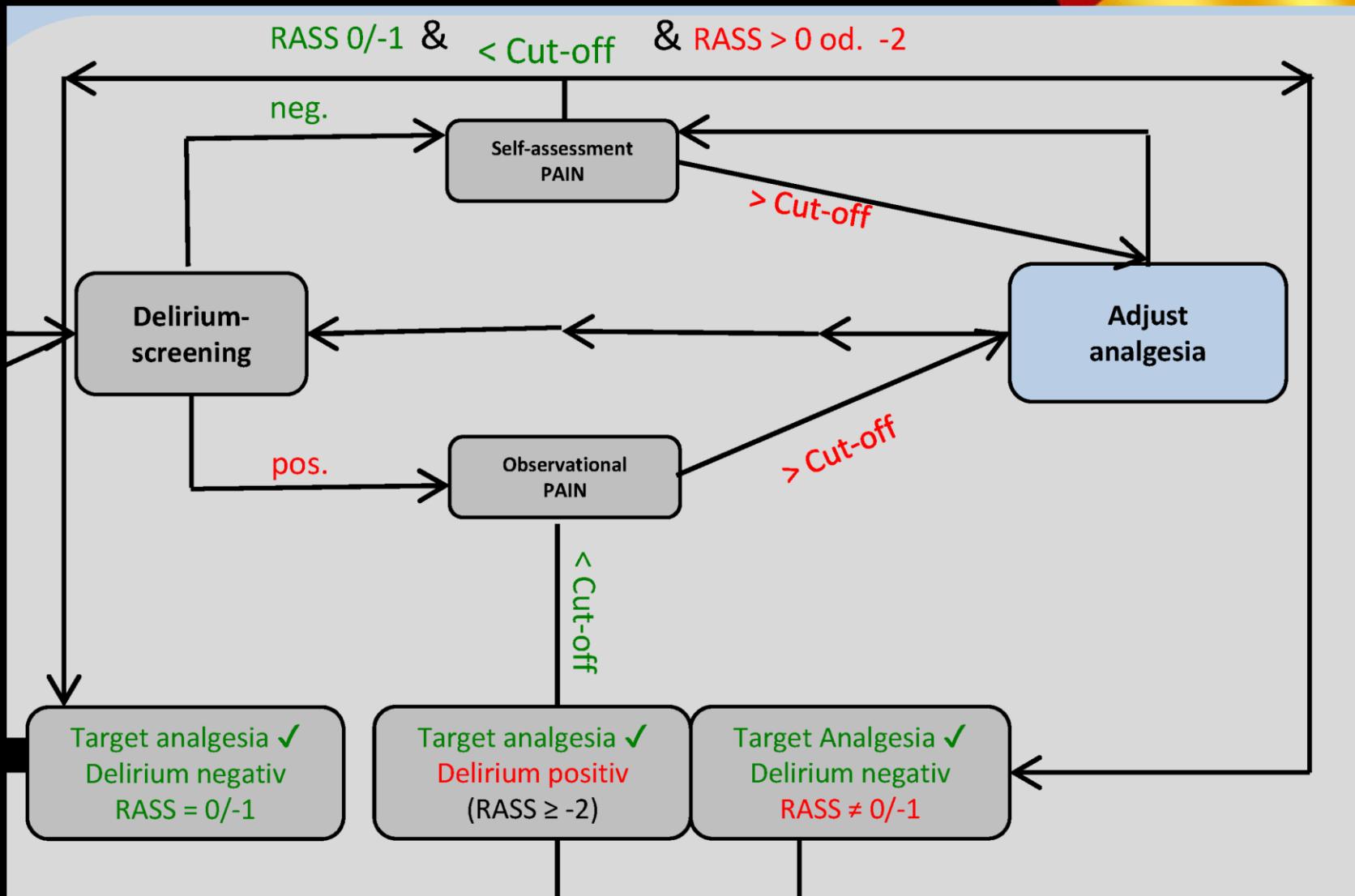
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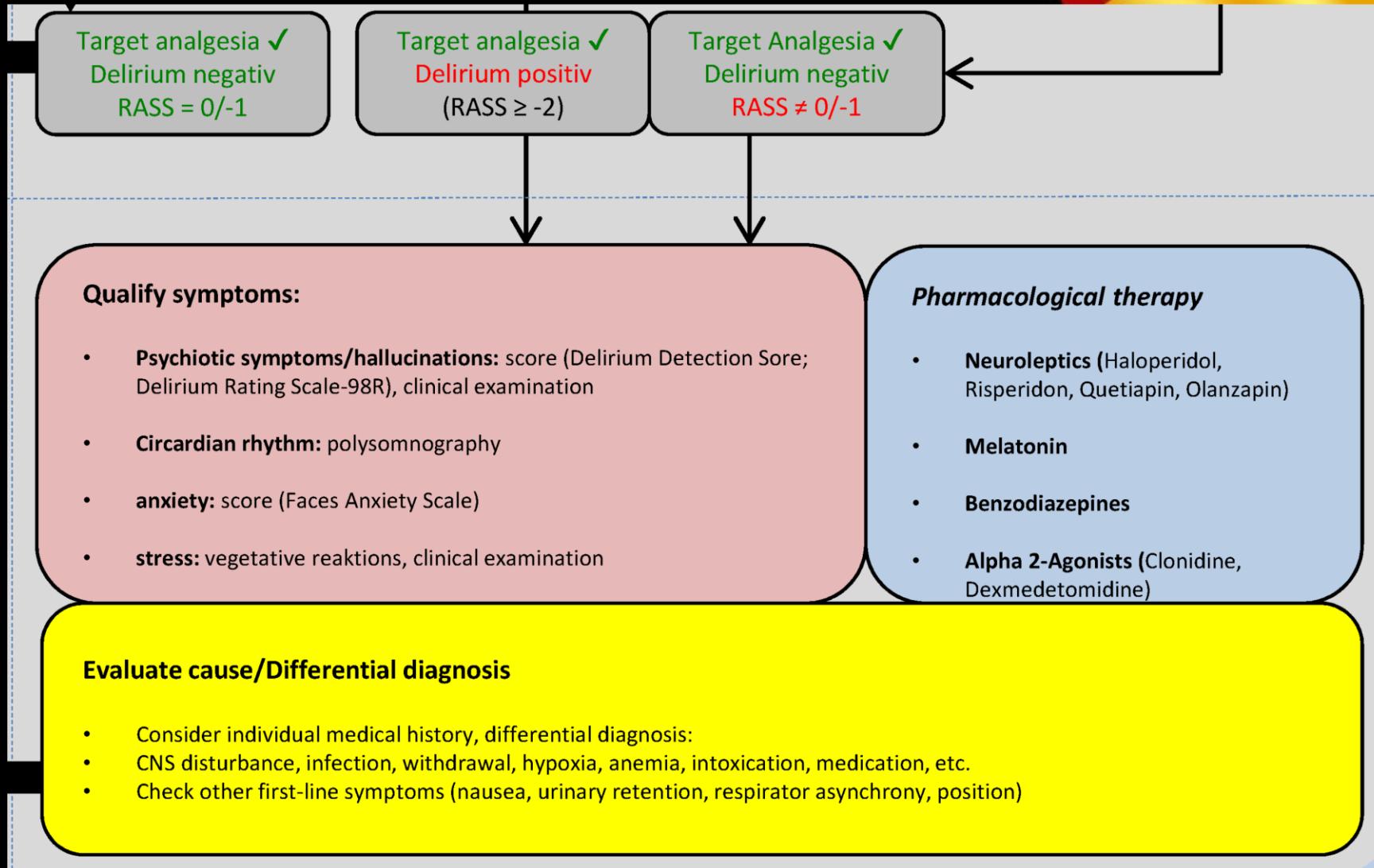
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3°



4°





Monitoring – general aspects	LoE	GoR
4.1 We recommend <u>patient-centered strategies</u> for personalized analgesia and sedation, in order to prevent anxiety and delirium. We recommend the <u>individual definition of therapeutic goals</u> , as well as adequate monitoring of treatment effects, whether intentional or adverse (107-109).	[107-109] 1b 2b 2b	A
4.2 The treatment target and the current degree of analgesia, sedation, anxiety, and delirium shall be <u>documented at least once per shift</u> (usually every 8 hours). This should be standard of care on all ICUs (110).	[110] 4	A
<i>Upgrading: relevance</i>		
4.3 We recommend the use of <u>validated scales</u> for the therapy control of analgesia, sedation, anxiety, and delirium (10).	[10] 1b	A

Monitoring of sedation	LoE	GoR
4.5 We recommend the clear definition of individual sedation goals, and to frequently adapt these goals to the changing clinical situation of the patient (22).	[22] 1b	A
4.6 We recommend the use of sedation and ventilation protocols with safety checks and failure criteria for all ICU-patients (111).	[111] 1b	A
4.7 We recommend the documentation of sedation goals and the current level of sedation at least once per shift (generally every 8 hours) (112).	[112] 5	A
<i>Upgrading: relevance</i>		
4.8 We recommend <u>the use of validated and reliable scores</u> (e.g. Richmond Agitation-Sedation Scale, RASS) (107, 113).	[107, 113] 1b	A
4.9 The suitability and significance of diagnostic devices are still unclear. However, we recommend the use of such devices, in a supporting role, on patients who are deeply sedated (RASS -4/-5) or under neuromuscular blockade, so as to promptly identify under or oversedation (114, 115, 116).	[114] 2b [115] 3b [116] 2a	A
<i>Upgrading: relevance</i>		
4.10 We recommend the use of EEG monitoring in order to identify non-convulsive seizure activity in patients with reduced level of consciousness (e.g., hypoactive delirium, which does not respond to a pharmacological therapy) (117).	[117] 2b	A
<i>Upgrading: clinical relevance / frequency</i>		



Sedation	LoE	GoR
5.c.1 We recommend a target RASS of 0/-1 for all ICU patients (21, 22).	[21] 1b [22] 1b	A
5.c.2 We recommend that sedation be reserved only for patients with special situations / indications (e.g. increased intracranial pressure) (22, 21), and not used generally.	[22] 1b [21] 1b	A
5.c.3 We recommend that the following aspects be considered regarding the choice of sedatives: 1) Specific indication and individual goal of sedation. 2) Pharmacokinetics and pharmacodynamics.	5	A
<i>Upgrading: relevance</i>		
5.c.4 We recommend the preferential use of controllable sedatives for sedation of ICU-patients (139-146).	[139] 2b [140-144] 1b [145] 2b [146] 1a	A



Moderate/deep sedation (target RASS ≤-2)	LoE	GoR
5.d.1 In case of mechanical ventilation, we recommend the use of propofol (off-label-use: after 7 days of usage and/or under 16 years of age; dosage limitation: ≤4mg/kg/hr) (147).	[147] 1a	A
5.d.2 Volatile anesthetics may be considered for mechanically ventilated patients, if short wake-up times are desired (148-154).	[148] 2b [149-154] 1b	0
<i>Downgrading: individual indication</i>		
5.d.3 Midazolam may be considered, under adequate monitoring of sedation depth, for sedation with target RASS ≤-2 (155).	[155] 1a	0
<i>Downgrading: alternatives</i>		
5.d.4 If there are no contraindications, we recommend daily spontaneous awakening trial (SAT) and spontaneous breathing trial (SBT) only in patients with a RASS ≤-2 (30, 31).	[30] 1a [31] 1b	A



Symptom oriented sedative therapy (target RASS 0/–1)	LoE	GoR
5.e.1 For the treatment of stress and vegetative reactions in adult ICU-patients, we suggest the use of <u>alpha-2</u> agonists (156-158). <i>Downgrading: additionally, non-pharmacological strategies are relevant, reduce/treat causes of stress</i>	[156] 2b [157] 1b [158] 1b	B
5.e.2 For the treatment of anxiety and agitation, we suggest a bolus application of <u>benzodiazepines</u> (titrated to target RASS 0/–1) (146). <i>Downgrading: treat causes of agitation, inconsistent evidence, indication</i>	[146] 1a	B
5.e.3 For the treatment of psychotic symptoms (independent of delirium), we recommend the use of <u>neuroleptics</u> (33).	[33] 1a	A
5.e.4 We suggest maintaining a <u>physiological day and night rhythm</u> in all ICU-patients. Pharmacological [81] and non-pharmacological options (159) (e.g., improving environmental conditions, such as light and noise restriction, minimizing interventions during nighttime (126)) are available. <i>Downgrading: feasibility, costs</i>	[81] 1b [159] 3b [126] 1b	B

SLEEP

SEDATION

Fully reversible

Spontaneous

Circadian

Essential
biological function

Cyclic
EEG stages
progression

Not reversible

Continuous
norepinephrine
secretion

Sleep with
altered
architecture

Muscle hypotonia

Temperature disregulation

Disconjugate eye movement

Respiration depression

- 2 nazioni – 21 esperti
- 472 references
- 51 raccomandazioni (5 A – 29 B)



Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

Barr J, *Crit Care Med*, 2013

- 9 nazioni – 21 esperti
- 467 references
- 137 raccomandazioni (74 A – 63 B)



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www.elsevier.es/medintensiva

SPECIAL ARTICLE

Clinical practice guidelines for evidence-based management of sedoanalgesia in critically ill adult patients[☆]



Quali farmaci usiamo ?



Available drugs

Analgesics:

- Opioids (remifentanil, morphin, fentanyl, sufentanil, alfentanil, oxycodone, hydromorfone, tramadol)
- NSAIDs, acetaminophen

Sedatives:

- BZDP (Diazepam, Lorazepam, Midazolam)
- Propofol
- α_2 -agonist (clonidine, dexmedetomidine)
- Atypical:
 - Butyrophenone (Haloperidol, Droperidol)
 - Etomidate
 - Ketamin
 - Barbiturates (Sodium thiopental, Phenobarbital)
 - Inhalational agents (Halogenated – AnaConDa / Mirus – Xenon)

ORIGINAL ARTICLE

Early Sedation with Dexmedetomidine in Critically Ill Patients

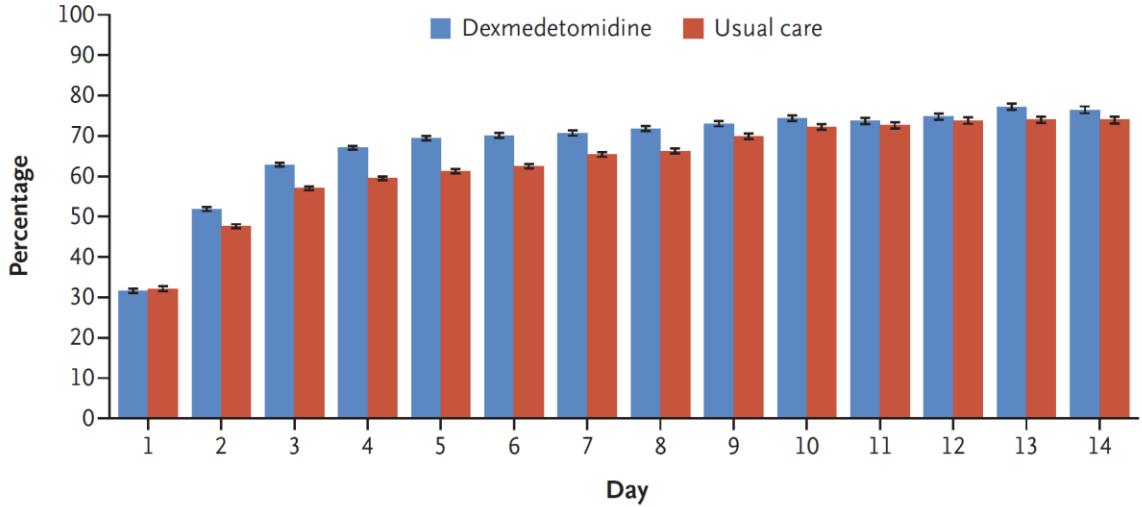
Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass,
S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala,
M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group
and the SPICE III Investigators*

ABSTRACT

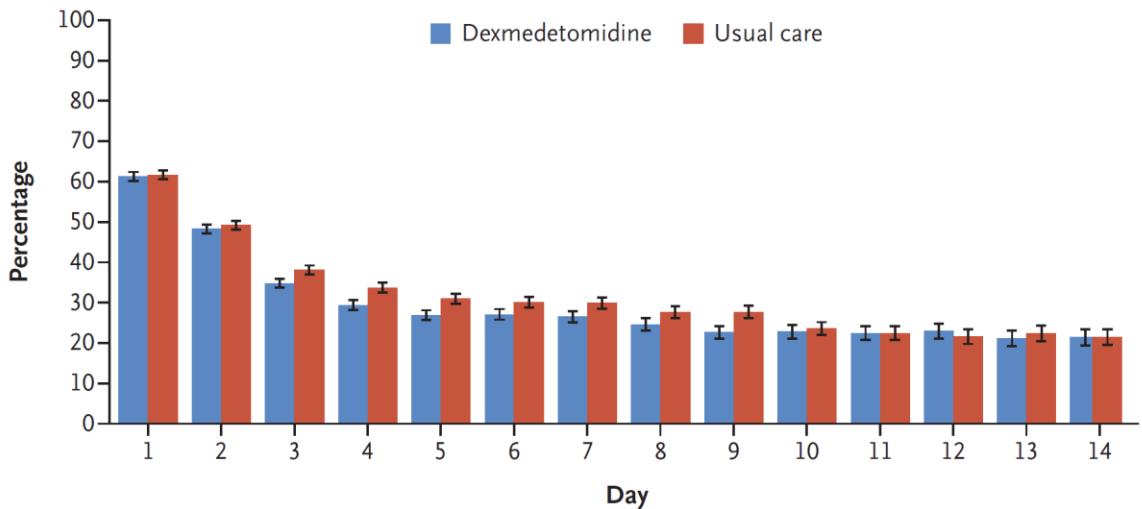
BACKGROUND

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Shehabi at Monash University, School of Clinical Sciences, Level 5, E Block, Monash Medical Centre, Clayton 3168, VIC, Australia.

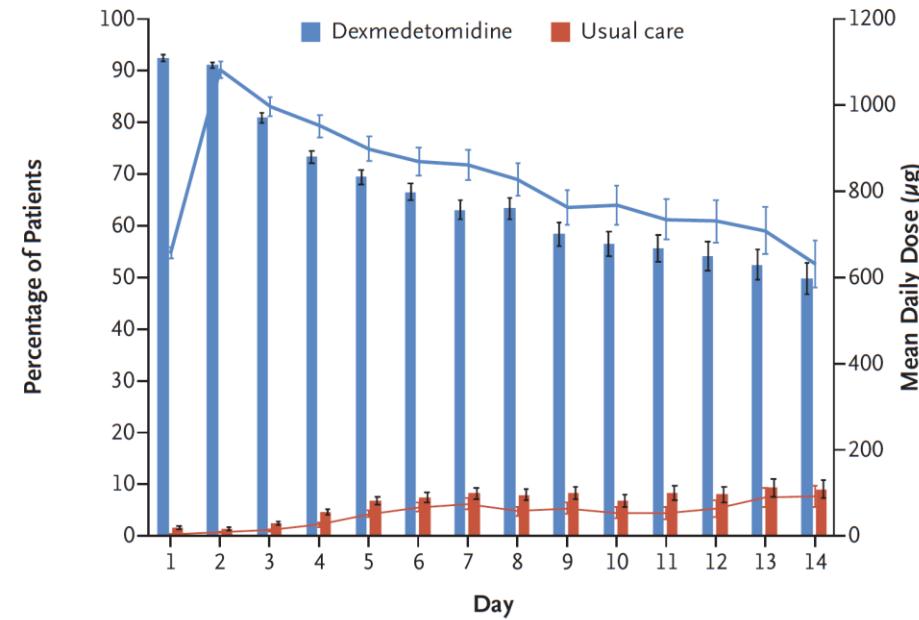
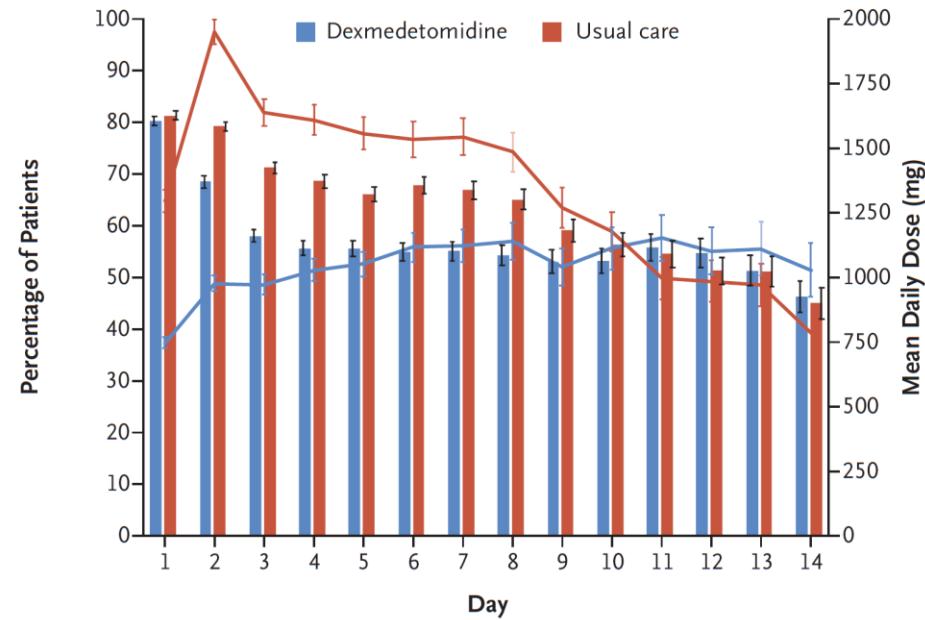
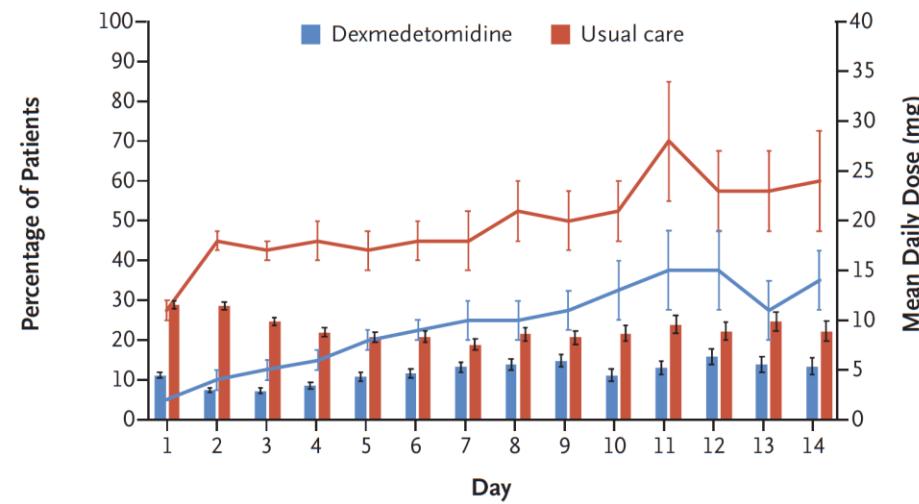
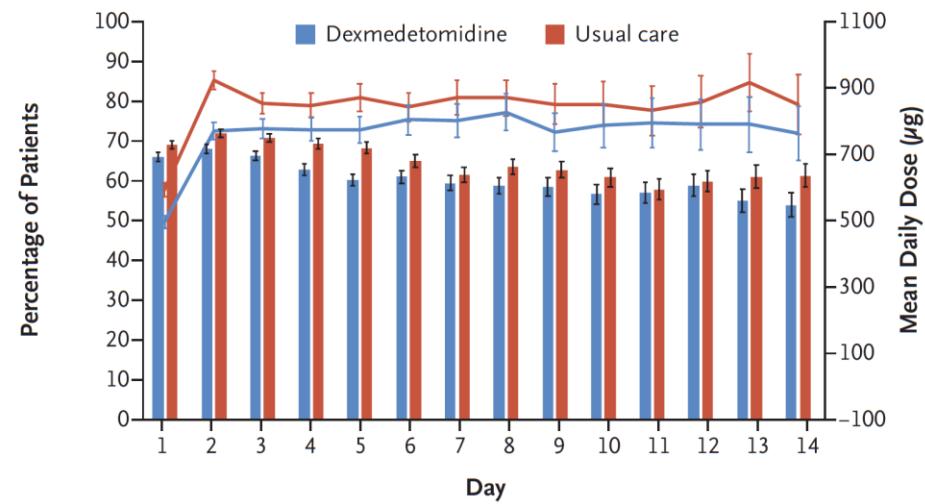
Dexmedetomidine produces sedation while maintaining a degree of arousability and may reduce the duration of mechanical ventilation and delirium among patients in the intensive care unit (ICU). The use of dexmedetomidine as the sole or primary sedative agent in patients undergoing mechanical ventilation has not been extensively studied.

A Percentage of RASS Scores at Target -2 to +1**Daily No. of RASS Assessments**

Dexmedetomidine	6286	10,562	9405	8035	6858	5839	5018	4305	3734	3330	2931	2577	2290	2080
Usual care	6309	10,606	9659	8349	7180	6202	5364	4672	4064	3514	3101	2784	2538	2367

B Patients with a Clinical Indication for Deep Sedation**No. at Risk**

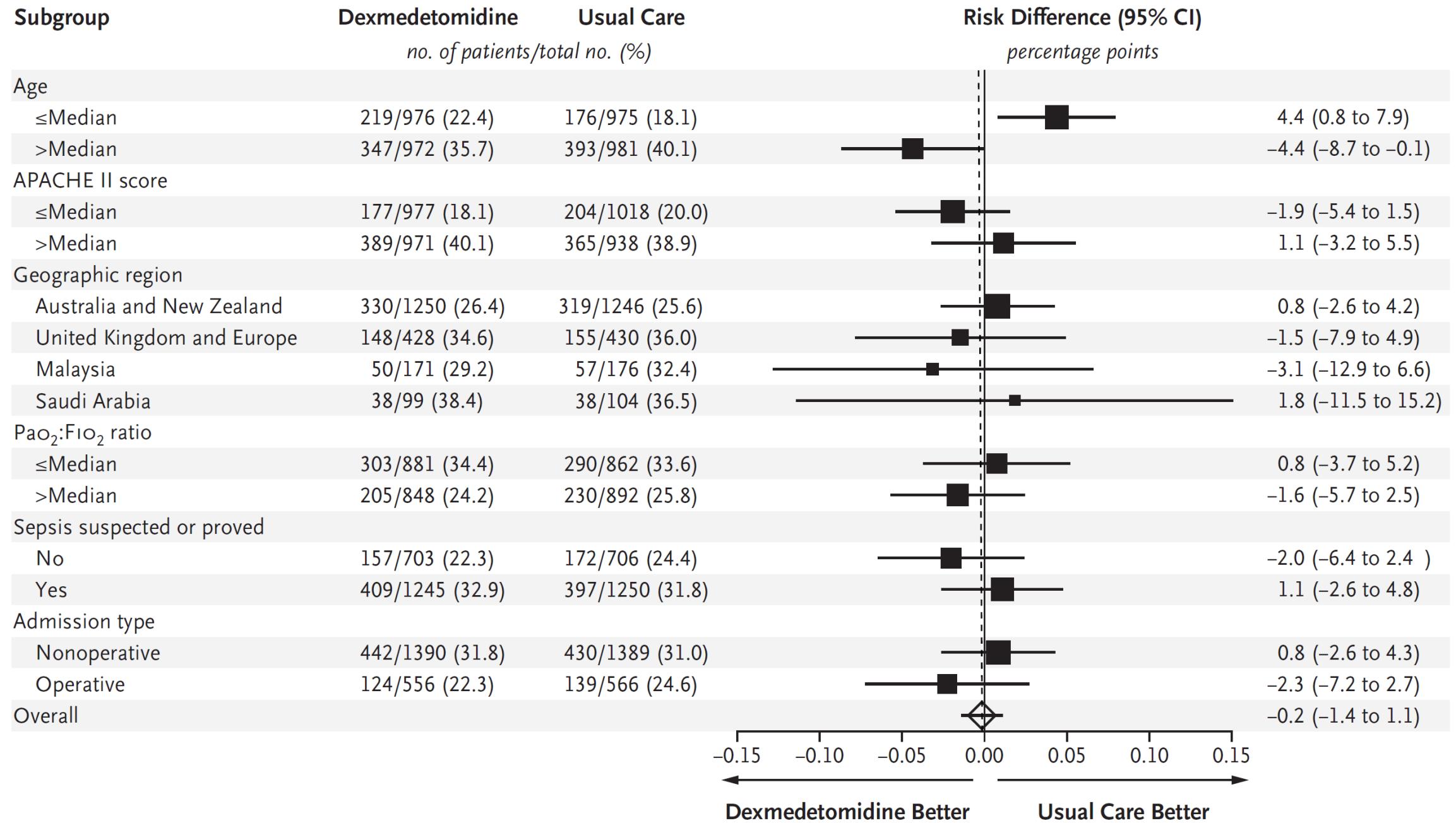
Dexmedetomidine	1952	1915	1775	1551	1351	1151	991	849	747	645	583	515	453	407
Usual care	1963	1928	1798	1610	1384	1201	1045	921	798	698	613	550	496	463

A Dexmedetomidine**B Propofol****C Midazolam****D Fentanyl****No. at Risk**

Usual care	1963	1928	1798	1610	1384	1201	1045	921	798	698	613	550	496	463
Dexmedetomidine	1952	1915	1775	1551	1351	1151	991	849	747	645	583	515	453	407

No. at Risk

Usual care	1963	1928	1798	1610	1384	1201	1045	921	798	698	613	550	496	463
Dexmedetomidine	1952	1915	1775	1551	1351	1151	991	849	747	645	583	515	453	407



RESEARCH

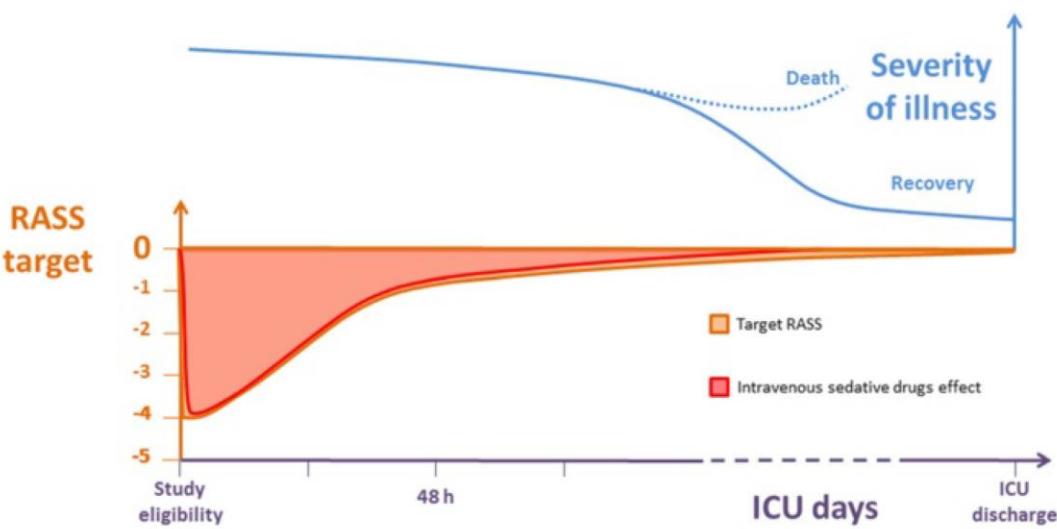
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Enteral versus intravenous approach for the sedation of critically ill patients: a randomized and controlled trial

Giovanni Mistraletti^{1,2*} , Michele Umbrello², Silvia Salini³, Paolo Cadringher⁴, Paolo Formenti², Davide Chiumello^{2,5}, Cristina Villa¹, Riccarda Russo⁴, Silvia Francesconi⁶, Federico Valdambrini⁷, Giacomo Bellani⁸, Alessandra Palo⁹, Francesca Riccardi¹⁰, Enrica Ferretti¹¹, Maurilio Festa¹², Anna Maria Gado¹³, Martina Taverna¹⁴, Cristina Pinna¹⁵, Alessandro Barbiero³, Pier Alda Ferrari³, Gaetano Iapichino^{1,2} and the SedaEN investigators



Propofol (1-6mg/kg*h) or Midazolam (0.03-0.2mg/kg*h) i.v. []

RCT

Invasive procedures and clinical stabilization
Use of sedative drugs for «patient adaptation» to critical illnesses
(anxiety/agitation, oxygen consumption decrease, compliance with mechanical ventilation, ...)

Reasons for sedation

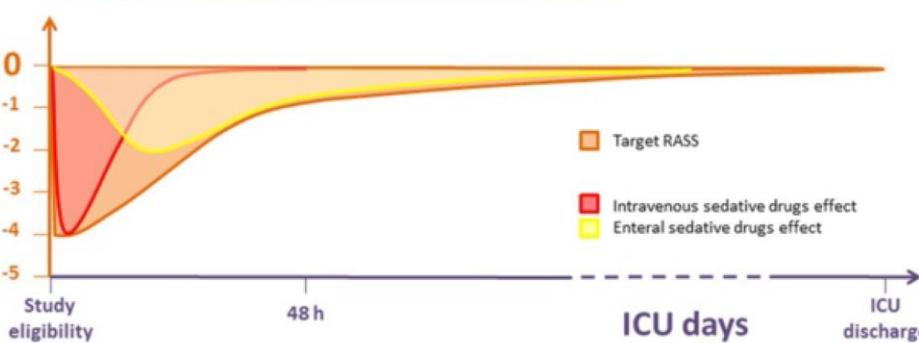
Propofol or Midazolam i.v.

Melatonin (6mg/die) via NGT/NJT

Hydroxyzine (max 600mg/die) via NGT/NJT

Lorazepam (max 16mg/die) via NGT/NJT

RASS target



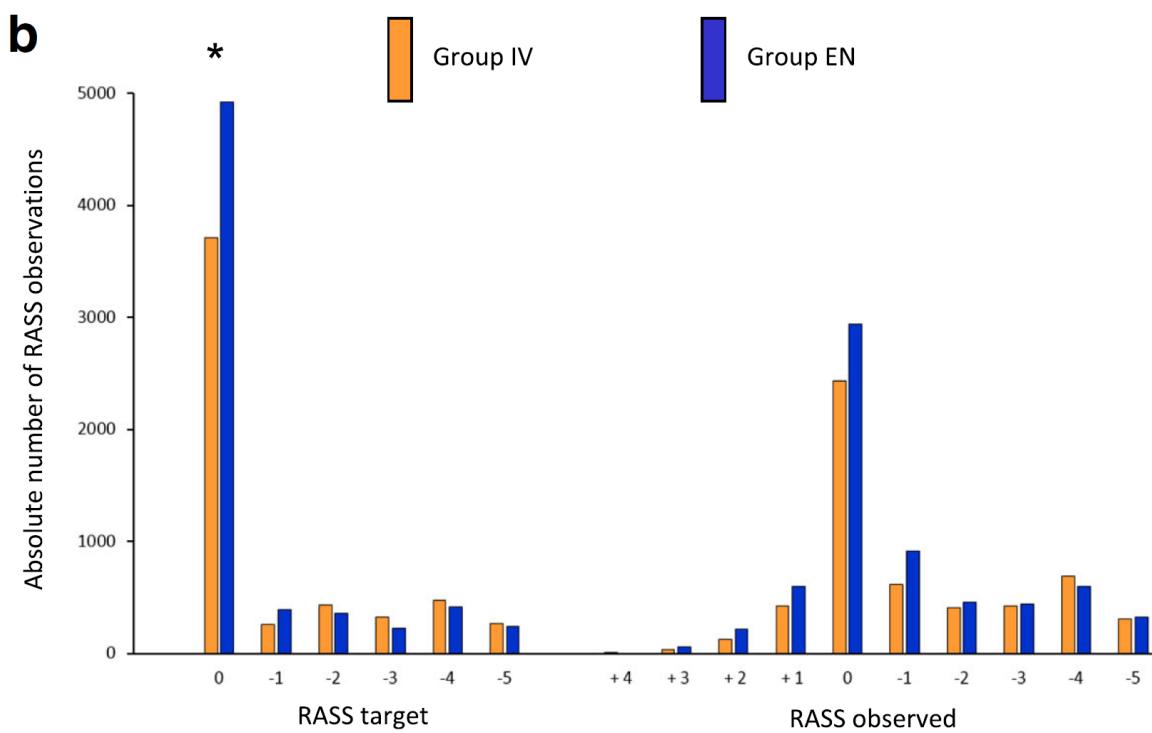
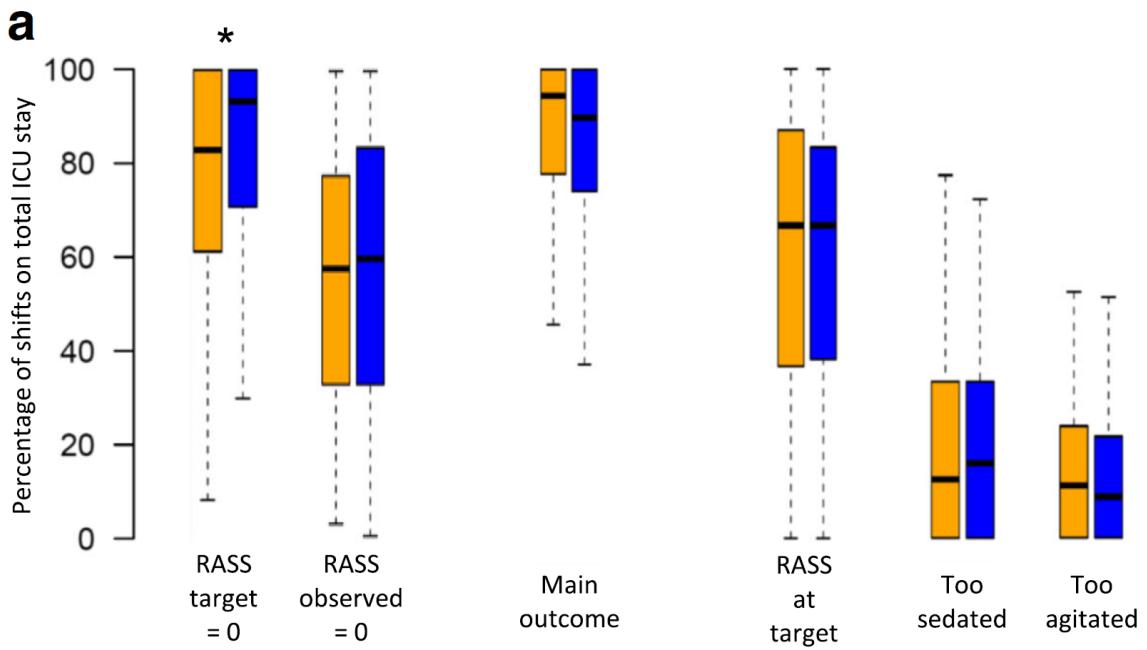


Table 2 Study outcomes

	Group IV (N = 165)	Group EN (N = 174)	P value
Percentage of shifts at target RASS = 0, median [IQR]	82.9 [61.3–100]	93.3 [70.8–100]	< 0.01
Percentage of shifts at observed RASS = 0/– 1, median [IQR]	57.9 [33.3–77.8]	60.1 [33.3–83.7]	0.53
Main outcome			
Percentage of shifts at RASS observed = target ± 1, median [IQR]	94.4 [77.8–100]	89.8 [74.1–100]	0.20
Secondary outcomes			
Percentage of adequate sedation, as judged by nurses, median [IQR]	92.4 [80.9–100]	89.7 [76.2–100]	0.11
Percentage of shifts with protocol violation, median [IQR]	0 [0–0]	0 [0–24.1]	< 0.01
Patients with protocol violation, n (%)	7 (4.2)	81 (46.6)	< 0.01
Coma-free days	27 [19–28]	27 [18–28]	0.80
Delirium-free days	27 [19–28]	27 [15–28]	0.40
Coma and delirium-free days	25 [11–28]	25 [10–28]	0.61
Ventilator-free days	21 [3–27]	22 [2–26]	0.89
Length of ICU stay	10 [6–18]	10 [6–18]	0.75
Mortality			
In ICU, n (%)	41 (24.8)	45 (25.9)	0.90
In hospital, n (%)	54 (32.7)	62 (35.6)	0.65
One year, n (%)	68 (43.9)	71 (43.0)	0.82
Daily cost for planned sedatives, €/ventday	1.64 [0.15–4.78]	0.38 [0.22–0.60]	< 0.01
Daily cost for unplanned sedatives, €/ventday	0 [0–0]	0.16 [0–2.15]	< 0.01
Daily cost for all neuroactive drugs, €/ventday	4.15 [1.20–20.19]	2.39 [0.75–9.78]	0.01
Self-removal of ET tube, n (%)	4 (2.4)	14 (8.1)	0.03
Need to replace ET tube, n (%)	3 (1.8)	10 (5.7)	0.09
Self-removal of other invasive tools, n (%)	21 (12.7)	29 (16.7)	0.36
Unscheduled neurological tests, n (%)	30 (18.2)	33 (19.0)	0.89

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SedaEN

Intervento

vs

SedaEV

Controllo

- Melatonina + Idrossizina e Lorazepam

- Propofol o Midazolam



For each sedative, please check:

- Pharmacokinetics
- Neurological effects
- Cardio-respiratory effects
- Endocrine and metabolic effects
- Side effects – risks for that patient
- Indications

Canadian survey of the use of sedatives, analgesics & NMBA in ICU...

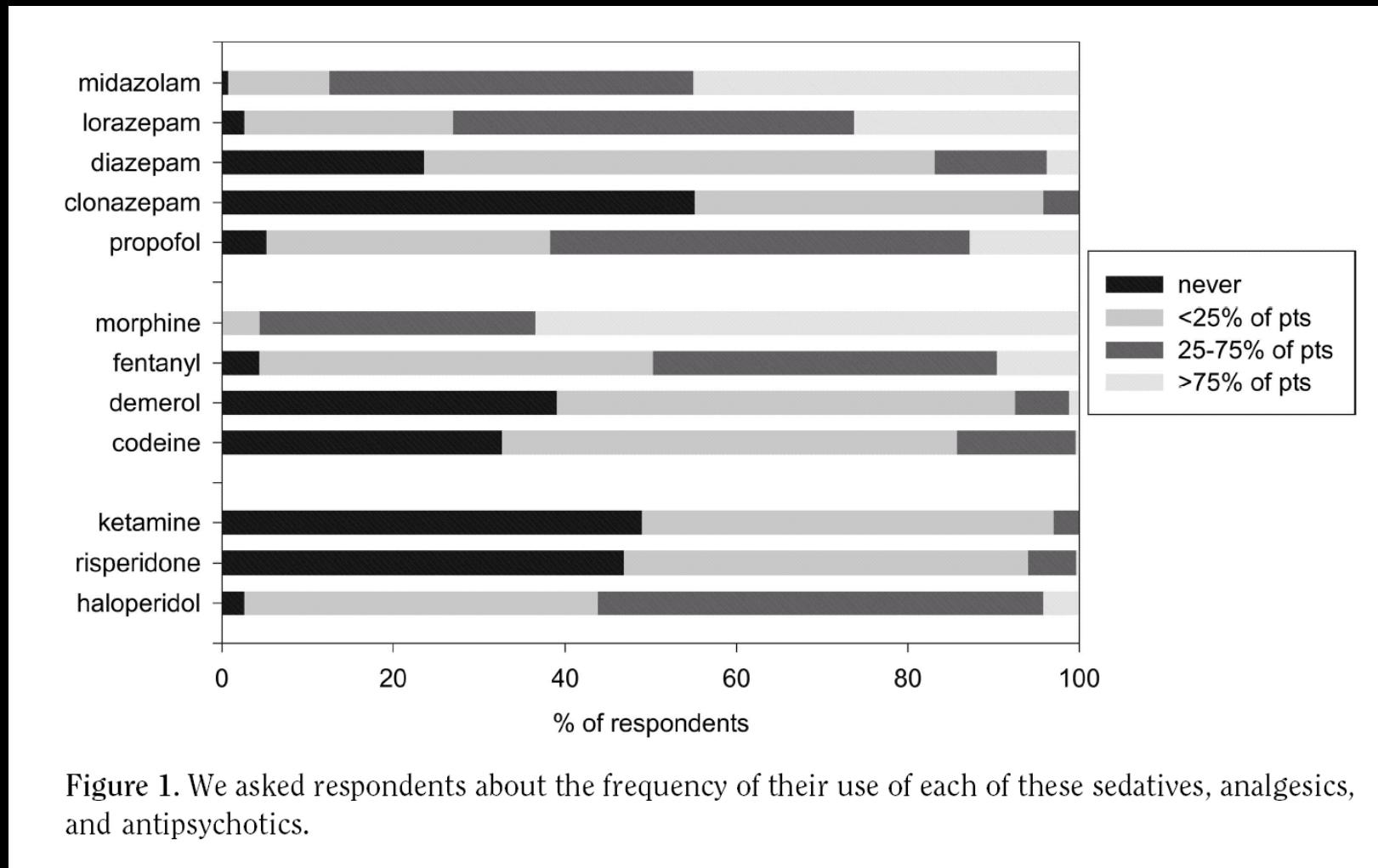


Figure 1. We asked respondents about the frequency of their use of each of these sedatives, analgesics, and antipsychotics.

Metha S, et al.,
Crit Care Med,
2006

Uno sguardo sui miorilassanti

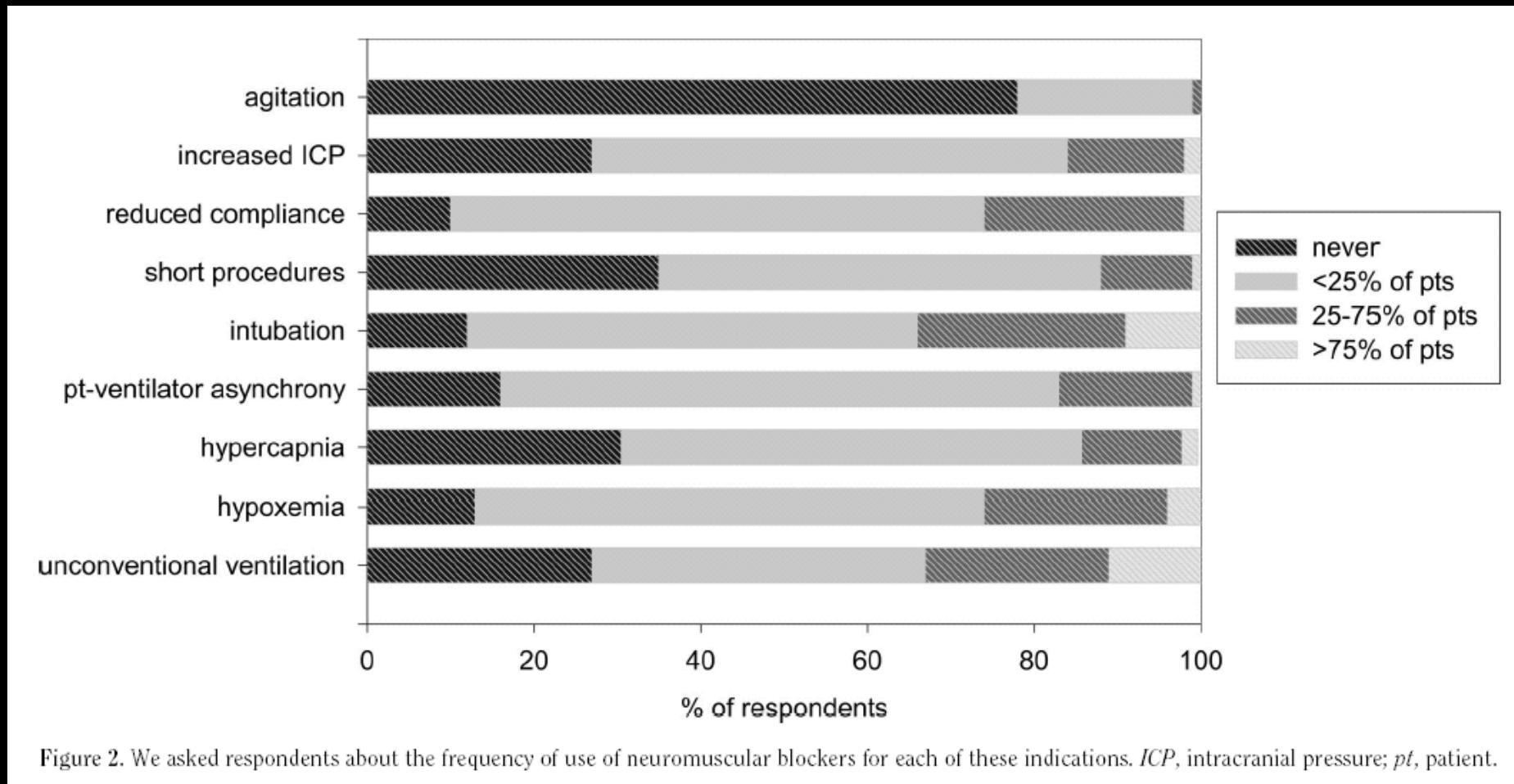


Figure 2. We asked respondents about the frequency of use of neuromuscular blockers for each of these indications. *ICP*, intracranial pressure; *pt*, patient.

Il sonno della ragione genera mostri...

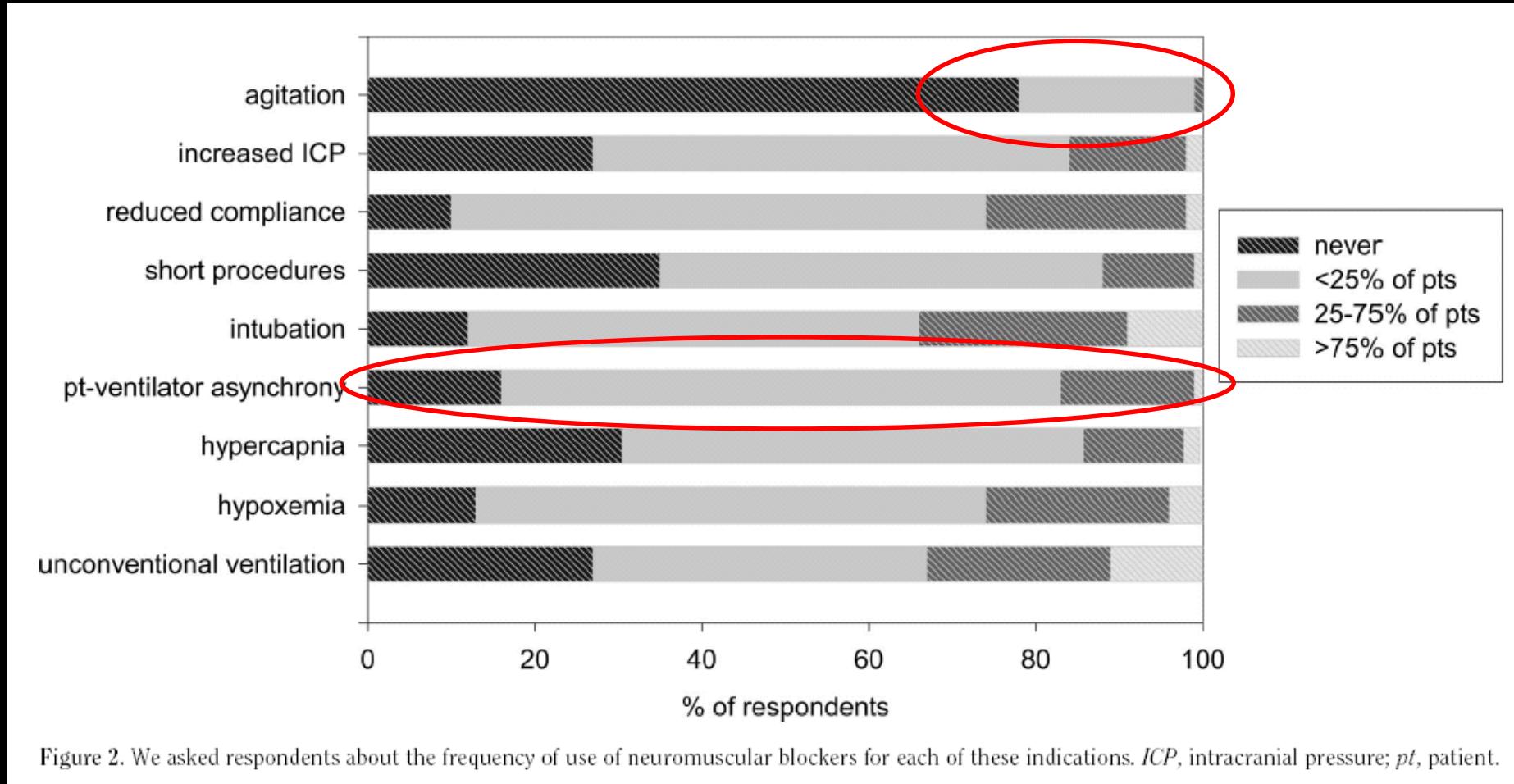


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... ! ! !

Metha S, et al., *Crit Care Med*, 2006

The NEW ENGLAND JOURNAL *of MEDICINE*

ESTABLISHED IN 1812

SEPTEMBER 16, 2010

VOL. 363 NO. 12

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D.,
Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D.,
Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D.,
Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D.,
for the ACURASYS Study Investigators*

ABSTRACT

Neuromuscular Block Disturbance

Laurent Papazian, M.D., Ph.D., Jean-Marie Foret, M.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jean-Marie Seghboyan, M.D., Jean-Michel Constant, M.D., Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., and the ACU Study Group
for the ACU Study

BACKGROUND

In patients undergoing mechanical ventilation for acute respiratory distress syndrome (ARDS), neuromuscular blocking agents may reduce ventilator-induced lung injury but may also affect clinical outcomes after 2 days of therapy with patients with early, severe ARDS.

METHODS

In this multicenter, double-blind trial, 340 patients with ARDS were randomly assigned to receive either cisatracurium or placebo (162 patients). Severe ARDS was defined as arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) ratio with a positive end-expiratory pressure of 5 cm of water or more and PaO_2 of 6 to 8 ml per kilogram of predicted body weight. The portion of patients who died either before hospital study enrollment (i.e., the 90-day in-hospital mortality) covariates and baseline differences between groups.

RESULTS

The hazard ratio for death at 90 days in the cisatracurium group, compared with the placebo group, was 0.68 (95% confidence interval, 0.48 to 0.88; $P=0.001$). After adjustment for both the baseline $\text{PaO}_2:\text{FiO}_2$ and the Acute Physiology II score, the crude 90-day mortality in the cisatracurium group and 40.7% (95% CI, 36.0% to 45.0%; $P=0.08$). Mortality at 28 days was 23.7% (95% CI, 19.0% to 33.3%) (95% CI, 26.5 to 40.9) with placebo ($P=0.12$). Paresis did not differ significantly between the two groups.

CONCLUSIONS

In patients with severe ARDS, early administration of cisatracurium improved the adjusted 90-day survival and reduced the risk of paresis without increasing muscle weakness. (Funded by Marseille and the Programme Hospitalier de Recherche National; ClinicalTrials.gov number NCT00431311.)

Table 2. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic†	Cisatracurium (N = 177)	Placebo (N = 162)	P Value
Age — yr	58 ± 16	58 ± 15	0.70
Tidal volume — ml/kg of predicted body weight	6.55 ± 1.12	6.48 ± 0.92	0.52
Minute ventilation — liters/min	10.0 ± 2.5	10.1 ± 2.2	0.83
PEEP applied — cm of water	9.2 ± 3.2	9.2 ± 3.5	0.87
Plateau pressure — cm of water	25.0 ± 5.1	24.4 ± 4.7	0.32
Respiratory-system compliance — ml/cm of water	31.5 ± 11.6	31.9 ± 10.7	0.71
FiO_2	0.79 ± 0.19	0.77 ± 0.20	0.33
$\text{PaO}_2:\text{FiO}_2$ ‡	106 ± 36	115 ± 41	0.03
pH	7.31 ± 0.10	7.32 ± 0.10	0.11
PaO_2 — mm Hg	80 ± 24	85 ± 28	0.09
PaCO_2 — mm Hg	47 ± 11	47 ± 11	0.62
Prone position or inhaled nitric oxide or almitrine mesylate — no. (%)	33 (18.6)	23 (14.2)	0.31
SAPS II§	50 ± 16	47 ± 14	0.15

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for the ACURASYS Study Investigators*

METHODS

In this multicenter, double-blind trial, 340 patients presenting to the intensive care unit (ICU) with an onset of severe ARDS within the previous 48 hours were randomly assigned to receive, for 48 hours, either cisatracurium besylate (178 patients) or placebo (162 patients). Severe ARDS was defined as a ratio of the partial pressure

study enrollment (i.e., the 90-day in-hospital mortality rate), adjusted for predefined covariates and baseline differences between groups with the use of a Cox model.

RESULTS

The hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68 (95% confidence interval [CI], 0.48 to 0.98; $P=0.04$), after adjustment for both the baseline $\text{PaO}_2/\text{FiO}_2$ and plateau pressure and the Simplified Acute Physiology II score. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group ($P=0.08$). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo ($P=0.05$). The rate of ICU-acquired paresis did not differ significantly between the two groups.

CONCLUSIONS

In patients with severe ARDS, early administration of a neuromuscular blocking agent improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness. (Funded by Assistance Publique—Hôpitaux de Marseille and the Programme Hospitalier de Recherche Clinique Régional 2004-26 of the French Ministry of Health; ClinicalTrials.gov number, NCT00299650.)

(J.-M.C.); Centre Hospitalier, Avignon (P.C.); Hôpital Caremeau, Nîmes (J.-Y.L.); Hôpital de la Croix-Rousse, Lyon (C.G.); and Hôpital du Cavale Blanche, Brest (G. Prat) — all in France. Address reprint requests to Dr. Papazian at Service de Réanimation Médicale, Hôpital Nord, Chemin des Bourrely, 13009 Marseille, France, or at laurent.papazian@ap-hm.fr.

*The ARDS et Curarisation Systematique (ACURASYS) study investigators are listed in the Appendix.

N Engl J Med 2010;363:1107-16.
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Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

In patients undergoing mechanical ventilation for the acute respiratory distress syndrome (ARDS), neuromuscular blocking agents may improve oxygenation and decrease ventilator-induced lung injury but may also cause muscle weakness. We evaluated clinical outcomes after 2 days of therapy with neuromuscular blocking agents in patients with early, severe ARDS.

METHODS

In this multicenter, double-blind trial, 340 patients presenting to the intensive care unit (ICU) with an onset of severe ARDS within the previous 48 hours were randomly assigned to receive, for 48 hours, either cisatracurium besylate (178 patients) or placebo (162 patients). Severe ARDS was defined as a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) of less than 150, with a positive end-expiratory pressure of 5 cm or more of water and a tidal volume of 6 to 8 ml per kilogram of predicted body weight. The primary outcome was the proportion of patients who died either before hospital discharge or within 90 days after study enrollment (i.e., the 90-day in-hospital mortality rate), adjusted for predefined covariates and baseline differences between groups with the use of a Cox model.

RESULTS

The hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68 (95% confidence interval [CI], 0.48 to 0.98; $P=0.04$), after adjustment for both the baseline $\text{PaO}_2:\text{FiO}_2$ and plateau pressure and the Simplified Acute Physiology II score. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group ($P=0.08$). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo ($P=0.05$). The rate of ICU-acquired paresis did not differ significantly between the two groups.

CONCLUSIONS

In patients with severe ARDS, early administration of a neuromuscular blocking agent improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness. (Funded by Assistance Publique-Hôpitaux de Marseille and the Programme Hospitalier de Recherche Clinique Régional 2004-26 of the French Ministry of Health; ClinicalTrials.gov number, NCT00299650.)

STUDY TREATMENT

Cisatracurium besylate (150-mg formulation, GlaxoSmithKline) and placebo were prepared in identical separate 30-ml vials for intravenous infusion. Peripheral-nerve stimulators were not permitted. The Ramsay sedation scale was used to adapt sedative requirements. The scale assigns the conscious state a score of 1 (anxious, agitated, or restless) to 6 (no response on glabellar tap). Once the assigned Ramsay sedation score was 6 and the ventilator settings were adjusted (Table 1), a 3-ml rapid intravenous infusion of 15 mg of cisatracurium besylate or placebo was administered,

From Assistance Publique-Hôpitaux de Marseille Unité d'Infectiologie et d'Immunologie (URM Infection et Recherche) et Service de Recherche Clinique (C.R.) et Faculté de Médecine de la Méditerranée (F.M.M); Hôpital Sainte-Élisabeth (G. Perrin); Hôpital Sainte-Élisabeth (A.G.); Hôpital Sainte-Élisabeth (S.J.); Hôpital Sainte-Élisabeth (P.C.); Hôpital Sainte-Élisabeth (J.-M.C.); Centre de Formation Médicale (Dr. G. Perrin); Institut Méditerranéen des Biorobotiques (Dr. Laurent Papazian)

*The ARDS study (ACURASYS) is listed in the Table of Contents.

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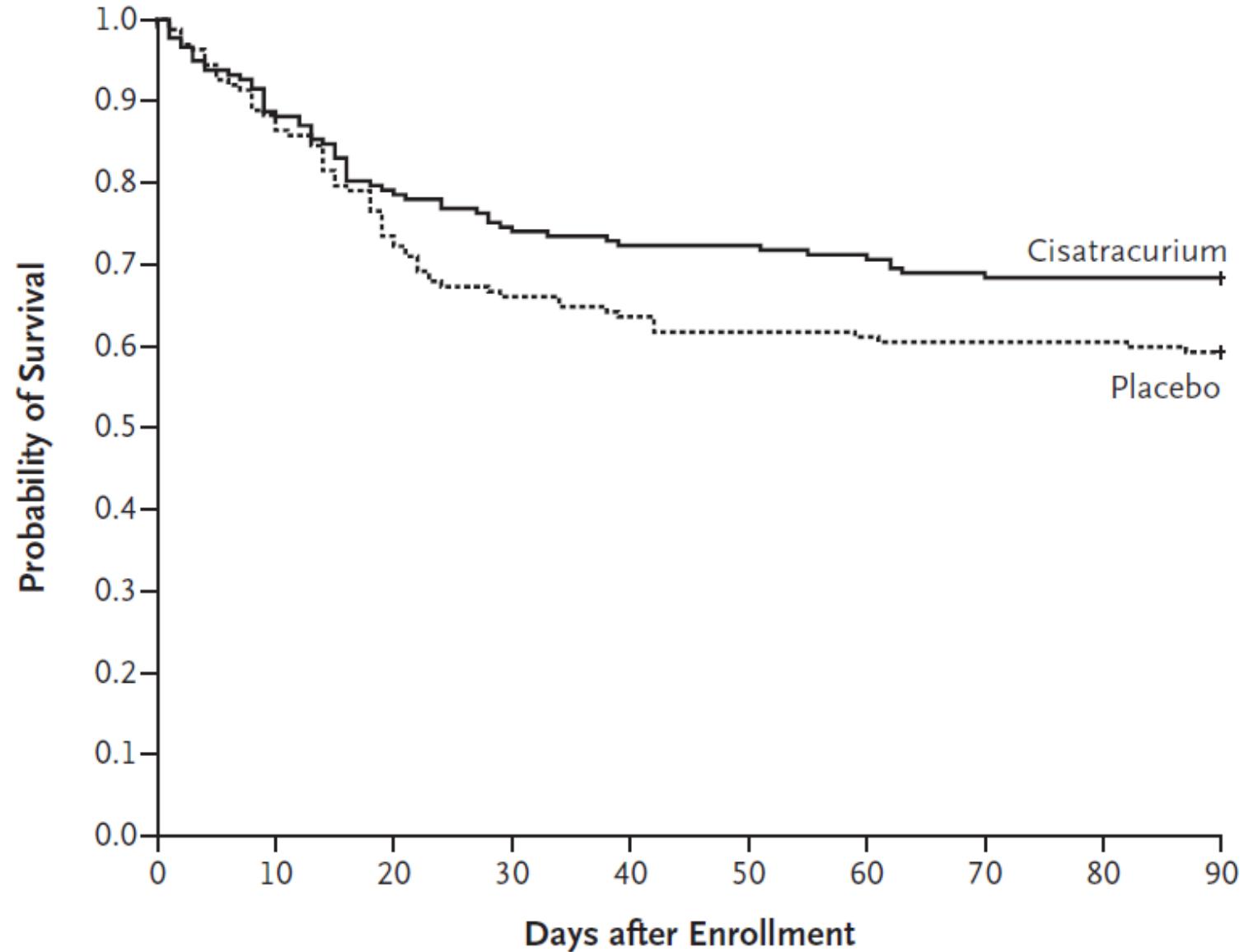


Figure 2. Probability of Survival through Day 90, According to Study Group.

Papazian,
NEJM, 2010

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

BASELINE CHARACTERISTICS

We enrolled 340 patients, of whom 178 were randomly assigned to cisatracurium and 162 to placebo. We excluded 986 patients (Fig. 1). One patient in the cisatracurium group withdrew consent before treatment was started, and data for this patient were therefore not included in the analysis.





Reducing Iatrogenic Risks

ICU-Acquired Delirium and Weakness—Crossing the Quality Chasm

Eduard E. Vasilevskis, MD; E. Wesley Ely, MPH, MD, FCCP; Theodore Speroff, PhD; Brenda T. Pun, RN, MSN, ACNP; Leanne Boehm, RN, MSN, ACNS-BC; and Robert S. Dittus, MPH, MD

ICUs are experiencing an epidemic of patients with acute brain dysfunction (delirium) and weakness, both associated with increased mortality and long-term disability. These conditions are commonly acquired in the ICU and are often initiated or exacerbated by sedation and ventilation decisions and management. Despite > 10 years of evidence revealing the hazards of delirium, the quality chasm between current and ideal processes of care continues to exist. Monitoring of delirium and sedation levels remains inconsistent. In addition, sedation, ventilation, and physical therapy practices proven successful at reducing the frequency and severity of adverse outcomes are not routinely practiced. In this article, we advocate for the adoption and implementation of a standard bundle of ICU measures with great potential to reduce the burden of ICU-acquired delirium and weakness. Individual components of this bundle are evidence based and can help standardize communication, improve interdisciplinary care, reduce mortality, and improve cognitive and functional outcomes. We refer to this as the “ABCDE bundle,” for awakening and breathing coordination, delirium monitoring, and exercise/early mobility. This evidence-based bundle of practices will build a bridge across the current quality chasm from the “front end” to the “back end” of critical care and toward improved cognitive and functional outcomes for ICU survivors.

CHEST 2010; 138(5):1224–1233

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MAY 23, 2019

VOL. 380 NO. 21

Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

ABSTRACT

BACKGROUND

The benefits of early continuous neuromuscular blockade in patients with acute respiratory distress syndrome (ARDS) who are receiving mechanical ventilation remain unclear.

The members of the writing committee (Marc Moss, M.D., David T. Huang, M.D., M.P.H., Roy G. Brower, M.D., Niall D. Ferguson, M.D., Adit A. Ginde, M.D.,

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We randomly assigned patients with moderate-to-severe ARDS (defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of <150 mm Hg with a positive end-expiratory pressure [PEEP] of ≥8 cm of water) to a 48-hour continuous infusion of cisatracurium with concomitant deep sedation (intervention group) or to a usual-care approach without routine neuromuscular blockade and with lighter sedation targets (control group). The same mechanical-ventilation strategies were used in both groups, including a strategy involving a high PEEP. The primary end point was in-hospital death from any cause at 90 days.

RESULTS

The trial was stopped at the second interim analysis for futility. We enrolled 1006 patients early after the onset of moderate-to-severe ARDS (median, 7.6 hours after onset). During the first 48 hours after randomization, 488 of the 501 patients (97.4%) in the intervention group started a continuous infusion of cisatracurium (median duration of infusion, 47.8 hours; median dose, 1807 mg), and 86 of the 505 patients (17.0%) in the control group received a neuromuscular blocking agent (median dose, 38 mg). At 90 days, 213 patients (42.5%) in the intervention group and 216 (42.8%) in the control group had died before hospital discharge (between-group difference, −0.3 percentage points; 95% confidence interval, −6.4 to 5.9; $P=0.93$). While in the hospital, patients in the intervention group were less physically active and had more adverse cardiovascular events than patients in the control group. There were no consistent between-group differences in end points assessed at 3, 6, and 12 months.

CONCLUSIONS

Among patients with moderate-to-severe ARDS who were treated with a strategy involving a high PEEP, there was no significant difference in mortality at 90 days between patients who received an early and continuous cisatracurium infusion and those who were treated with a usual-care approach with lighter sedation targets. (Funded by the National Heart, Lung, and Blood Institute; ROSE ClinicalTrials.gov number, NCT02509078.)

The members of the writing committee include Marc Moss, M.D., David E. Ferguson, M.D., Adit A. Gajalakshmi, M.P.H., M.N. Gong, M.D., Christopher J. Korsom, M.D., Stephanie G. Lai, M.D., Douglas Hayden, Ph.D., R. Edward Phillips, M.D., Peter C. Hou, M.D., Michael J. Hough, M.D., Theodore J. Iwashita, Ph.D., Akram Khan, M.D., Kathleen M.D., Ph.D., Daniel Talmor, M.D., B. Taylor Thompson, M.D., Ulysse, M.S., Donald M. Yeager, M.D., Derek C. Angus, M.D., M.P.H., and Michael J. Fertel, M.D., responsible for the overall design and conduct of the study. The members of the writing committee are listed in the Appendix. Address correspondence to Dr. Angus at the University of Pittsburgh, 3550 Terrace Street, Suite 15261, or at angusdc@upmc.edu.

*A full list of the investigators involved in the investigation of Systemic Early Neuromuscular Blockade (ROSE) Prevention and Early Treatment of Acute Lung Injury (PETAL) is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa1901686
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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Intervention Group (N=501)	Control Group (N=505)
Age — yr	56.6±14.7	55.1±15.9
Female sex — no. (%)†	210 (41.9)	236 (46.7)
White race — no. (%)†	361 (72.1)	344 (68.1)
Shock at baseline — no. (%)	276 (55.1)	309 (61.2)
Median time from eligibility to randomization (IQR) — hr	8.2 (4.0–16.4)	6.8 (3.3–14.5)
Neuromuscular blockade use between meeting inclusion criteria and randomization — no./total no. (%)	55/484 (11.4)	50/484 (10.3)
Primary cause of lung injury — no. (%)		
Pneumonia	292 (58.3)	301 (59.6)
Aspiration	91 (18.2)	75 (14.9)
Nonpulmonary sepsis	68 (13.6)	71 (14.1)
Other cause	50 (10.0)	58 (11.5)
Assessments and measurements		
APACHE III score‡	103.9±30.1	104.9±30.1
Total SOFA score§	8.7±3.6	8.8±3.6
Tidal volume — ml/kg of predicted body weight¶	6.3±0.9	6.3±0.9
F _i O ₂	0.8±0.2	0.8±0.2
Inspiratory plateau pressure — cm of water**	25.5±6.0	25.7±6.1
PEEP — cm of water††	12.6±3.6	12.5±3.6
Pao ₂ :F _i O ₂ — mm Hg ‡‡	98.7±27.9	99.5±27.9
Imputed Pao ₂ :F _i O ₂ — mm Hg§§	94.8±26.7	93.2±28.9

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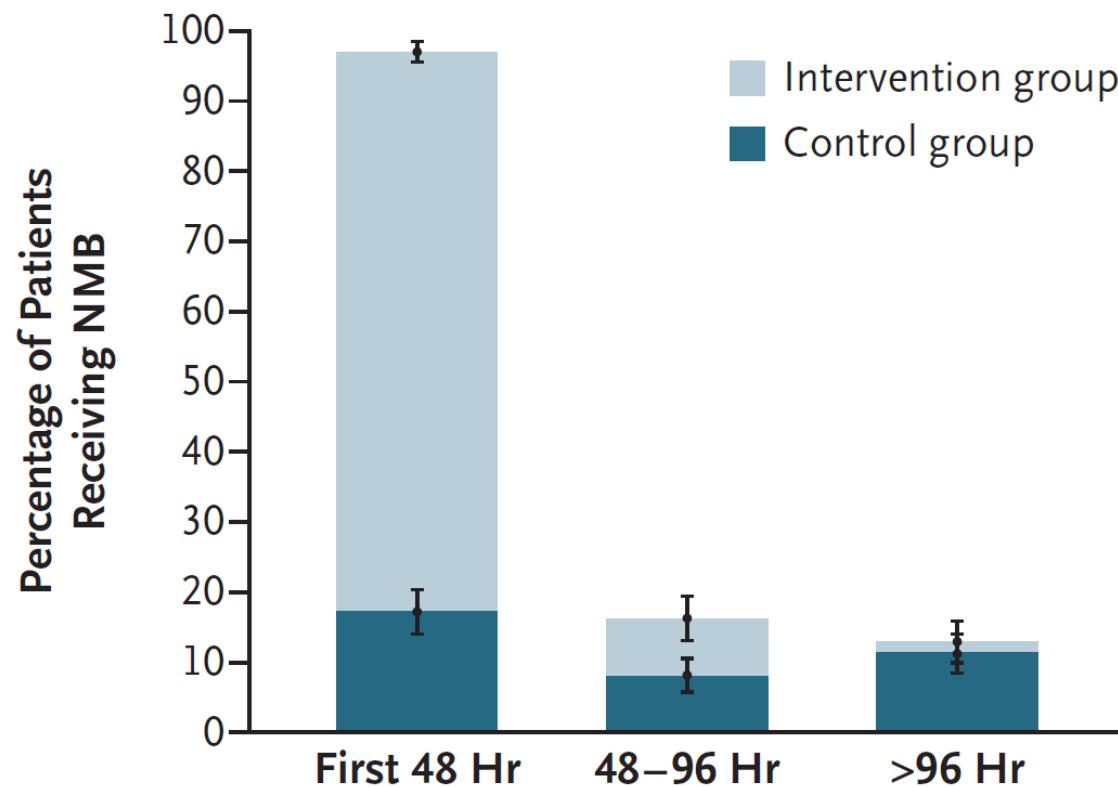
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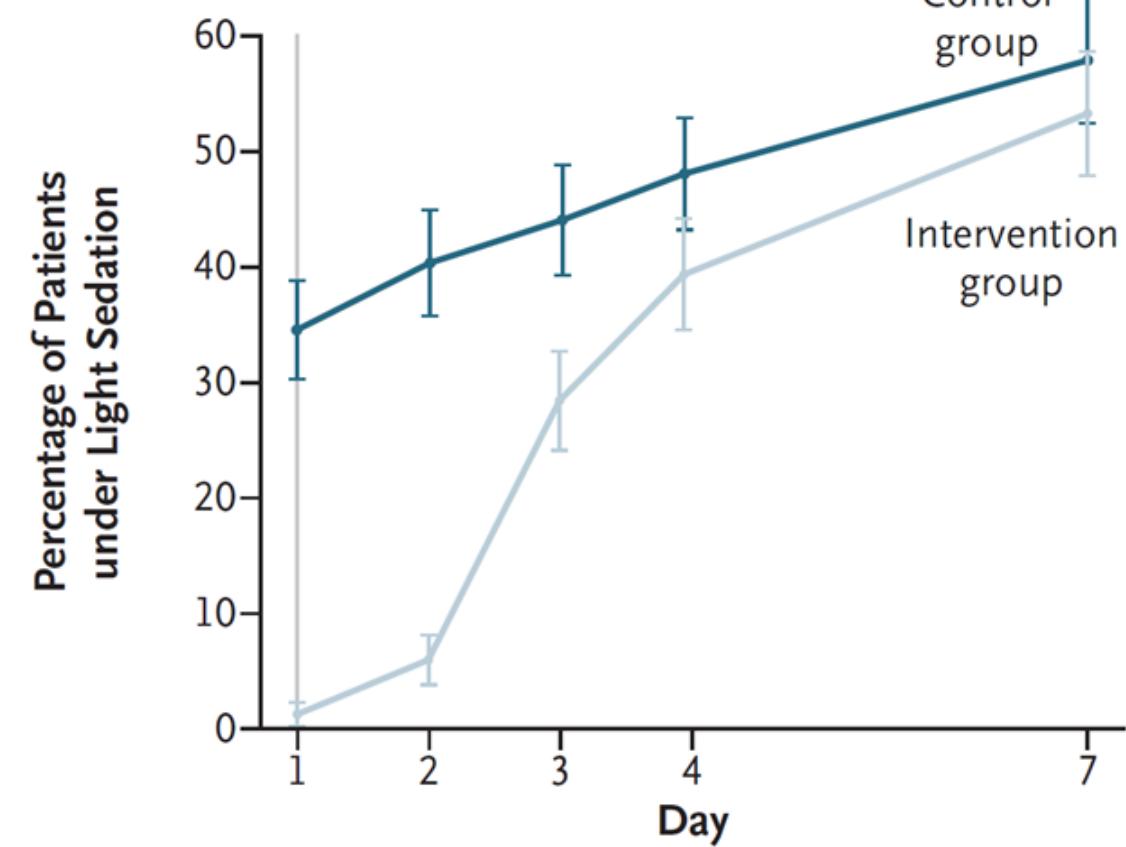
Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

A NMB



(Funded by the National Heart, Lung, and Blood Institute; ROSE ClinicalTrials.gov number, NCT02509078.)

B Light Sedation



Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network

ABSTRACT

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The benefits of early continuous neuromuscular blockade in patients with acute respiratory distress syndrome (ARDS) who are receiving mechanical ventilation remain unclear.

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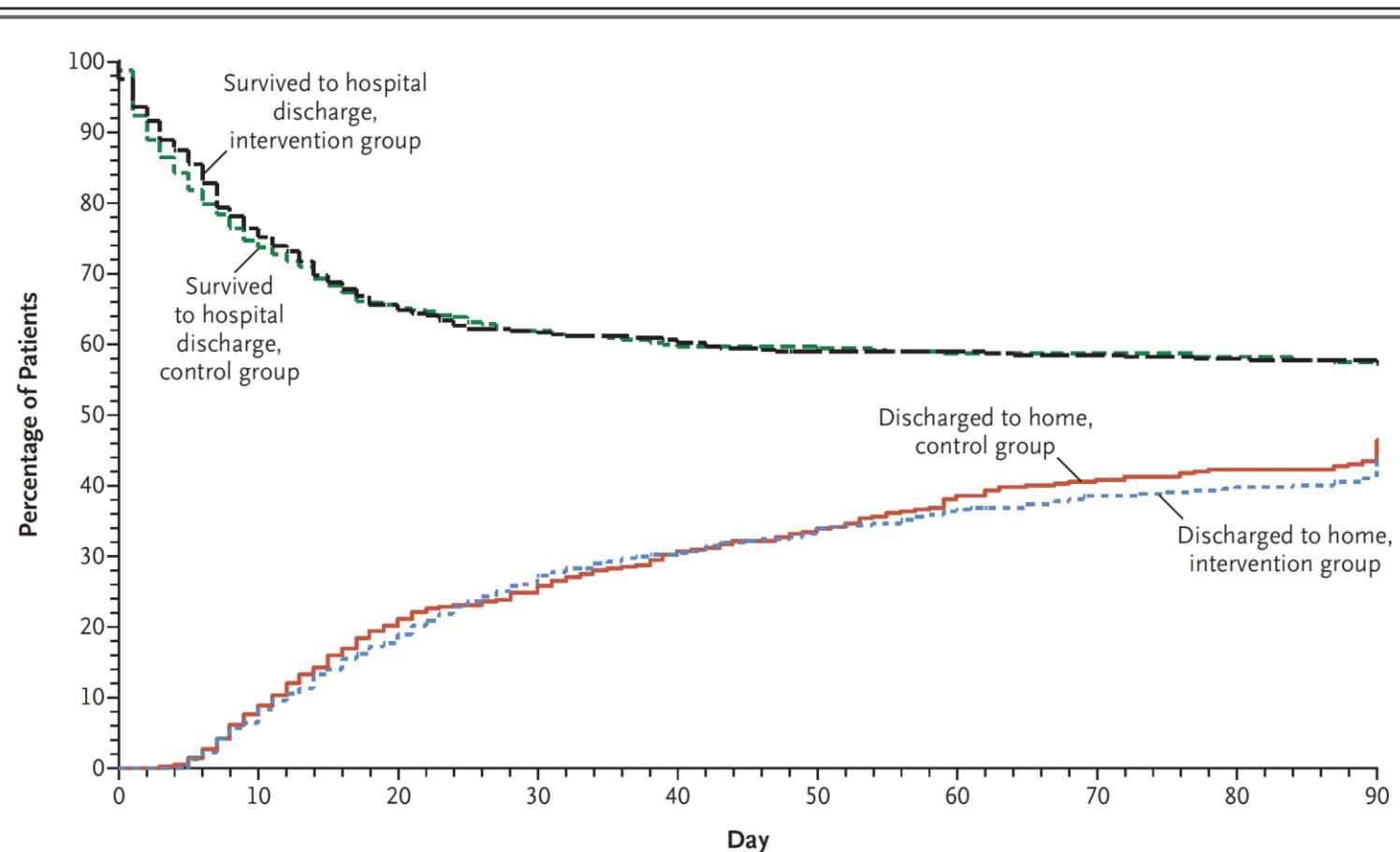
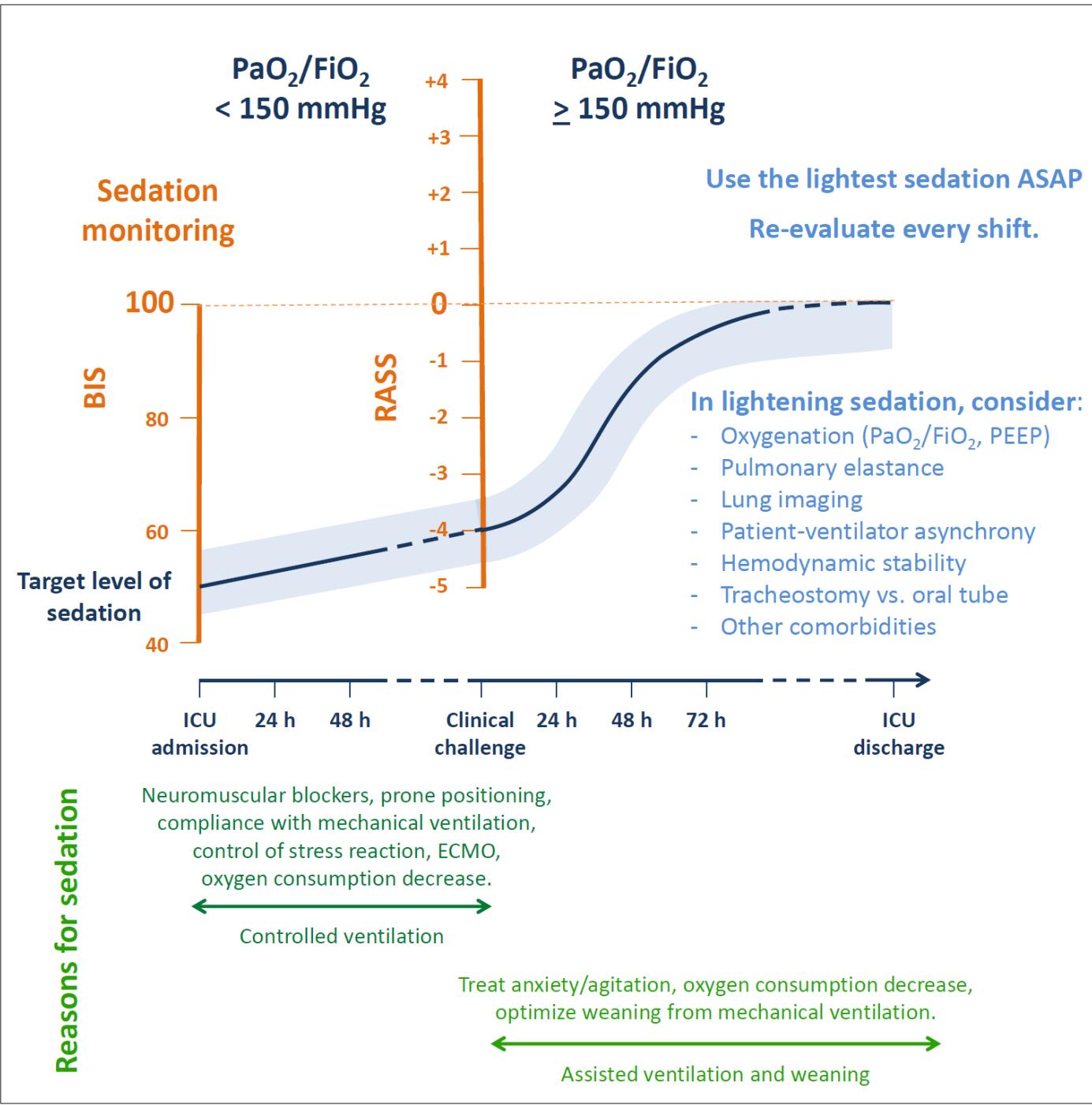


Figure 3. Patients Who Survived to Hospital Discharge and Were Discharged Home during the First 90 Days after Randomization.

The period of hospitalization included transfer to other health care facilities.



REVIEW

Open Access

Neuromuscular blocking agents in acute respiratory distress syndrome: updated systematic review and meta-analysis of randomized trials



Nehal Tarazan¹, Moayad Alshehri^{1,2}, Sameer Sharif³, Zainab Al Duhailib^{1,4}, Morten Hylander Møller⁵, Emilie Belley-Cote¹, Mohammed Alshahrani⁶, John Centofanti¹, Lauralyn McIntyre^{7,8}, Bandar Baw¹, Maureen Meade^{1,9}, Waleed Alhazzani^{1,9*}  and for the GUIDE Group

* Correspondence: waleed.al-hazzani@medportal.ca

¹Department of Medicine, McMaster University, Hamilton, Canada

⁹Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON L8S 4K1, Canada

Full list of author information is available at the end of the article

Abstract

Purpose: Existing clinical practice guidelines support the use of neuromuscular blocking agents (NMBA) in acute respiratory distress syndrome (ARDS); however, a recent large randomized clinical trial (RCT) has questioned this practice. Therefore, we updated a previous systematic review to determine the efficacy and safety of NMBA in ARDS.

Methods: We searched MEDLINE, EMBASE (October 2012 to July 2019), the Cochrane

REVIEW

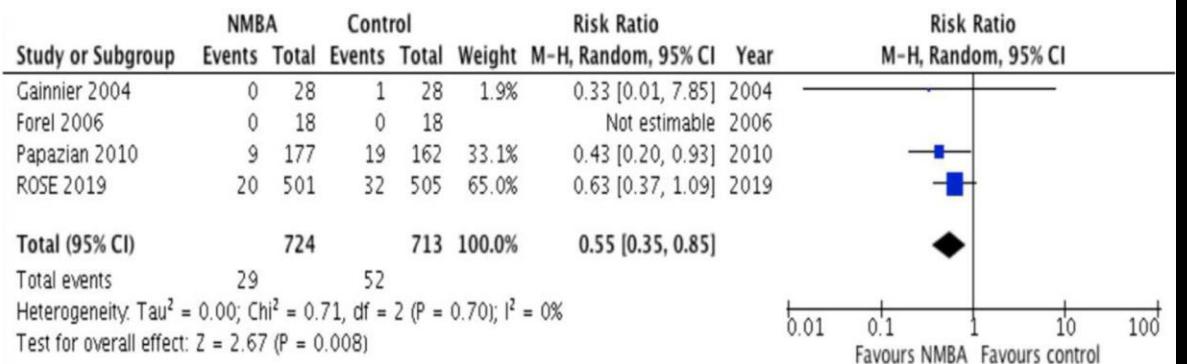
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Neuromuscular blocking agents in acute respiratory distress syndrome: updated systematic review and meta-analysis of

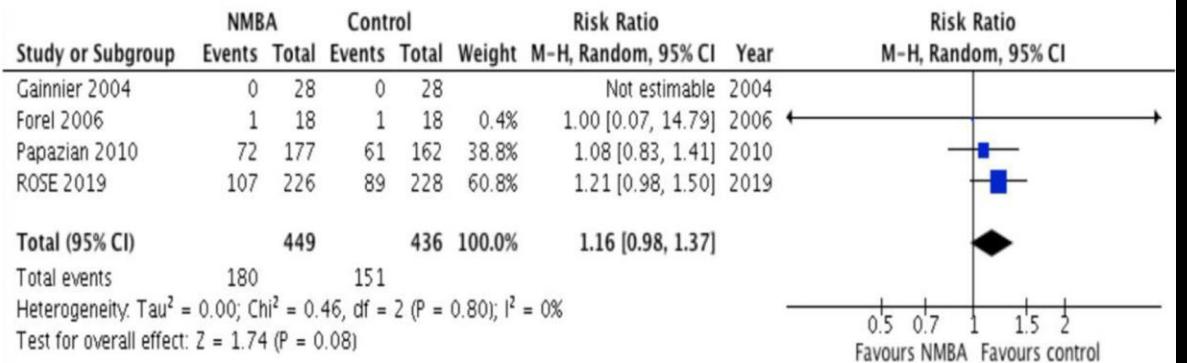


Conclusions: Inconsistency in study methods and findings precluded the pooling of all trials for mortality. In a pre-planned sensitivity analysis, the impact of NMBA infusion on mortality depends on the strategy used in the control arm, showing reduced mortality when compared to deep sedation, but no effect on mortality when compared to lighter sedation. In both situations, a continuous NMBA infusion may reduce the risk of barotrauma, but the effects on other patient-important outcomes remain unclear. Future research, including an individual patient data meta-analysis, could help clarify some of the observed findings in this updated systematic review.

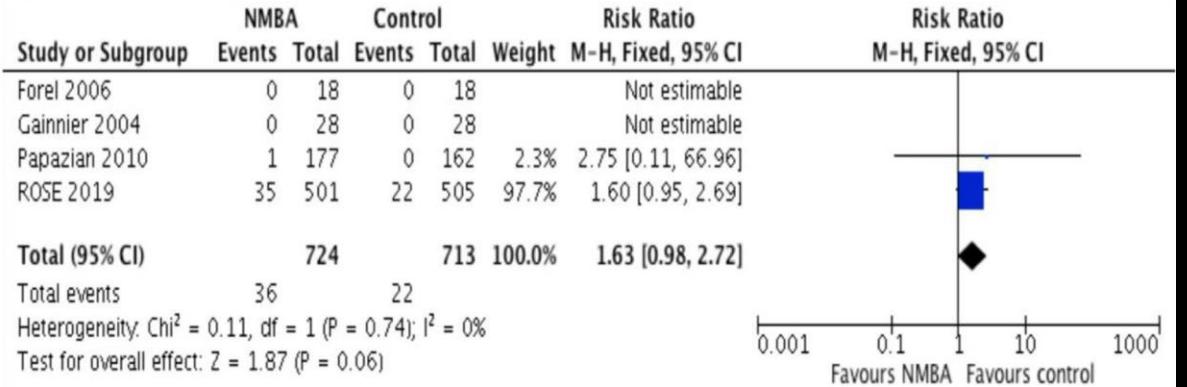
A



B



C



Barotrauma

ICU-acquired weakness

Adverse events

Comparison of Cisatracurium Versus Atracurium in Early ARDS

Leanne Moore PharmD, Charles Joseph Kramer PharmD, Sophie Delcoix-Lopes MSc, and Ariel M Modrykamien MD

BACKGROUND: Administration of cisatracurium in severe ARDS decreases in-hospital mortality. Whether clinical outcomes are cisatracurium-specific or related with all neuromuscular blockers is unknown. This study aimed to compare outcomes in severe ARDS patients treated with cisatracurium versus atracurium. **METHODS:** Patients admitted in ICUs with a diagnosis of severe ARDS and treated with neuromuscular blocking agents within 72 h of diagnosis were included. Subjects treated with cisatracurium versus atracurium were compared. The primary outcome was improvement in oxygenation, defined as the difference of P_{aO_2}/F_{IO_2} at 72 h post-initiation of neuromuscular blocking agents. Secondary outcomes were ventilator-free days at day 28, ICU and hospital lengths of stay, and hospital mortality. **RESULTS:** Seventy-six subjects with ARDS were included in the study. Eighteen subjects (24%) were treated with atracurium, whereas 58 (76%) were treated with cisatracurium. Equivalent dosages of sedation and analgesia as well as use of brain function monitoring technology were similar between both groups. There were no differences in clinical outcomes. Specifically, improvement of P_{aO_2}/F_{IO_2} was a median (interquartile range [IQR]) of 65 (25–162) in the atracurium group and 66 (IQR 16–147) in the cisatracurium group ($P = .65$).

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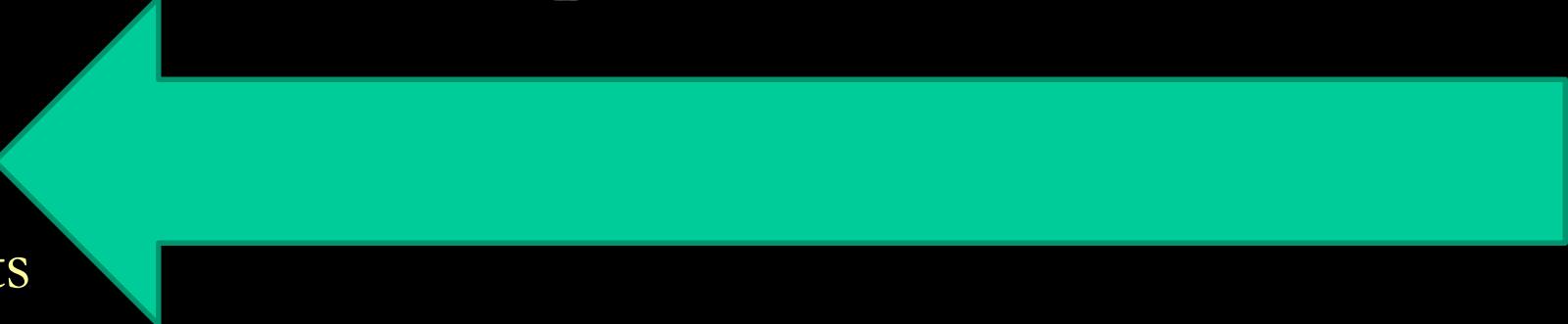
CONCLUSIONS: Among subjects with early severe ARDS, the utilization of atracurium versus cisatracurium within 72 h of admission was not associated with significant differences in clinical outcomes. **Key words:** ARDS; neuromuscular blockers; mechanical ventilation; oxygenation. [Respir Care 2017;62(7):947–952. © 2017 Daedalus Enterprises]

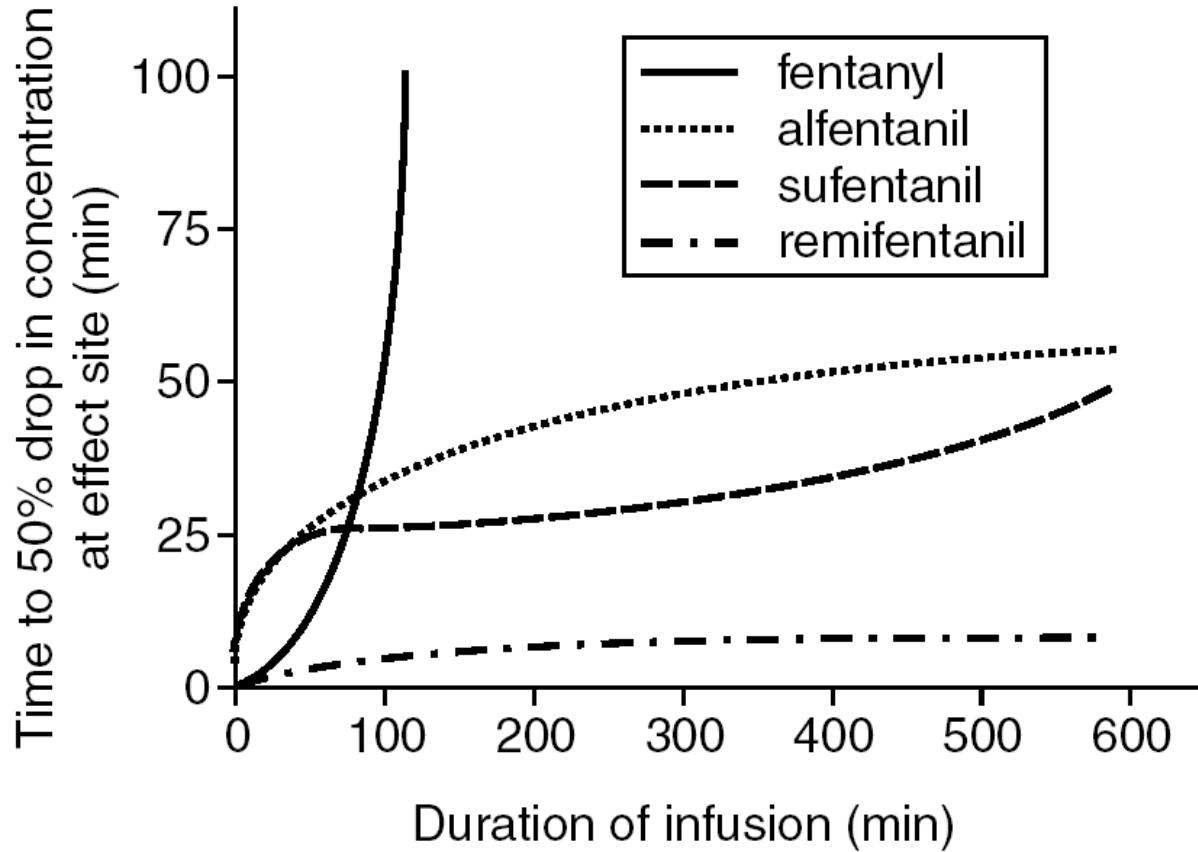
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Take home message... *IMHO*...

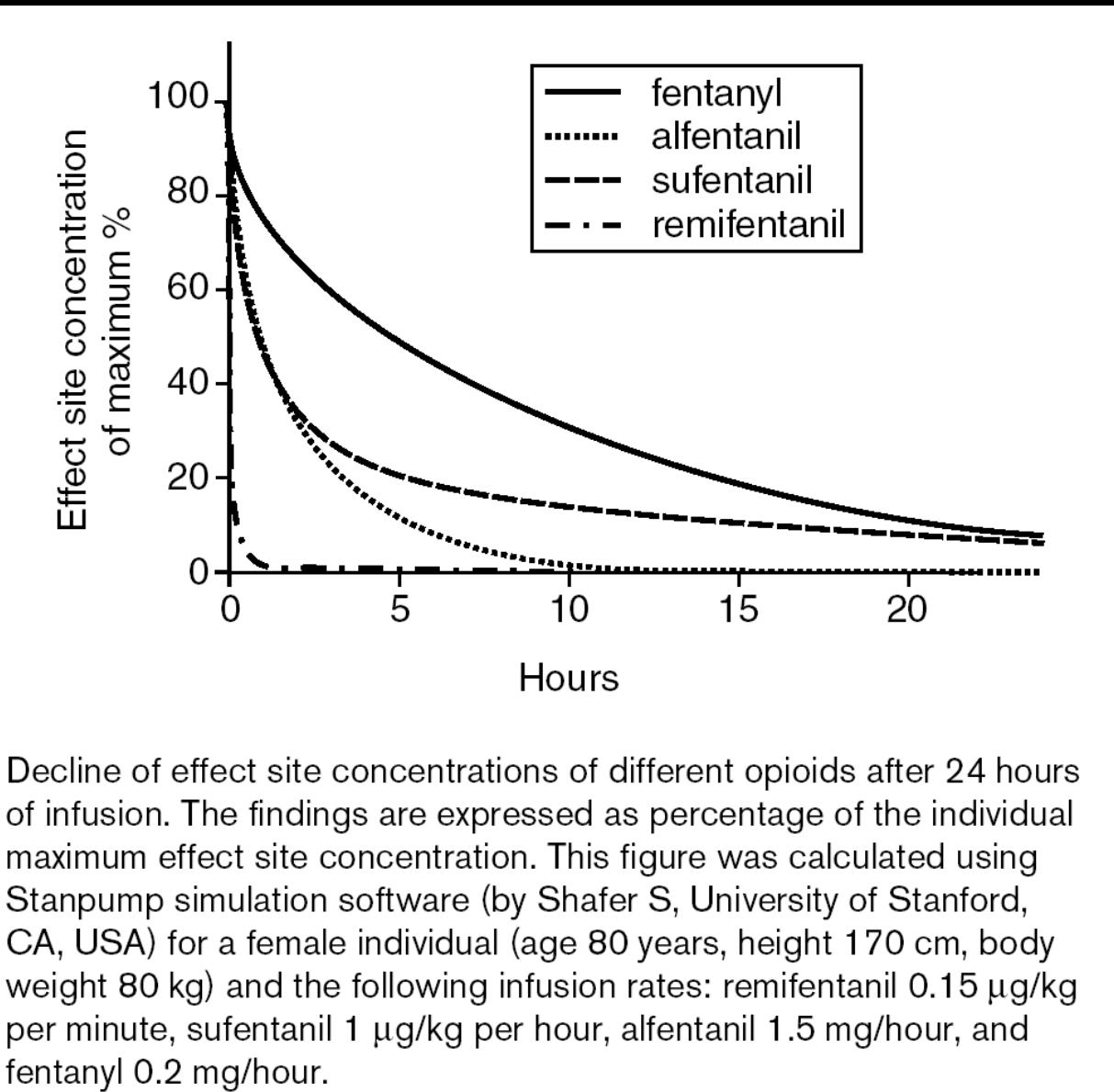


For each sedative, please check:

- Pharmacokinetics
 - Neurological effects
 - Cardio-respiratory effects
 - Endocrine and metabolic effects
- 
- Side effects – risks for that patient
 - Indications

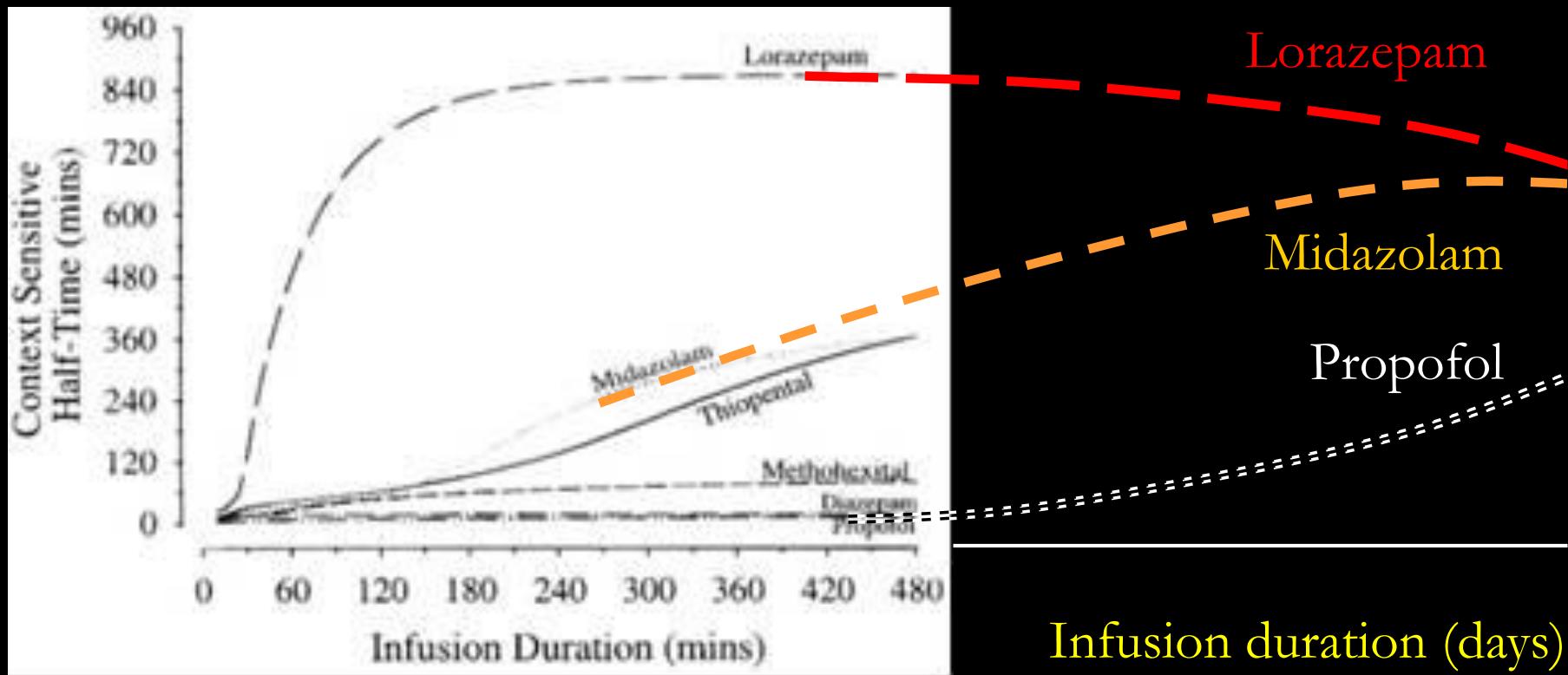


Context-sensitive half-times of remifentanil and the other 4-anilido-piperidine opioids. Remifentanil has a context-sensitive half-time of 3 to 4 minutes, regardless of the duration of infusion, whereas continuous infusion of the other opioids results in accumulation and considerable prolongation of effect, making these opioids intermediate-acting or long-acting agents, depending on the duration of infusion.



Decline of effect site concentrations of different opioids after 24 hours of infusion. The findings are expressed as percentage of the individual maximum effect site concentration. This figure was calculated using Stanpump simulation software (by Shafer S, University of Stanford, CA, USA) for a female individual (age 80 years, height 170 cm, body weight 80 kg) and the following infusion rates: remifentanil 0.15 µg/kg per minute, sufentanil 1 µg/kg per hour, alfentanil 1.5 mg/hour, and fentanyl 0.2 mg/hour.

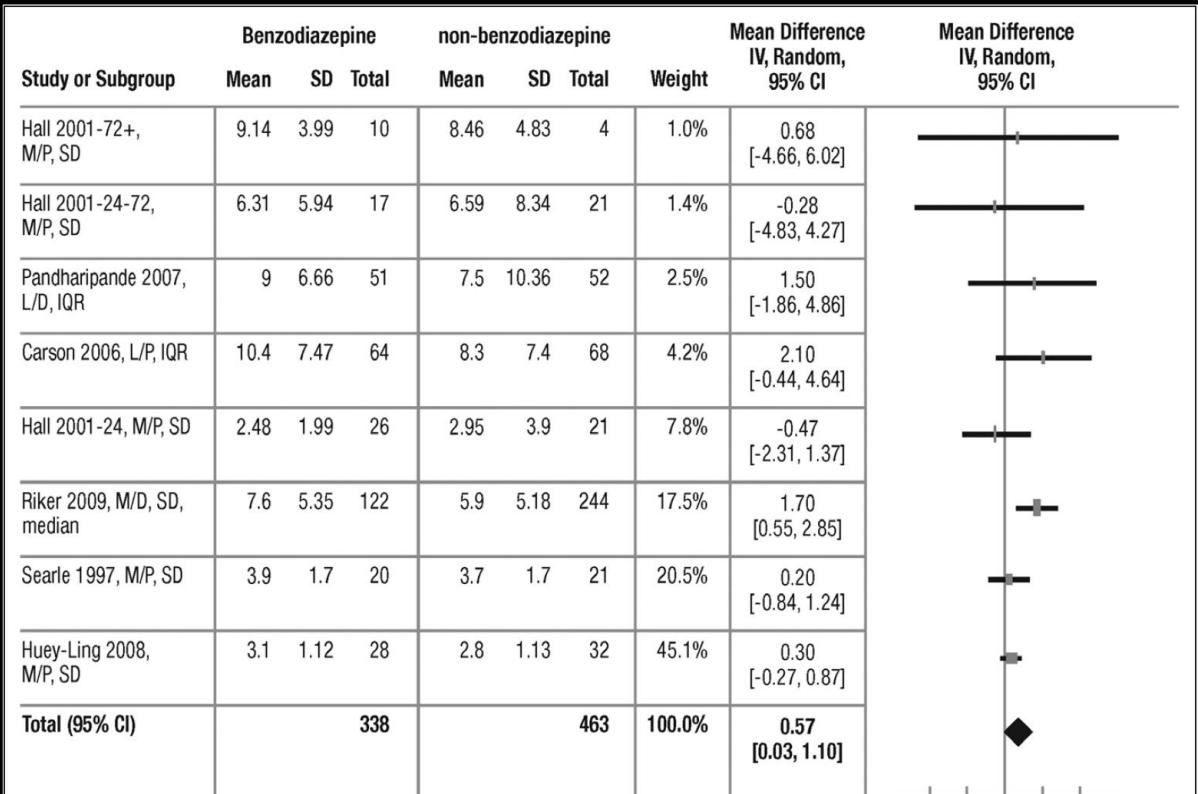
Succede anche per i sedativi ...





Special Article

Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit



Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 8.03$, $df = 7$ ($p = 0.33$), $I^2 = 13\%$
Test for overall effect $Z = 2.08$ ($p = 0.04$)



ICU-LOS
0.5 days less

by using
non-BZDP



Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit



In summary, the current literature supports modest differences in outcomes with benzodiazepine-based vs. nonbenzodiazepine-based sedation.



Special Article

**Clinical Practice Guidelines for the Management
of Pain, Agitation, and Delirium in Adult Patients
in the Intensive Care Unit**



We recommend that sedative medications be titrated to maintain a light rather than deep level of sedation in adult ICU patients, unless clinically contraindicated (+1B).

We suggest that sedation strategies using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients (+2B).



Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

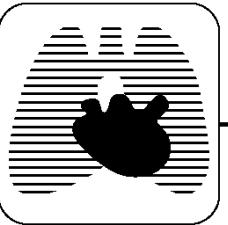


We have learned that the methods of administering and titrating these medications can affect patient outcomes as much as drug choice (7–16). For most ICU patients, a safe and effective strategy that ensures patient comfort while maintaining a light level of sedation is associated with improved clinical outcomes (9–13, 16–20).



Il livello di sedazione ideale
varia per ogni paziente
e per ogni momento della storia clinica...



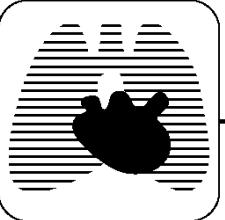


Patient-Focused Sedation and Analgesia in the ICU*

Curtis N. Sessler, MD, FCCP; and Kimberly Varney, PharmD

Patient-focused sedation and analgesia in the ICU encompasses a strategy of comprehensive structured management that matches initial evaluation, monitoring, medication selection, and the use of protocols with patient characteristics and needs. This is best accomplished through interdisciplinary management by physicians, nurses, and pharmacists. An early consideration is that of the potential predisposing and precipitating factors, as well as prior sedative or analgesic use, factors that may influence pharmacologic and supportive therapy. Frequent monitoring with validated tools improves communication among clinicians and plays an important role in detecting and treating pain and agitation while avoiding excessive or prolonged sedation. Patient-focused management encompasses selecting medications best suited to patient characteristics, including the presence of organ dysfunction that may influence drug metabolism or excessive risk for side effects. The use of protocols to optimize drug therapy has emerged as a key component of management, resulting in reductions in the duration of sedation, mechanical ventilation, and ICU length of stay demonstrated with strategies to titrate medications to specific targets, daily interruption of sedation, intermittent rather than continuous therapy, and analgesia-based therapy. While much attention is paid to the initiation and maintenance of therapy, greater emphasis must be placed on careful de-escalation of therapy in order to avoid analgesic or sedative withdrawal. Finally, more work is needed to explore the relationship of critical illness and sedation management with long-term psychological outcomes.

(CHEST 2008; 133:552–565)



Patient-Focused Sedation and Analgesia in the ICU*

Curtis N. Sessler, MD, FCCP; and Kimberly Varney, PharmD

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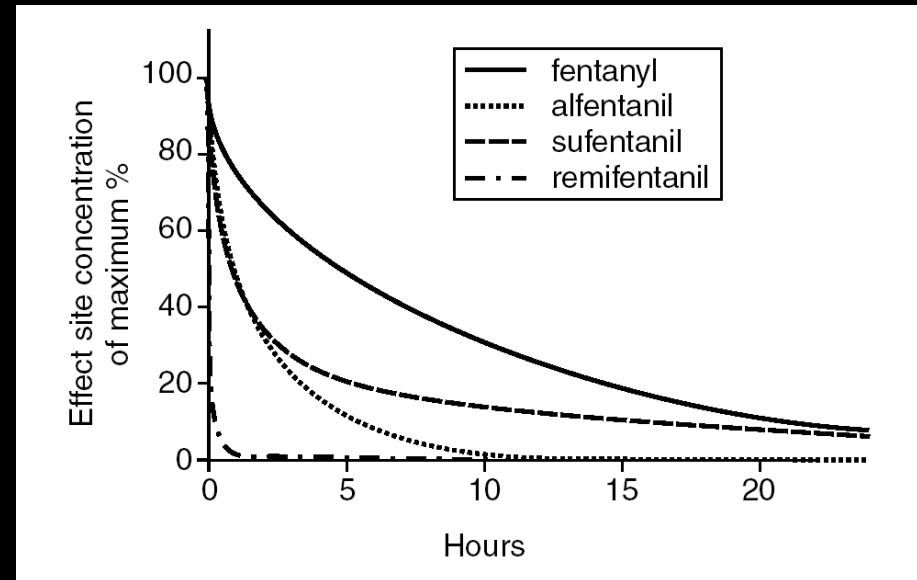
Organizzazione interna...



Cosa c'entra con la sedazione ?

1

Altissima preparazione professionale



Cosa c'entra con la sedazione ?

2

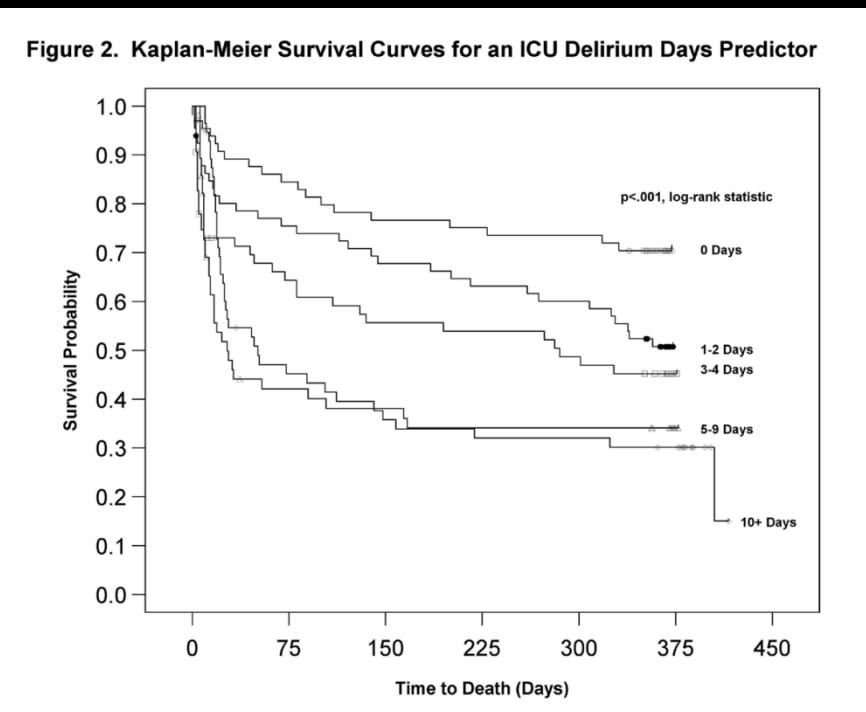
Non si può fare da soli



Cosa c'entra con la sedazione ?

3

...lo puoi fare solo oggi.



Quali dosaggi usiamo ?



TAVOLA SINOTTICA ANALGESICI

	FARMACO	PREPARAZIONE	EFFICACIA EQUINALGESICA	METABOLISMO	ELIMINAZIONE	BOLO	MANTENIMENTO	INSUFFICIENZA RENALE	INSUFFICIENZA EPATICA	ANZIANO
ENDOVENA	MORFINA <i>(Morphine)</i>	10 mg	1	Epatico	Renale, Fecale	0.05 mg/kg in 5-15 min	100 - età/die	X	↓ dosi	↓ dosi
	FENTANYL <i>(Fentanest®)</i>	100 γ	1	Epatico	Renale	1-2 γ/kg	Max 2 γ/kg x h	↓ dosi	↓ dosi	↓ dosi
	REMIFENTANIL <i>(Ultiva®)</i>	1 mg	100	Esterasi plasmatiche e tissutali	Indipendente da metabolismo epatico e renale	Non raccomandato	0.006-0.7 γ/kg x min	✓	✓	✓
	SUFENTANIL <i>(Sufentanil®)</i>	50 γ	1	Epatico	Renale	0,5-2 γ/kg	0,15 – 0,7 γ/kg x h	✓	✓	✓
	TRAMADOL <i>(Contramal®)</i>	100 mg	1	Epatico	Renale	Max 100 mg	Max 600 mg/die	↓ dosi	↓ dosi	↓ dosi
	BUPRENORFINA <i>(Temgesic®)</i>	0.3 mg	1	Epatico	Fecale	Max 0.6 mg	Max 2,4 mg/die	✓	↓ dosi	✓
	KETOPROFENE <i>(Artrosilene®)</i>	100 mg	0,35	Epatico	Renale	Max 100 mg	Max 300 mg/die	X	↓ dosi	↓ dosi
	PARACETAMOLO <i>(Perfalgan®)</i>	1000 mg	0,26	Epatico	Renale	Max 1000 mg	Max 4000 mg/die	↓ dosi	X	✓
ENTERALE	PARACETAMOLO CODEINA <i>(Tachidol®)</i>	500 mg + 30 mg	0,25	Epatico	Renale	Max 500 + 30 mg	Max 3000 + 180 mg/die	↓ dosi	X	↓ dosi
	MORFINA <i>(Oramorph®)</i>	10 mg	0,33	Epatico	Renale, Fecale	10 mg	(100 – età) x 3/die	X	↓ dosi	↓ dosi
	PARACETAMOLO OSSICODONE <i>(Depalgos®)</i>	325 mg+ 5 mg	0,25	Epatico	Renale	325 mg + 5 mg	Max 3900 mg + 60 mg	✓	✓	✓
	IDROMORFONE <i>(Jurnista®)</i>	4 mg	2	Epatico	Renale	8 mg/die	Da titolare con aumenti di 4-8 mg/die	↓ dosi	X	↓ dosi
TD	FENTANYL <i>(Durogesic®)</i>	4,2 mg pari a 25 γ/h	2,67	Epatico	Renale, Fecale	25 γ/h	Max 300 γ/h	✓	✓	✓

TAVOLA SINOTTICA SEDATIVI

	FARMACO	METABOLISMO	ELIMINAZIONE	BOLO	MANTENIMENTO	INSUFFICIENZA RENALE	INSUFFICIENZA EPATICA	ANZIANO
ENDOVENA	PROPOFOL (Diprivan®)	Epatico	Renale	0,5 mg/kg	4-6 mg/kg x h	✓	↓ dosi	↓ dosi
	MIDAZOLAM (Ipnovel®)	Epatico	Epatica, Renale	0,03 - 0,3 mg/kg	0,03-0,2 mg/kg x h	✓	↓ dosi	↓ dosi
	KETAMINA (Ketanest®)	Epatico	Renale, Fecale	Max 4,5 mg/kg	0,3-0,15 γ/kg x min	X	X	↓ dosi
ENTERALE	IDROSSIZINA (Atarax®)	Epatico	Renale	50-100 mg	Max 600 mg/die	↓ dosi	↓ dosi	↓ dosi
	LORAZEPAM (Tavor®)	Epatico	Renale	1-4 mg	Max 16 mg/die	↓ dosi	X	↓ dosi
	MELATONINA (Tranquillus®)	Epatico	Renale	3 mg x 2	Max 20 mg/die	✓	✓	✓

TAVOLA SINOTTICA ANTIPSICOTICI

	FARMACO	METABOLISMO	ELIMINAZIONE	BOLO	MANTENIMENTO	INSUFFICIENZA RENALE	INSUFFICIENZA EPATICA	ANZIANO
ENTERALE	OLANZAPINA (Zyprexa®)	Epatico	Renale	10 mg/die	10-15 mg/die	✓	✓	✓
	ALOPERIDOLIO (Haladol®)	Epatico	Fecale, Renale	0,5 - 5 mg	Max 20 mg/die	✓	✓	↓ dosi
	QUIETAPINA (Seroquel®)	Epatico	Renale, Fecale	50 mg 1°g, 2 volte/die	100 mg 2°g 200 mg 3°g 300 mg 4°g	✓	✓	✓
	RISPERIDONE (Risperdal®)	Epatico	Renale, Fecale	1 mg x2/die	Max 6 mg/die dal 2° giorno	✓	✓	✓
	CLOTIAPINA (Entumin®)	Epatico	Renale, Fecale	100 mg	Max 900 mg/die	X	✓	✓

Tutto ciò che avreste voluto chiedere
sulla sedazione e miorisoluzione...
e non avete mai osato farlo:

È il momento di fare DOMANDE!!!

Se sono le 12:15 → finale breve → vai a diapo 121

Se sono le 12:00 → finale delirium → vai a diapo 152

Se il pubblico vuole approfondire il tema dei
miorilassanti → vai a diapo 276



Monitoring of ICU Patients

Patient Comfort		
Pain	Sedation	Delirium
VNR-Pain		
BPS	RASS	CAM-ICU
CPOT	SAS	ICDSC

1° Analgesia

- I pazienti non devono avere dolore!
- E' opportuno ridurre l'utilizzo di antidolorifici (soprattutto oppiacei) al minimo considerando gli effetti collaterali



Misura comportamentale del dolore nei pazienti ricoverati in Terapia Intensiva

BEHAVIORAL PAIN SCALE (BPS)

BPS per pazienti intubati

	1	2	3	4
Espressione facciale				
A				
	rilassato	fronte aggrottata	occhi chiusi	dignitante
Movimenti degli arti superiori				
B				
	immobili	piegati	contratti	retratti
	Se indeciso: controlla il tono muscolare mobilizzando passivamente l'arto superiore			
Adattamento alla ventilazione meccanica				
C				
	adattato	tossisce	asincrono	non ventilabile

BPS-NI per pazienti non intubati

	1	2	3	4
Espressione facciale				
	rilassato	fronte aggrottata	occhi chiusi	dignitante
Movimenti degli arti superiori				
	immobili	piegati	contratti	retratti
	Se indeciso: controlla il tono muscolare mobilizzando passivamente l'arto superiore			
Vocalizzazione				
	non emette lamenti di dolore	si lamenta <3 volte/min e per <3 sec	si lamenta >3 volte/min o per >3 sec	emette urla o lamenti verbali o trattiene il respiro

A + **B** + **C** = **VALORE TOTALE BPS o BPS-NI** da 3 (assente) a 12 (massimo), misura le manifestazioni comportamentali del dolore.

Tratto da: Chanques G. et al., Intensive Care Medicine 2009, Vol. 35, 2060-2067
Tradotto in italiano da G. Mistraletti e S. Barelli

2° Sedazione



The Richmond Agitation - Sedation Scale (RASS)

+ 4	Combattivo	Chiaramente combattivo, violento, potenziale pericolo per se stesso o per lo staff
+ 3	Molto agitato	Aggressivo, rischio evidente di rimozione invasività
+ 2	Agitato	Frequenti movimenti afinalistici, disadattamento alla ventilazione meccanica
+ 1	Irrequieto	Ansioso ma senza movimenti aggressivi e vigorosi
0	Sveglio e tranquillo	Comprende i periodi di sonno fisiologico



Sessler CN, Gosnell MS, Grap MJ, et al.

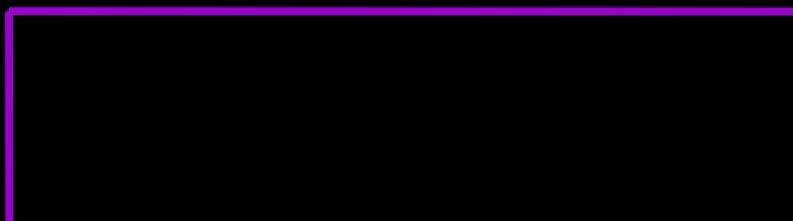
The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients

Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338-44.

The Richmond Agitation - Sedation Scale (RASS)

+ 4	Combattivo
+ 3	Molto agitato
+ 2	Agitato
+ 1	Irrequieto
0	Sveglio e tranquillo

- 1	Soporoso	Non completamente sveglio, apre gli occhi allo stimolo verbale, mantiene il contatto visivo > 10 secondi
- 2	Lievemente sedato	Brevi risvegli allo stimolo verbale, contatto visivo < 10 secondi
- 3	Moderatamente sedato	Movimenti o apertura degli occhi allo stimolo verbale (ma senza contatto visivo)



Sessler CN, Gosnell MS, Grap MJ, et al.

The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients

Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338-44.

The Richmond Agitation - Sedation Scale (RASS)

+ 4	Combattivo
+ 3	Molto agitato
+ 2	Agitato
+ 1	Irrequieto
0	Sveglio e tranquillo

- 1	Soporoso
- 2	Lievemente sedato
- 3	Moderatamente sedato

- 4	Sedazione profonda
- 5	Non risvegliabile

Non risposta allo stimolo verbale,
movimenti o apertura occhi alla stimolazione tattile/dolorosa

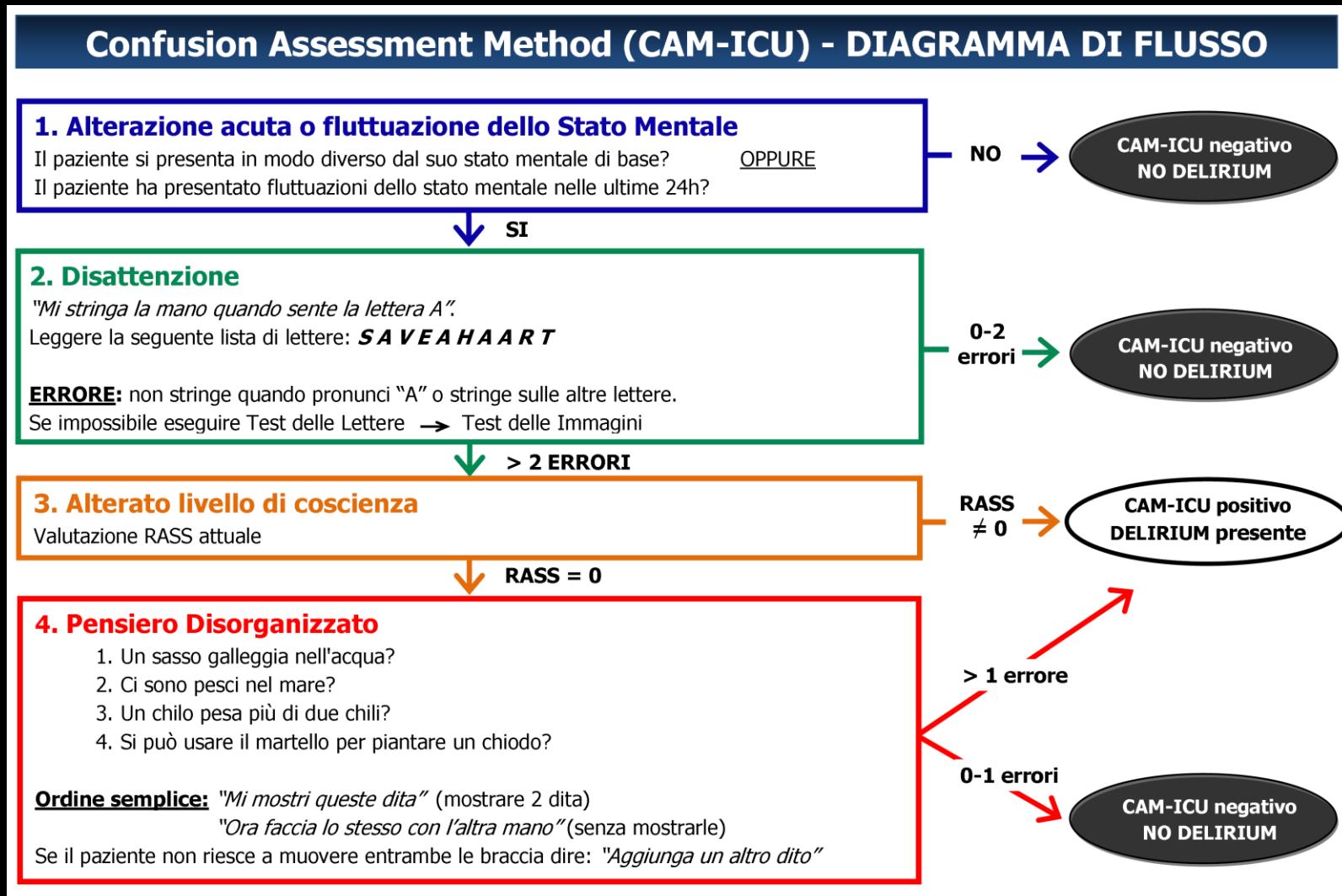
Nessuna risposta alla stimolazione tattile/dolorosa

Sessler CN, Gosnell MS, Grap MJ, et al.

The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients

Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338-44.

3° Delirium



www.icudelirium.org

ICU Delirium
and COGNITIVE IMPAIRMENT STUDY GROUP

VANDERBILT UNIVERSITY
MEDICAL CENTER

MONROE CARELL JR.
Children's Hospital
at Vanderbilt

United States
DEPARTMENT OF VETERANS AFFAIRS



for Medical Professionals

for Patients and Families

Search

GO

Search results powered by Vanderbilt University

ABCDEFs of Prevention and Safety

ABCDEF is a standard bundle of ICU measures that includes spontaneous **Assess for and manage pain**, Both Spontaneous Awakening Trials (SAT) & Spontaneous Breathing Trials (SBT), attention to the **Choice of sedation and analgesia**, **Delirium monitoring and**

[SUPPORT THE RESEARCH](#)

what is Delirium?

Delirium is basically

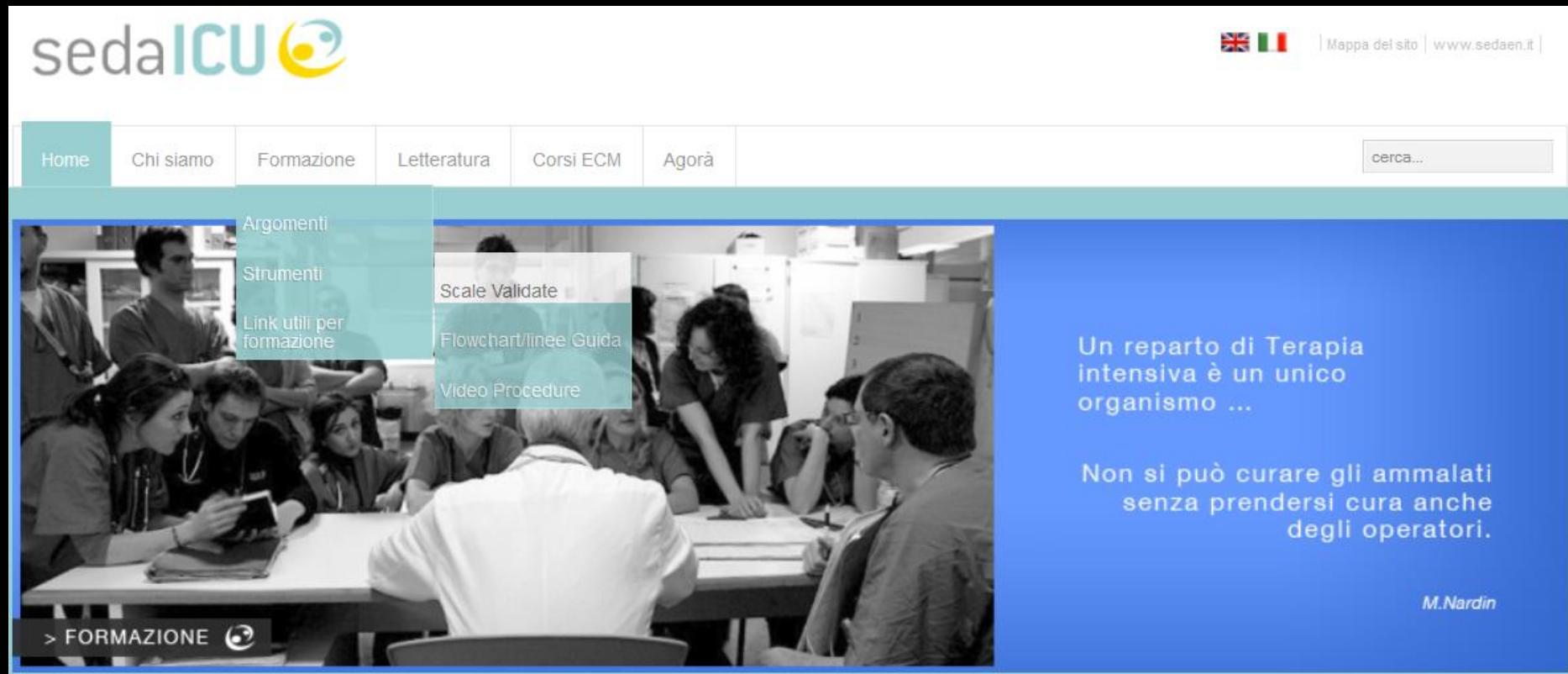
Progetto



per la formazione degli operatori :

www.sedaicu.it

Formazione degli operatori



The screenshot shows the homepage of the sedalCU website. At the top, there is a navigation bar with links for Home, Chi siamo, Formazione, Letteratura, Corsi ECM, Agorà, and a search bar labeled "cerca...". The main content area features a large image of a group of healthcare professionals in a training session. Overlaid on this image are several text elements: "Argomenti", "Strumenti", and "Link utili per formazione" on the left; "Scale Validate", "Flowchart/linee Guida", and "Video Procedure" in the center; and a quote from M. Nardin on the right. The quote reads: "Un reparto di Terapia intensiva è un unico organismo ..." and "Non si può curare gli ammalati senza prendersi cura anche degli operatori."

Home

BENVENUTI su sedalCU !

SedalCU.it è un sito utile a **infermieri e medici di Terapia Intensiva**, per lavorare meglio. L'obiettivo è curare bene i pazienti critici, e così migliorare il loro outcome. Per ottenerlo, gli operatori devono avere occasioni di **formazione efficace**, che li renda più soddisfatti e più competenti.

Siamo davanti ad una grande sfida, un cambio epocale nell'approccio ai pazienti critici: non più "sedati"

Stiamo assistendo in Terapia Intensiva ad una profonda sfida culturale: pazienti svegli, parenti presenti, staff consapevole dei limiti e delle possibilità. Non è facile "cambiare testa", ma è il primo passo per stare meglio. Tutti.

Disponibilità 24/7

Materiale utile al lavoro quotidiano

   | Mappa del sito | www.sedaen.it |

[Home](#) [Chi siamo](#) [Formazione](#) [Letteratura](#) [Corsi ECM](#) [Agorà](#) cerca...

[Home](#) ▶ [Formazione](#) ▶ [Strumenti](#) ▶ [Scale Validate](#)

Scale Validate - strumenti "pronti all'uso"

In questa pagina puoi trovare dei files immediatamente utili per il tuo lavoro quotidiano.
Se vuoi, [aggiungi questa pagina ai preferiti del tuo browser!](#)

Per misurare il dolore:

- [Verbal Numeric Rating \(VNR\)](#)
- [Behavioral Pain Scale \(BPS\)](#)

Per misurare sedazione ed agitazione:

- [Richmond Agitation Sedation Scale \(RASS\) - scheda di pronto utilizzo](#)
- [Tavola sinottica delle scale di sedazione/agitazione](#)
- [Protocollo ABC \(Girard TD, Lancet 2008\)](#)

Per misurare il delirium:

- [Livello di coscienza e funzionamento cognitivo](#)
- [Confusion Assessment Method for the ICU \(CAM-ICU\) - manuale di istruzioni](#)
- [CAM-ICU - spiegazione breve](#)
- [CAM-ICU - scheda di lavoro](#)
- [CAM-ICU - diagramma di flusso](#)
- [CAM-ICU - schede tascabili](#)
- [CAM-ICU - 10 consigli da tenere sempre a mente](#)
- [CAM-ICU - scheda per valutazioni crociate](#)



Un reparto di Terapia Intensiva è un unico organismo... Non si può curare gli ammalati senza prendersi cura anche degli operatori.

Link veloci

Gestire il dolore

 [Flowchart dolore](#)

Il problema più
frequente è il paziente
troppo sedato!

MONITORAGGIO NEUROLOGICO

		infermieri					
medici		Mattino	Pome	Notte			
	Dolore (num + lett)						
	Ansia						
	Contenzione	si	no	si	no	si	no
	RASS						
	Sonno (ore)						
	Agitazione (ore)						
	CAM-ICU (Delirium)	+	-	+	-	+	-
	Valutazione tp. sedativa	I	A	E	I	A	E

BPS
da 3 (minimo)
a 12 (massimo)

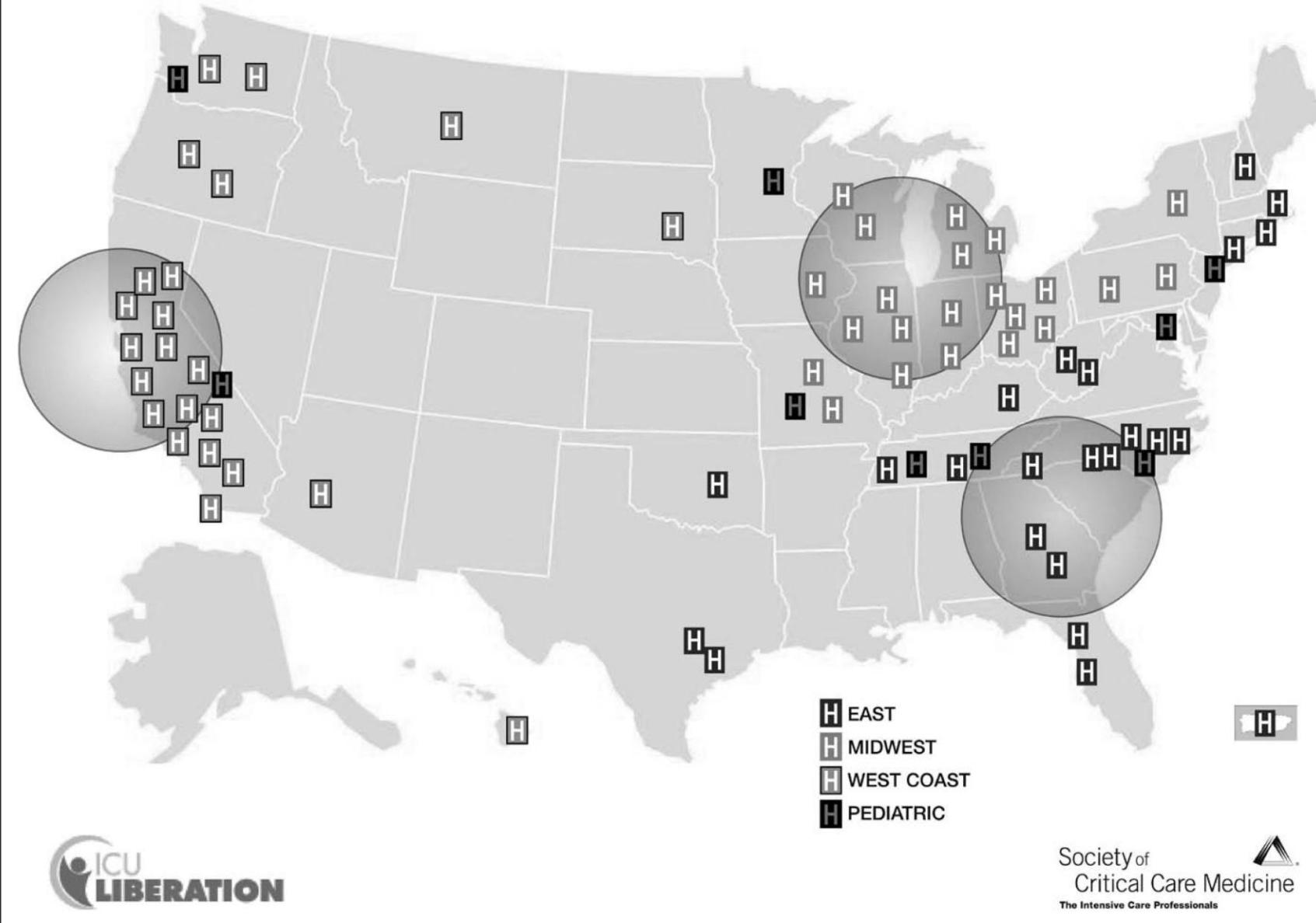
VNR
da 0 (minimo)
a 10 (massimo)

da - 5 (minimo)
a + 4 (massimo)

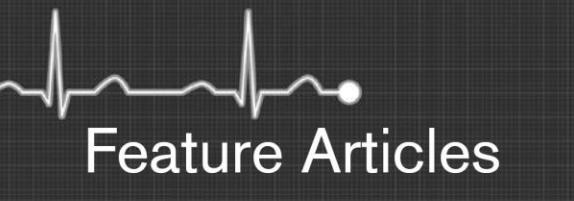
I - insufficiente
A - adeguata
E - eccessiva

- A** ssess for and manage pain
- B** oth spontaneous awakening and breathing trials
- C** hoice of sedation and analgesia
- D** elirium: assess, prevent and manage
- E** arly mobility and exercise
- F** amily engagement and empowerment

ICU Liberation Hospitals and Regions



WEly, Crit Care Med 2017



Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults

Brenda T. Pun, DNP, RN, FCCM¹; Michele C. Balas, PhD, RN, CCRN-K, FCCM, FAAN^{2,3}; Mary Ann Barnes-Daly, MS, RN, CCRN-K, DC⁴; Jennifer L. Thompson, MPH⁵; J. Matthew Aldrich, MD⁶; Juliana Barr, MD, FCCM^{7,8}; Diane Byrum MSN, RN, CCRN-K, CCNS, FCCM⁹; Shannon S. Carson, MD¹⁰; John W. Devlin, PharmD, FCCM¹¹; Heidi J. Engel, PT, DPT¹²; Cheryl L. Esbrook, OTR/L, BCPR¹³; Ken D. Hargett, MHA, FAARC, FCCM¹⁴; Lori Harmon, RRT, MBA, CPHQ¹⁵; Christina Hielsberg, MA¹⁵; James C. Jackson, PsyD¹; Tamra L. Kelly, BS, RRT, MHA⁴; Vishakha Kumar, MD, MBA¹⁵; Lawson Millner, RRT¹⁶; Alexandra Morse, PharmD⁴; Christiane S. Perme, PT, CCS, FCCM¹⁴; Patricia J. Posa, BSN, MSA, CCRN-K¹⁷; Kathleen A. Puntillo, PhD, RN, FCCM, FAAN¹⁸; William D. Schweickert, MD¹⁹; Joanna L. Stollings, PharmD, FCCM²⁰; Alai Tan, PhD²; Lucy D'Agostino McGowan, PhD²¹; E. Wesley Ely, MD, MPH, FCCM^{1,22}

Objective: Decades-old, common ICU practices including deep sedation, immobilization, and limited family access are being challenged. We endeavoured to evaluate the relationship between ABCDEF bundle performance and patient-centered outcomes in critical care.

Design: Prospective, multicenter, cohort study from a national quality improvement collaborative.

Setting: 68 academic, community, and federal ICUs collected data during a 20-month period.

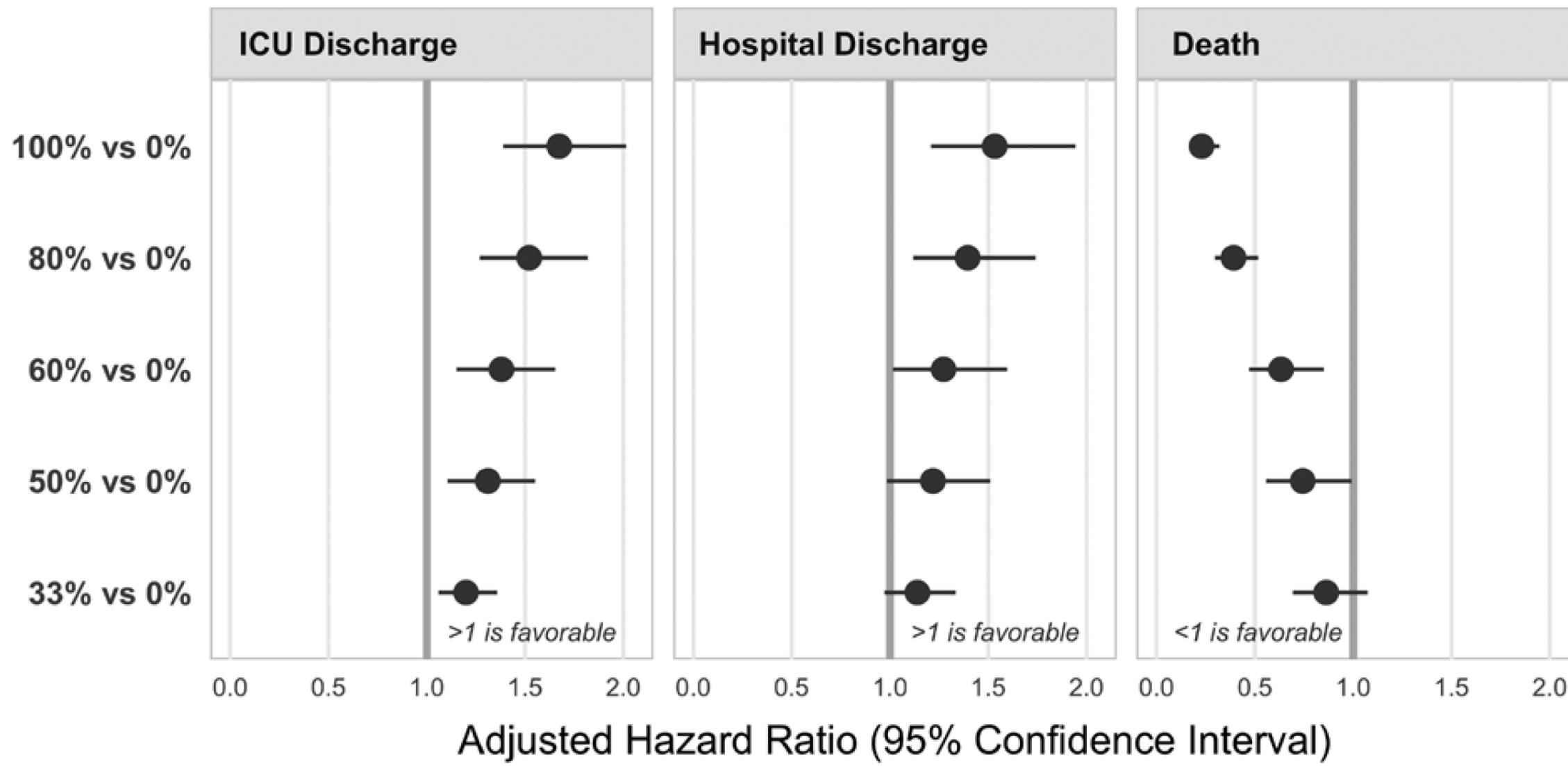
Patients: 15,226 adults with at least one ICU day.

Interventions: We defined ABCDEF bundle performance (our main exposure) in two ways: 1) complete performance (patient received every eligible bundle element on any given day) and 2) proportional performance (percentage of eligible bundle elements performed on any given day). We explored the association between complete and proportional ABCDEF bundle performance and three sets of outcomes: patient-related (mortality, ICU and hospital discharge), symptom-related (mechanical ventilation, coma, delirium, pain, restraint use), and system-related (ICU readmission, discharge destination). All models were adjusted for a minimum of 18 a priori determined potential confounders.

TABLE 2. Outcomes for Patients With Complete (vs Incomplete) ABCDEF Bundle Performance: Data are Adjusted Hazard Ratios and Adjusted Odds Ratios

Outcomes	Complete Bundle Performance	p Value
Patient-Related Outcomes	Adjusted Hazard Ratio (95% CI)	
ICU discharge ^a	1.17 (1.05–1.30)	< 0.004
Hospital discharge ^b	1.19 (1.01–1.40)	< 0.033
Death ^c	0.32 (0.17–0.62)	< 0.001
Symptom-Related Outcomes^d	AOR (95%CI)	
Mechanical ventilation	0.28 (0.22–0.36)	< 0.0001
Coma	0.35 (0.22–0.56)	< 0.0001
Delirium	0.60 (0.49–0.72)	< 0.0001
Significant pain	1.03 (0.88–1.21)	0.7000
Physical restraints	0.37 (0.30–0.46)	< 0.0001
System-Related Outcomes	AOR (95%CI)	
ICU readmission ^e	0.54 (0.37–0.79)	< 0.001
Discharge destination ^f	0.64 (0.51–0.80)	< 0.001

Proportion of ABCDEF Bundle Elements Performed



- A** ssess for and manage pain
- B** oth spontaneous awakening and breathing trials
- C** hoice of sedation and analgesia
- D** elirium: assess, prevent and manage
- E** arly mobility and exercise
- F** amily engagement and empowerment

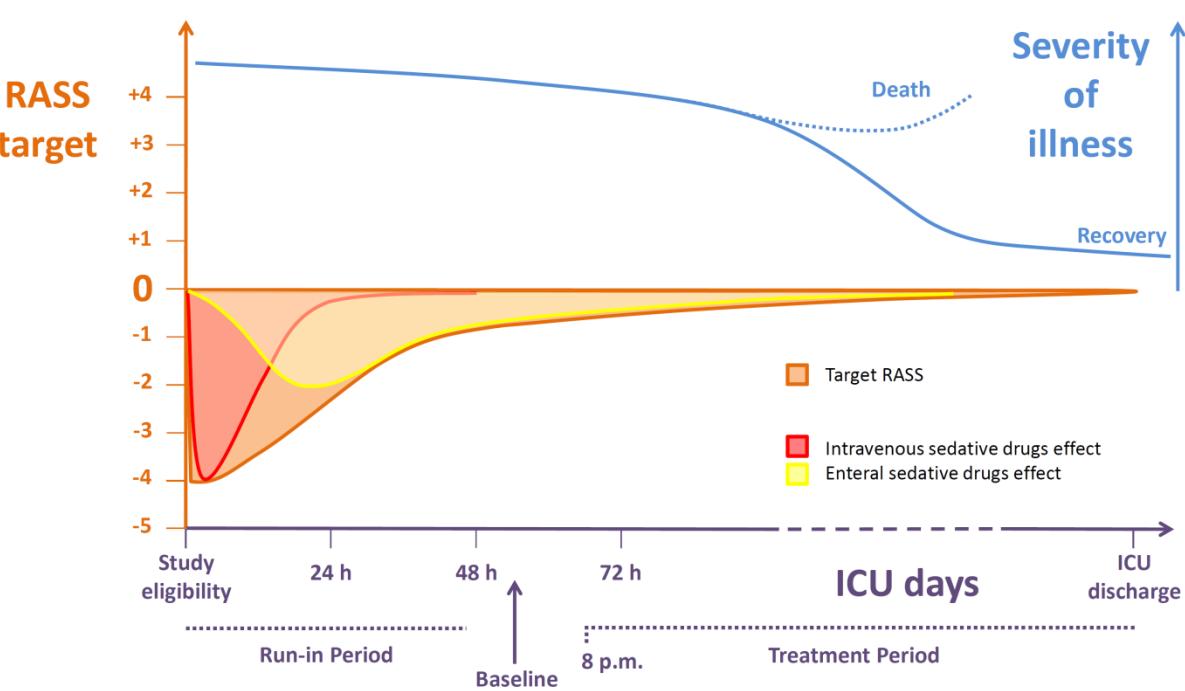


ORIGINAL ARTICLE

Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial

G. MISTRALETTI^{1, 2}, M. UMBRELLO², G. SABBATINI¹, S. MIORI¹, M. TAVERNA¹
B. CERRI², E. S. MANTOVANI², P. FORMENTI², P. SPANU², A. D'AGOSTINO³
S. SALINI⁴, A. MORABITO^{5, 6}, F. FRASCHINI⁷, R. J. REITER⁸, G. IAPICHINO^{1, 2}

¹Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy; ²U.O. Anestesia e Rianimazione, A. O. San Paolo-Polo Universitario, Milan, Italy; ³Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy; ⁴Dipartimento di Economia, Management e Metodi Quantitativi Università



Reasons for sedation

Invasive procedures and clinical stabilization

Use of sedative drugs for «patients adaptation» to critical illnesses (anxiety/agitation, oxygen consumption decrease, compliance with mechanical ventilation, ...)

Drugs provided by local guidelines

Propofol or Midazolam i.v.

Hydroxizine (max 600mg/die) via NGT/NJT

Lorazepam (max 16mg/die) via NGT/NJT

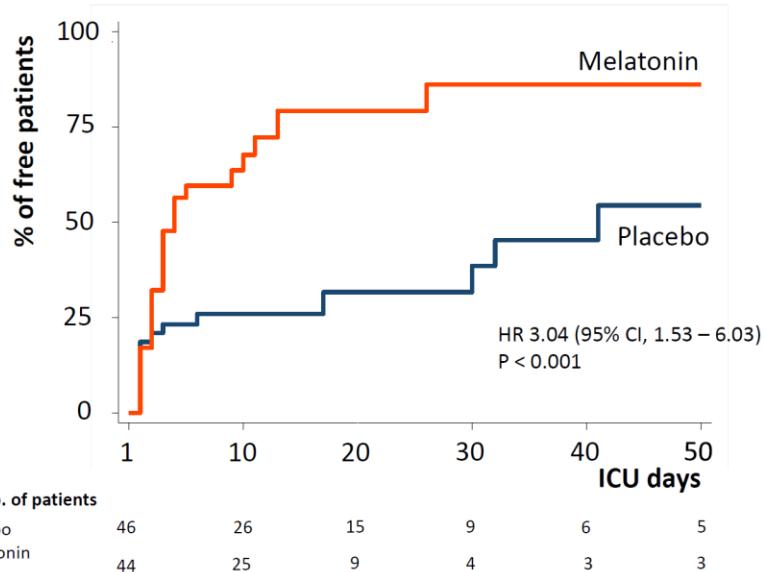
Melatonin (6mg/die) via NGT/NJT

Double-blind RCT

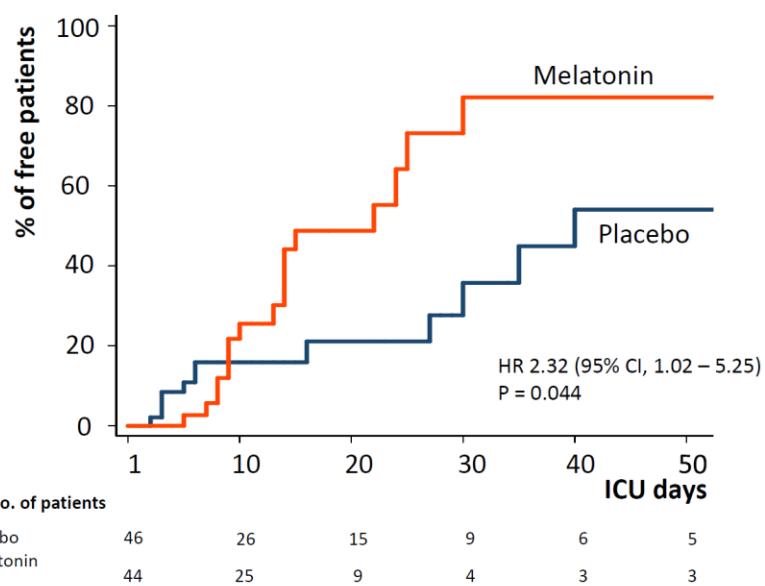
from 3rd ICU day to ICU discharge day

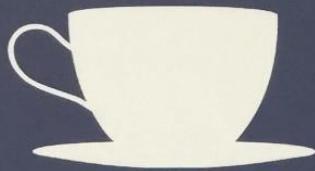
Placebo via NGT/NJT

A Primary outcome: weaning from sedative and analgesic drugs



B Secondary outcome: weaning from mechanical ventilation

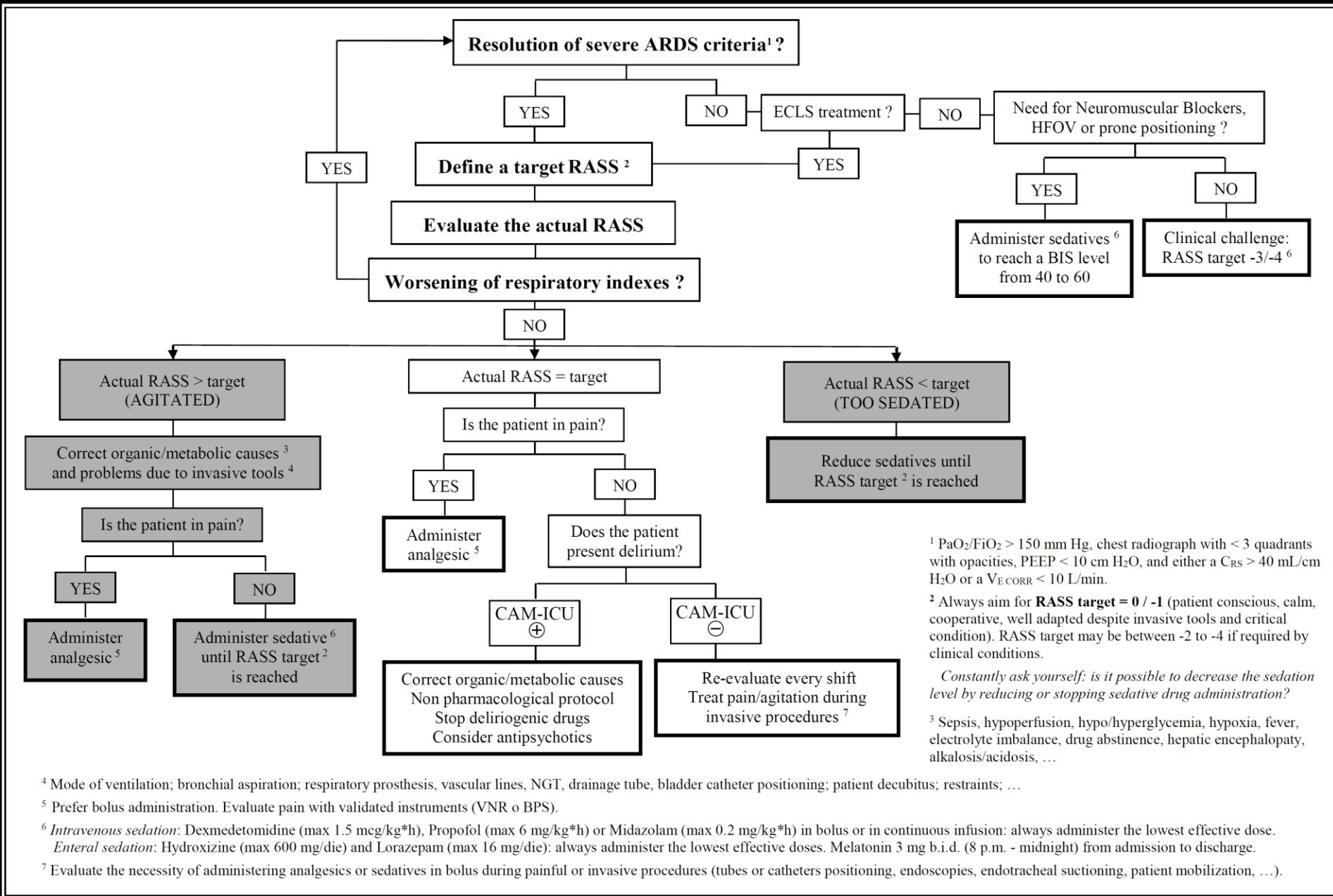




KEEP CALM
USE LESS
AND
TRUST IN
PHYSIOLOGY



... facendo una
«medicina di precisione»,
personalizzata,
in Terapia Intensiva.





Il nostro obiettivo
non può essere solo
aggiungere giorni alla vita.

Dobbiamo mettere
vita in quei giorni.

Grazie dell'attenzione



giovanni.mistraletti@unimi.it

Relazione su: “**sedazione, curarizzazione e monitoraggio**”

1) Quali scale per la misura di sedazione e agitazione hanno migliori proprietà psicometriche?

- a. Scala di Ramsay
- b. RASS e SAS**
- c. Glasgow Coma Scale
- d. CAM-ICU

2) Quali farmaci hanno un effetto protettivo sullo sviluppo di delirium in Terapia Intensiva?

- a. uso analgesico della ketamina al posto degli oppiacei
- b. aloperidolo al posto degli antipsicotici atipici
- c. sedativi non benzodiazepinici al posto delle benzodiazepine**
- d. anestetici inalatori al posto del propofol

3) Quali sono le strategie efficaci nel ridurre la prevalenza e la durata del delirium in Terapia Intensiva?

- a. utilizzare precocemente e mantenere nel tempo un target di sedazione cosciente
- b. implementare programmi di fisioterapia e mobilizzazione del paziente
- c. favorire l'ingresso dei familiari e impostare terapie condivise
- d. tutte le risposte precedenti sono corrette**

Le risposte giuste sono evidenziate in grassetto: 1)b, 2)c, 3)d.

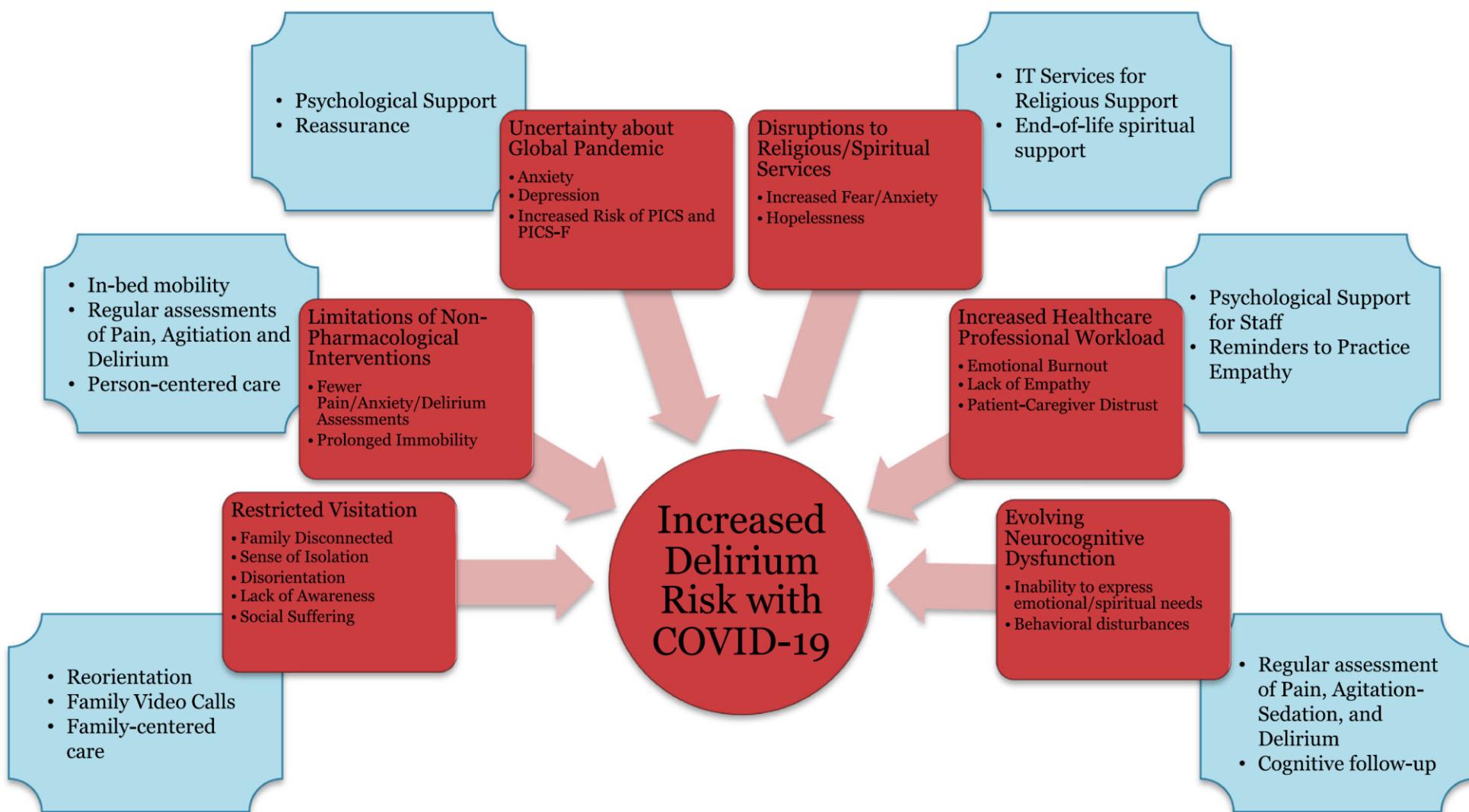


Fig. 1 Potential factors contributing to ICU delirium during the SARS-CoV-2 pandemic

Kotfis et al. *Critical Care* (2020) 24:176
<https://doi.org/10.1186/s13054-020-02882-x>

Critical Care

REVIEW

Open Access

COVID-19: ICU delirium management during SARS-CoV-2 pandemic

Katarzyna Kotfis^{1*}, Shawniqua Williams Roberson^{2,3,4}, Jo Ellen Wilson^{2,5,6}, Wojciech Dabrowski⁷, Brenda T. Pun² and E. Wesley Ely^{2,6,8}



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



Timothy D Girard, Jennifer L Thompson, Pratik P Pandharipande, Nathan E Brummel, James C Jackson, Mayur B Patel, Christopher G Hughes, Rameela Chandrasekhar, Brenda T Pun, Leanne M Boehm, Mark R Elstad, Richard B Goodman, Gordon R Bernard, Robert S Dittus, E W Ely

Summary

Background Delirium during critical illness results from numerous insults, which might be interconnected and yet individually contribute to long-term cognitive impairment. We sought to describe the prevalence and duration of clinical phenotypes of delirium (ie, phenotypes defined by clinical risk factors) and to understand associations between these clinical phenotypes and severity of subsequent long-term cognitive impairment.

Lancet Respir Med 2018;
6: 213–22

See Comment page 167

ICU Delirium and Cognitive Impairment Study Group at the

Panel: Delirium phenotypes

Hypoxic delirium

- Hypoxaemia* or
- Shock†

Septic delirium

- Known or suspected infection and
- 2+ systemic inflammatory response syndrome criteria‡

Sedative-associated delirium

- Receipt of benzodiazepine or
- Propofol or
- Opioid or
- Dexmedetomidine

Metabolic delirium

- Blood urea nitrogen >17.85 mmol/L or
- Glucose <2.5 mmol/L or
- International normalised ratio > 2.5 and [aspartate transaminase or alanine transaminase] >200 U/L or
- Sodium <120 mmol/L or
- Sodium >160 mmol/L

Unclassified delirium

- None of the above

*Two or more 15 min intervals during which lowest blood oxygen saturation level was <90%. †Lactate >4.4 mmol/L or two or more 15 min intervals during which lowest mean arterial pressure was <65 mm Hg. ‡Temperature >38°C or <36°C, heart rate > 90 beats per minute, respiratory rate higher than 20 breaths per min or PaCO_2 <32 mm Hg, or leucocyte count >12 000/mm³ or <4000/mm³.

	Enrolment cohort (n=1040)	Follow-up cohort (n=586)	APACHE II at ICU admission	24 (18–30)	23 (17–29)
Age (years)	62 (53–72)	61 (52–70)	SOFA at enrolment	9 (7–11)	8 (7–11)
Race			Mean daily SOFA in the ICU	7·2 (5·7–9·6)	6·6 (5·3–8·5)
White	946 (91%)	524 (89%)	Mechanically ventilated		
African American	87 (8%)	59 (10%)	Ever	923 (89%)	516 (88%)
Sex			Days after enrolment‡	3·1 (1·0–8·6)	2·2 (1·0–6·0)
Women	413 (40%)	239 (41%)	Benzodiazepine exposure		
Men	627 (60%)	347 (59%)	Ever	686 (66%)	364 (62%)
Education (years)	12 (12–14)	12 (12–14)	Mean 24 h dose in ICU (mg)‡§	5·8 (1·2–19·0)	5·7 (1·5–18·3)
Short ICODE	3·00 (3·00–3·12)	3·00 (3·00–3·12)	Opioid exposure		
Pre-existing cognitive impairment*	66 (6%)	35 (6%)	Ever	834 (80%)	458 (78%)
Charlson Comorbidity Index	2 (1–4)	2 (1–4)	Mean 24 h dose in ICU (μcg)‡¶	550 (148–1442)	586 (153–1307)
Admission diagnosis			Propofol exposure		
Sepsis/ARDS	373 (36%)	202 (34%)	Ever	521 (50%)	299 (51%)
Surgery	168 (16%)	100 (16%)	Mean 24 h dose in ICU (mg)‡	655 (185–1648)	589 (185–1578)
COPD, asthma, or other pulmonary disease†	134 (13%)	72 (12%)	Dexmedetomidine exposure		
Congestive heart failure, myocardial infarction, or cardiogenic shock	161 (15%)	92 (16%)	Ever	128 (12%)	79 (13%)
Airway protection	109 (10%)	62 (11%)	Mean 24 h dose in ICU (μcg)‡	147 (46–386)	139 (48–369)
Other	95 (9%)	52 (9%)	Length of stay (days)		
APACHE II at ICU admission	24 (18–30)	23 (17–29)	ICU	5·0 (2·8–11·1)	4·9 (2·7–10·0)
SOFA at enrolment	9 (7–11)	8 (7–11)	Hospital	10·0 (5·9–17·2)	10·0 (6·1–18·0)
Mean daily SOFA in the ICU	7·2 (5·7–9·6)	6·6 (5·3–8·5)			
Mechanically ventilated					
Ever	923 (89%)	516 (88%)			
Days after enrolment‡	3·1 (1·0–8·6)	2·2 (1·0–6·0)			
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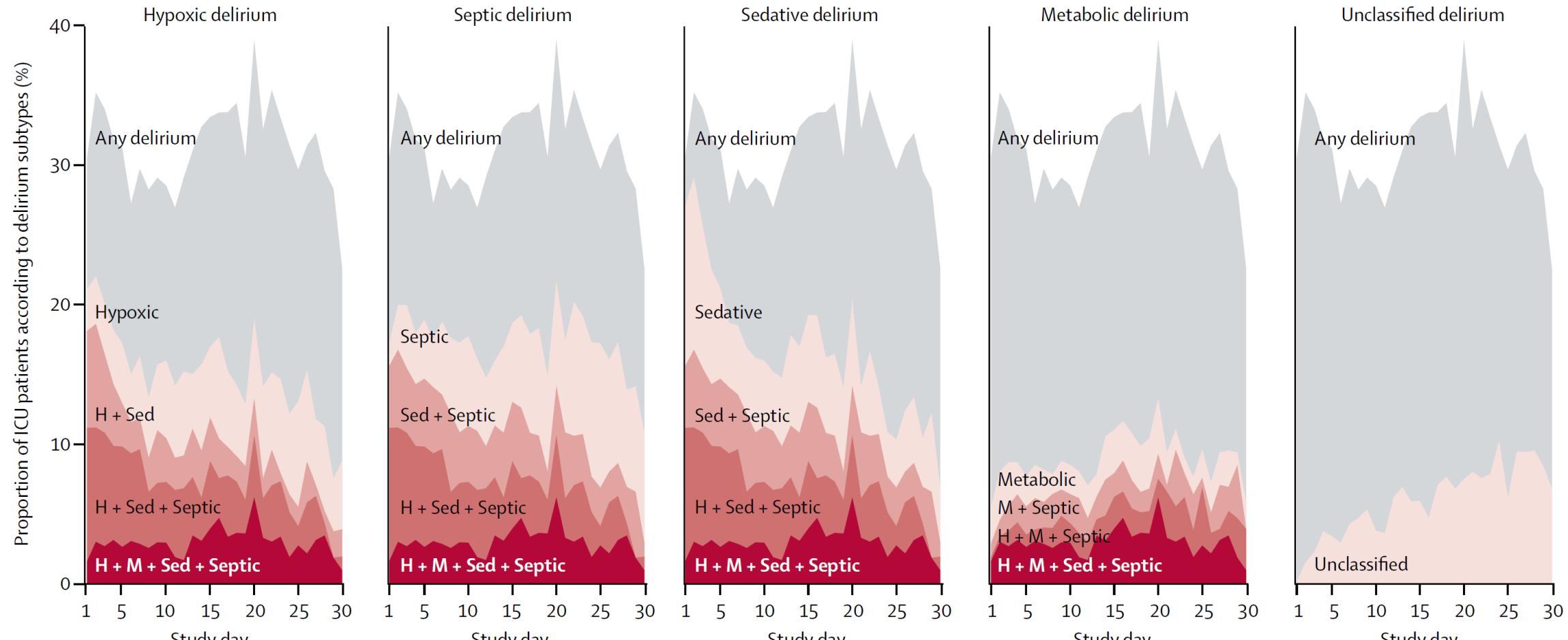
Data are median (IQR) or n/total (%). ARDS=acute respiratory distress syndrome. COPD=chronic obstructive pulmonary disease. ICU=intensive care unit. ICODE=Informant Questionnaire on Cognitive Decline in the Elderly. SOFA=Sequential Organ Failure Assessment. APACHE=Acute Physiologic Assessment and Chronic Health Evaluation. *Short ICODE >3·6. †Including pulmonary embolus and pulmonary fibrosis. ‡Among those exposed. §In midazolam equivalents. ¶In fentanyl equivalents.

Table 1: Participant characteristics

	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



Patients alive and in hospital

1038	905	575	353	226	145	102
1038	905	575	353	226	145	102
1038	905	575	353	226	145	102
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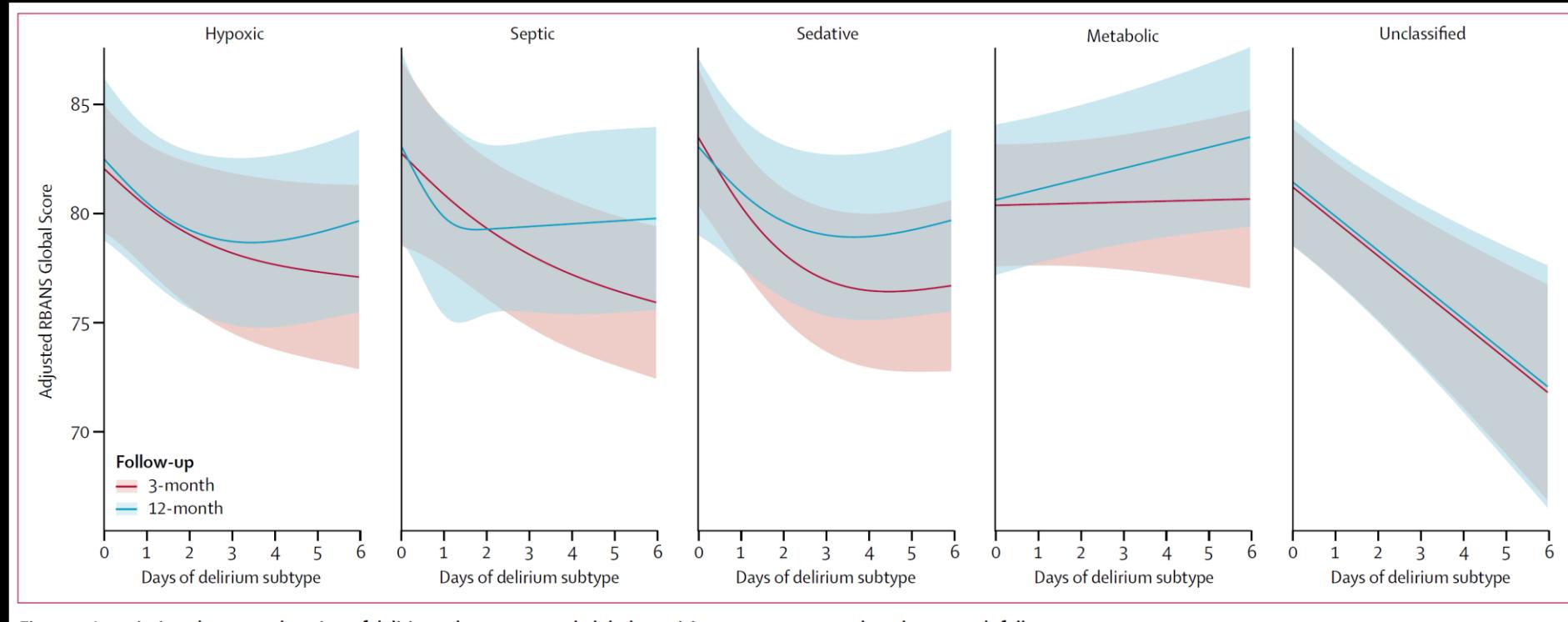


Figure 2: Associations between duration of delirium phenotypes and global cognition scores at 3-month and 12-month follow-up

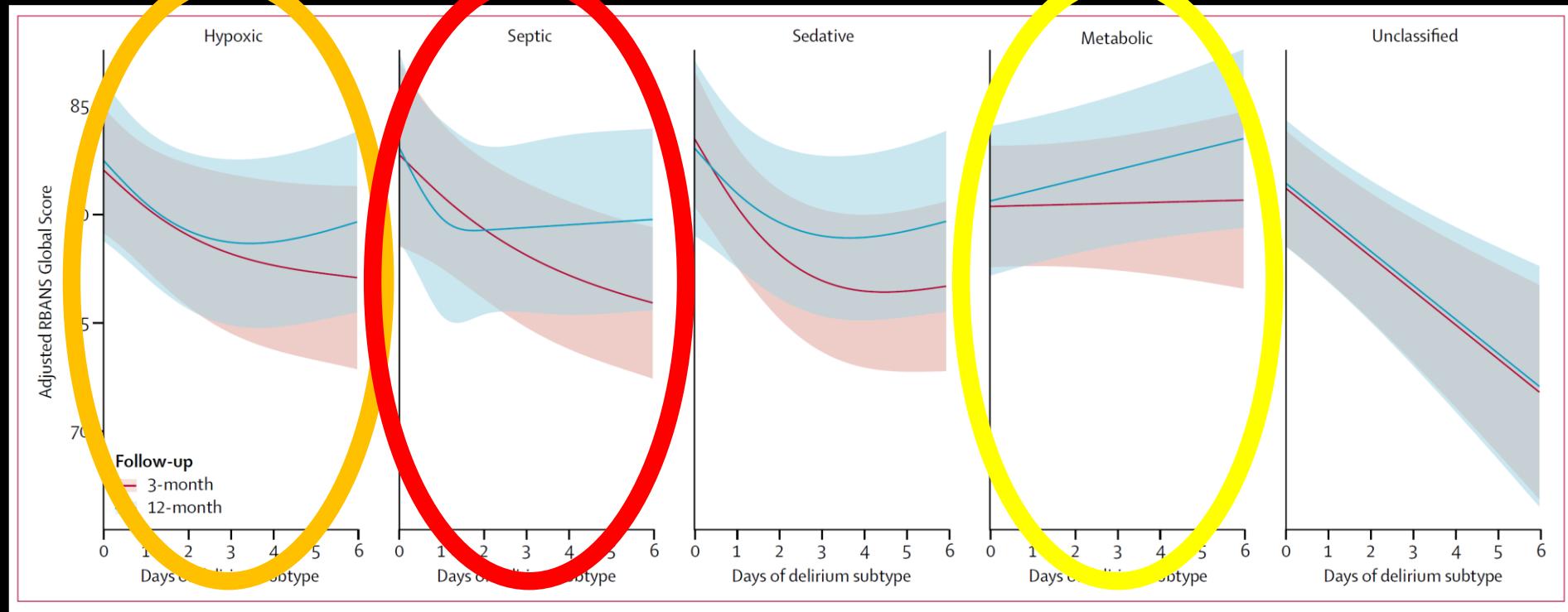


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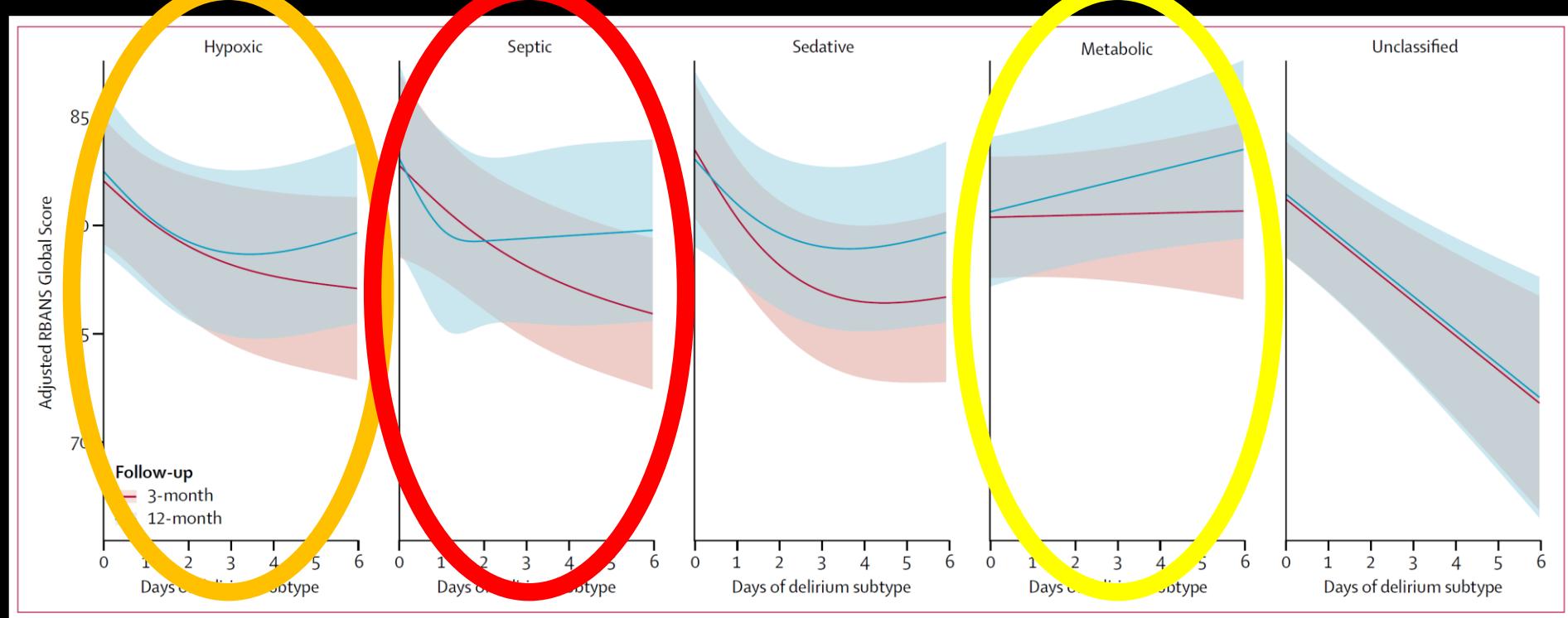
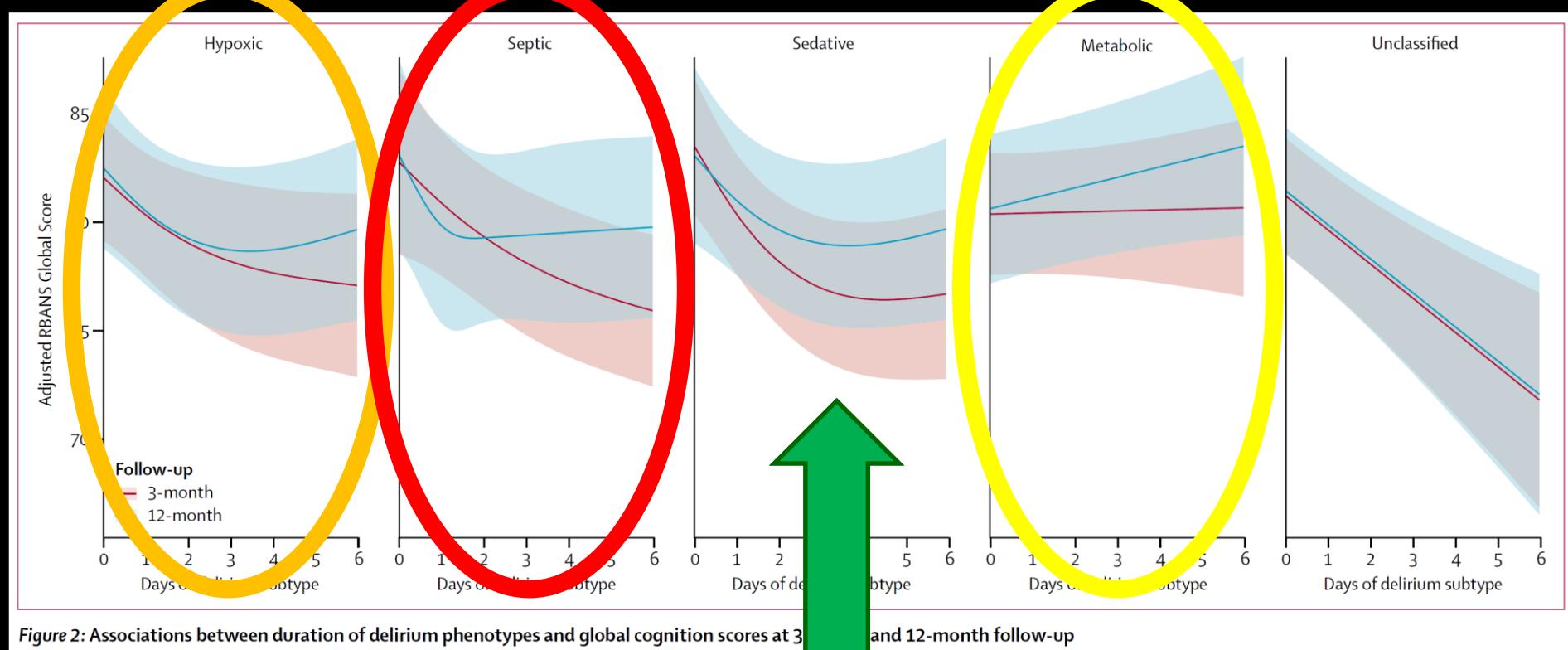


Figure 2: Associations between duration of delirium phenotypes and global cognition scores at 3-month and 12-month follow-up



Illness



delirio (in italiano):

Convinzione errata che non cede alle critiche e all'evidenza dei fatti.

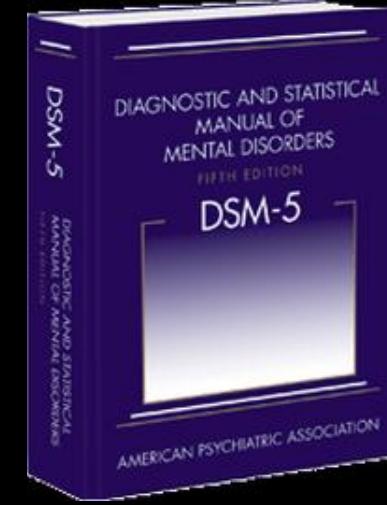
Profonda distorsione nella percezione soggettiva della realtà, tipicamente accompagnata da inappropriato senso di potere, che non rientra grazie al ragionamento...

Corrisponde all'inglese: delusion or hallucination

delirium (in italiano):

Modificazione acuta dello stato di coscienza o
decorso fluttuante, con disattenzione, e pensiero
disorganizzato o alterato livello di coscienza.

Corrisponde all'inglese: delirium



DSM-5: diagnostic criteria for delirium

Intensive Care Med (2008) 34:1907–1915
DOI 10.1007/s00134-008-1177-6

CLINICAL COMMENTARY

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A. C. Trompeo
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L. Gattinoni

**Understanding international differences
in terminology for delirium and other types
of acute brain dysfunction in critically ill
patients**

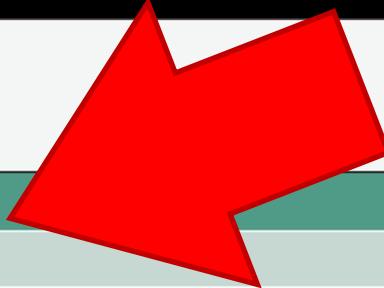
TABLE 1**DSM-5 CRITERIA FOR DELIRIUM DIAGNOSES**

Delirium	
A. There is an alteration in attention and awareness.	
B. The alteration represents an abrupt change from the client's baseline and fluctuates throughout the day.	
C. There is also an alteration in the client's cognition.	
D. The alterations in Criteria A and C are not better accounted for by another disorder.	
E. There is physical evidence that the alteration is caused by a medical condition, substance, or a variety of causes.	
Specifiers	
Substance intoxication delirium	Rather than substance intoxication, this diagnosis is made when the predominate symptoms are from Criteria A and C and are severe enough to constitute a medical emergency.
Substance withdrawal delirium	Rather than substance withdrawal, this diagnosis is made when the predominate symptoms are from Criteria A and C and are severe enough to constitute a medical emergency.

Note. DSM-5 = Diagnostic and Statistical Manual of Mental Disorders (5th ed.).

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«Dietro ogni problema
c'è un'opportunità»

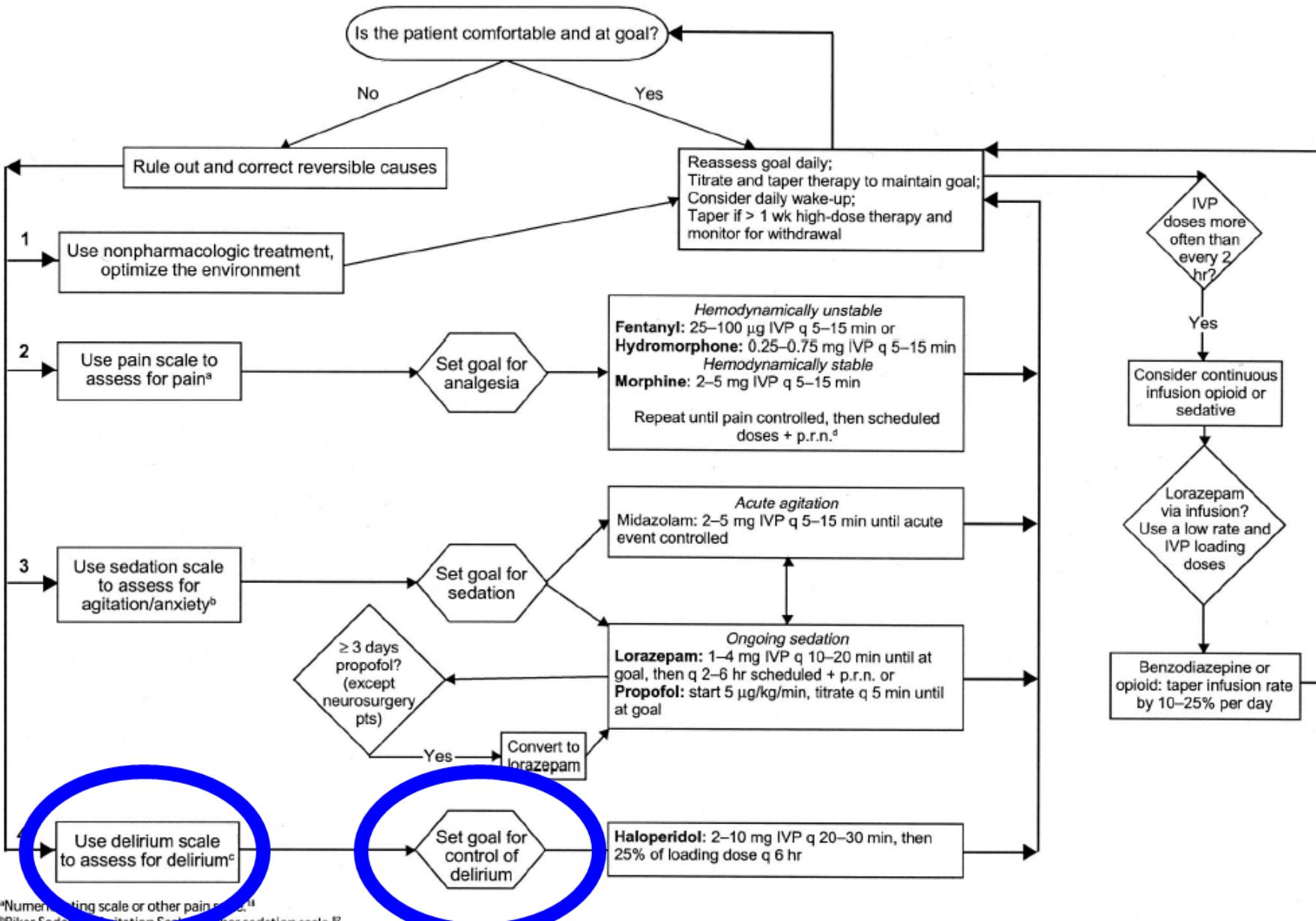
Guidelines SCCM 2002

Task-force for ICU analgesia & sedation

Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult

Judith Jacobi, PharmD, FCCM, BCPS; Gilles L. Fraser, PharmD, FCCM; Douglas B. Coursin, MD; Richard R. Riker, MD; Dorrie Fontaine, RN, DNSc, FAAN; Eric T. Wittbrodt, PharmD; Donald B. Chalfin, MD, MS, FCCM; Michael F. Masica, MD, MPH; H. Scott Bjerke, MD; William M. Coplin, MD; David W. Crippen, MD, FCCM; Barry D. Fuchs, MD; Ruth M. Kelleher, RN; Paul E. Marik, MDBCh, FCCM; Stanley A. Nasraway, Jr, MD, FCCM; Michael J. Murray, MD, PhD, FCCM; William T. Peruzzi, MD, FCCM; Philip D. Lumb, MB, BS, FCCM. Developed through the Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), in collaboration with the American Society of Health-System Pharmacists (ASHP), and in alliance with the American College of Chest Physicians; and approved by the Board of Regents of ACCM and the Council of SCCM and the ASHP Board of Directors

Crit Care Med 2002, 30 (1) 119-141



^aNumerical rating scale or other pain scale.⁴

^bRiker Sedation-Agitation Scale or other sedation scale.¹²

^cConfusion Assessment Method for the ICU.¹⁵

^dSee Table 1 for intermittent dosing for specific agents.

Peter E. Spronk
Bea Riekerk
José Hofhuis
Johannes H. Rommes

Occurrence of delirium is severely underestimated in the ICU during daily care

Table 2 Comparison between doctors and nurses with respect to the detection of delirium during 425 observation days in 46 ICU patients when the Confusion Assessment Method for the ICU (CAM-ICU) serves as the diagnostic standard

Clinical judgement of delirium presence	All observations (n = 425)		Comatose state	Hypoactive state		Active state		Hyperactive state	
			RASS -5/-4	RASS -3/-2/-1		RASS 0/+1		RASS +2/+3/+4/+5	
			(n = 105)	(n = 121)		(n = 196)		(n = 3)	
	Yes	No	NA	Yes	No	Yes	No	Yes	No
Nurse	CAM: +	31	58	0	21	28	9	29	1
	CAM: -	3	169	2	1	14	2	153	0
	CAM: NA	163	103	1	56	0	3	0	1
	Sensitivity	0.35	—	0.43	—	0.24	—	—	—
	Specificity	0.99	—	0.93	—	0.99	—	—	—
	PPV	0.91	—	0.95	—	0.82	—	—	—
	NPV	0.74	—	0.33	—	0.84	—	—	—
Physician	CAM: +	25	64	0	14	35	9	29	2
	CAM: -	0	172	2	0	15	0	155	0
	CAM: NA	163	103	1	56	0	3	0	1
	Sensitivity	0.28	—	0.29	—	0.24	—	—	—
	Specificity	0.99	—	1.00	—	1.00	—	—	—
	PPV	1.00	—	1.00	—	1.00	—	—	—
	NPV	0.73	—	0.30	—	0.84	—	—	—

NPV negative predictive value; PPV positive predictive value; NA not applicable



Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

Crit Care Med 2013, 41: 263-306

Assessment of ICU Patients

Patient Comfort		
Pain	Sedation	Delirium
<ul style="list-style-type: none">• 0-10 ScaleVAS-Pain<ul style="list-style-type: none">• BPS•PAINAD	Sedation Assessment Scales (RASS, SAS, MAAS, ...)	CAM-ICU IC-DSC

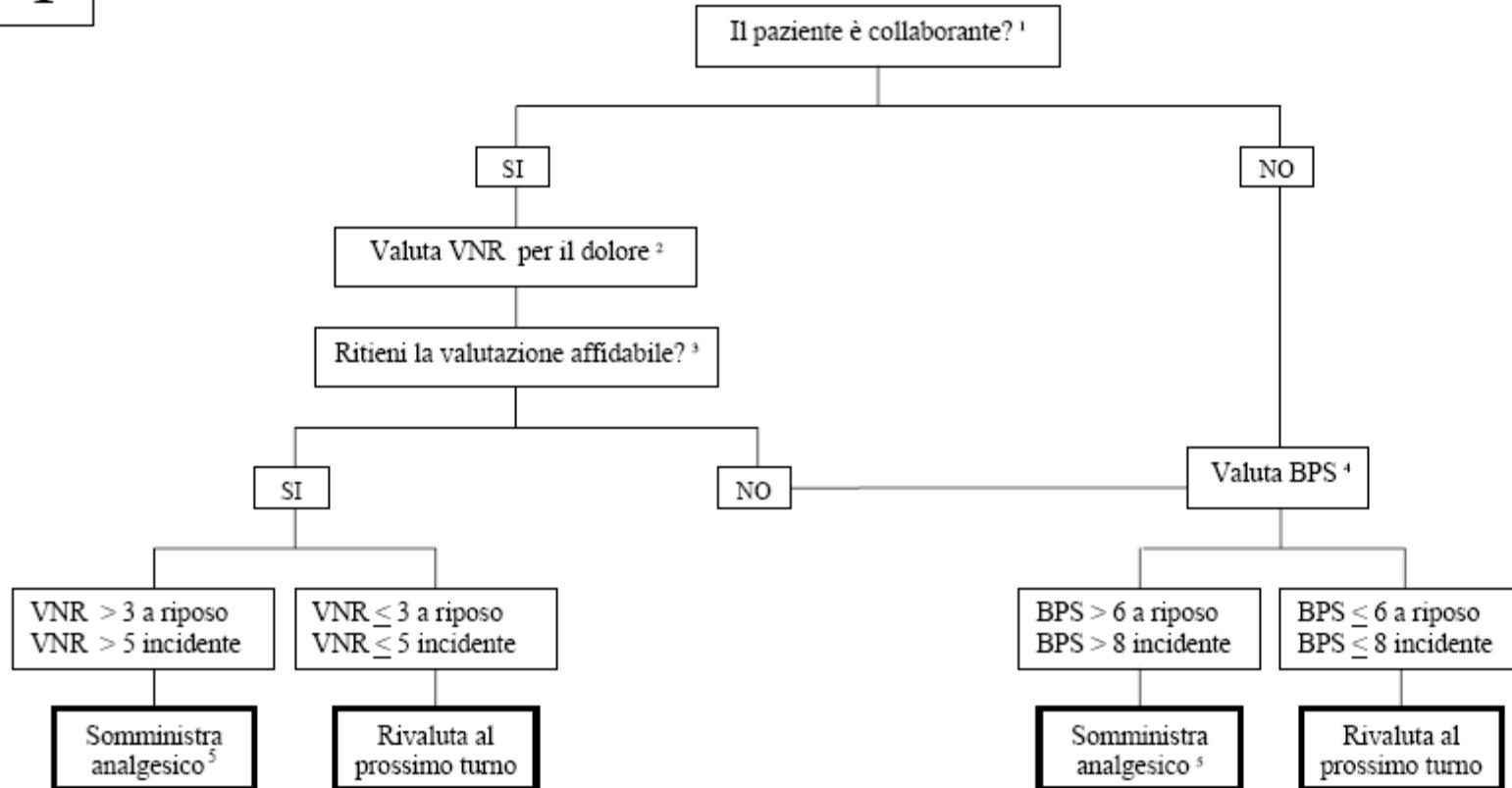
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GESTIONE DEL DOLORE IN TERAPIA INTENSIVA



¹ Considera non collaborante se: RASS < -2 / CAM-ICU \oplus / presenza di patologie psichiatriche / deficit neurologici / incompatibilità linguistiche / sordità.

² *Verbal Numeric Rating (VNR)* 0 = dolore assente, 10 = massimo dolore immaginabile.

Chiedi: "Quanto è il suo dolore adesso, fra 0 e 10?".

Considera sia il dolore a riposo che il dolore incidente (es.: colpo di tosse, bronco aspirazione, ...).

³ Una rilevazione è affidabile se tiene conto dei parametri soggettivi con cui il paziente valuta il suo dolore: aspetti culturali, familiari, religiosi, presenza di vantaggi secondari.

⁴ *Behavioral Pain Scale (BPS)* 3 = dolore assente, 12 = massimo dolore

- *Espressione Facciale*: 1. Rilassata / 2. Fronte Aggrottata / 3. Occhi chiusi / 4. Digrignante

- *Arti Superiori*: 1. Immobili / 2. Piegati / 3. Contratti / 4. Retratti

- *Compliance alla Ventilazione*: 1. Adattato / 2. Tossisce / 3. Asincrono / 4. Non ventilabile

⁵ Morfina: endovenosa
Bolo: 0.03 - 0.05 mg/kg ripetibile fino a 40 mg/die – Infusione continua: 5-30 μ g/h.

Fentanyl: endovenosa (da preferire se instabilità emodinamica/ allergia morfina/ insufficienza renale).
Bolo: 1-2/ μ g ripetibile fino a 500 μ g/die – Infusione continua: 1-2/ μ g/h (max 150 μ g/h).

Remifentanil: endovenosa (mai in bolo)
Bolo: mai – Infusione continua: 0.02-0.5/ μ g/min.

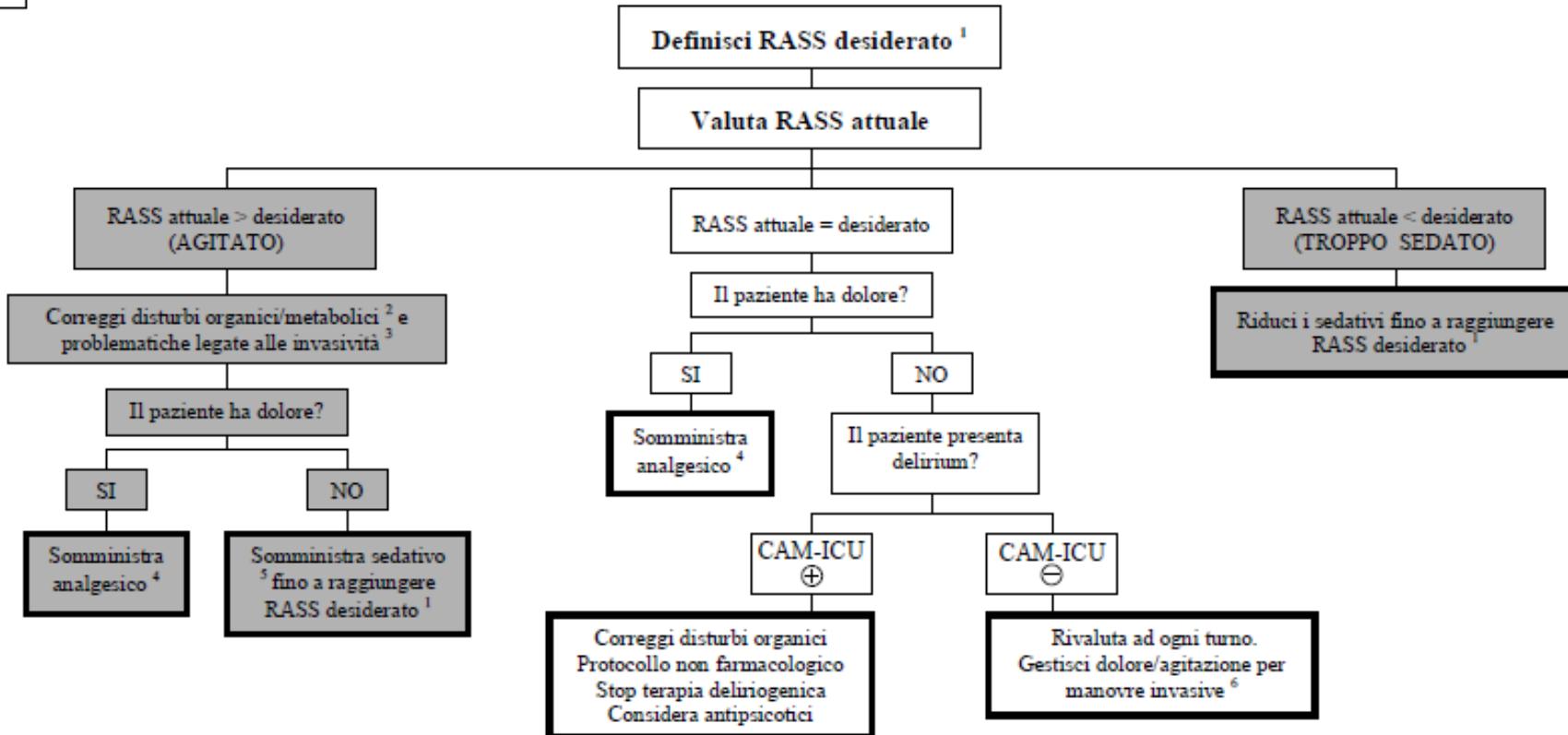
Considera Paracetamolo ev (max 15mg/kg ogni 6 h) / FANS / adiuvanti.

Assessment of ICU Patients

Patient Comfort		
Pain	Sedation	Delirium
<ul style="list-style-type: none">• 0-10 ScaleVAS-Pain• BPS•PAINAD	Sedation Assessment Scales (RASS, SAS, MAAS, ...)	CAM-ICU IC-DSC

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GESTIONE AGITAZIONE/SEDAZIONE IN TERAPIA INTENSIVA



¹ RASS sempre 'desiderato' = 0/-1 cioè paziente cosciente e ben adattato nonostante patologia e invasività.

Se le condizioni cliniche lo richiedono, RASS desiderato può essere fra -2 e -4.

Domanda costante: si può rendere più superficiale il livello di sedazione e quindi ridurre/cessare l'utilizzo di sedativi?

² Sепси, ipoperfusione, ipo/iperglycemia, ipossia, febbre, dislettrolitemie, astinenza, encefalopatia epatica, acidosi/alcalosi,...

³ Modalità di ventilazione; aspirazione secrezioni bronchiali; adeguatezza posizionamento protesi respiratorie, incannulamenti vascolari, SNG, tubi di drenaggio, CV; decubito del paziente; mezzi di contenzione fisica,...

⁴ Preferisci somministrazione a boli. Stima con strumenti validati (VNR o BPS).

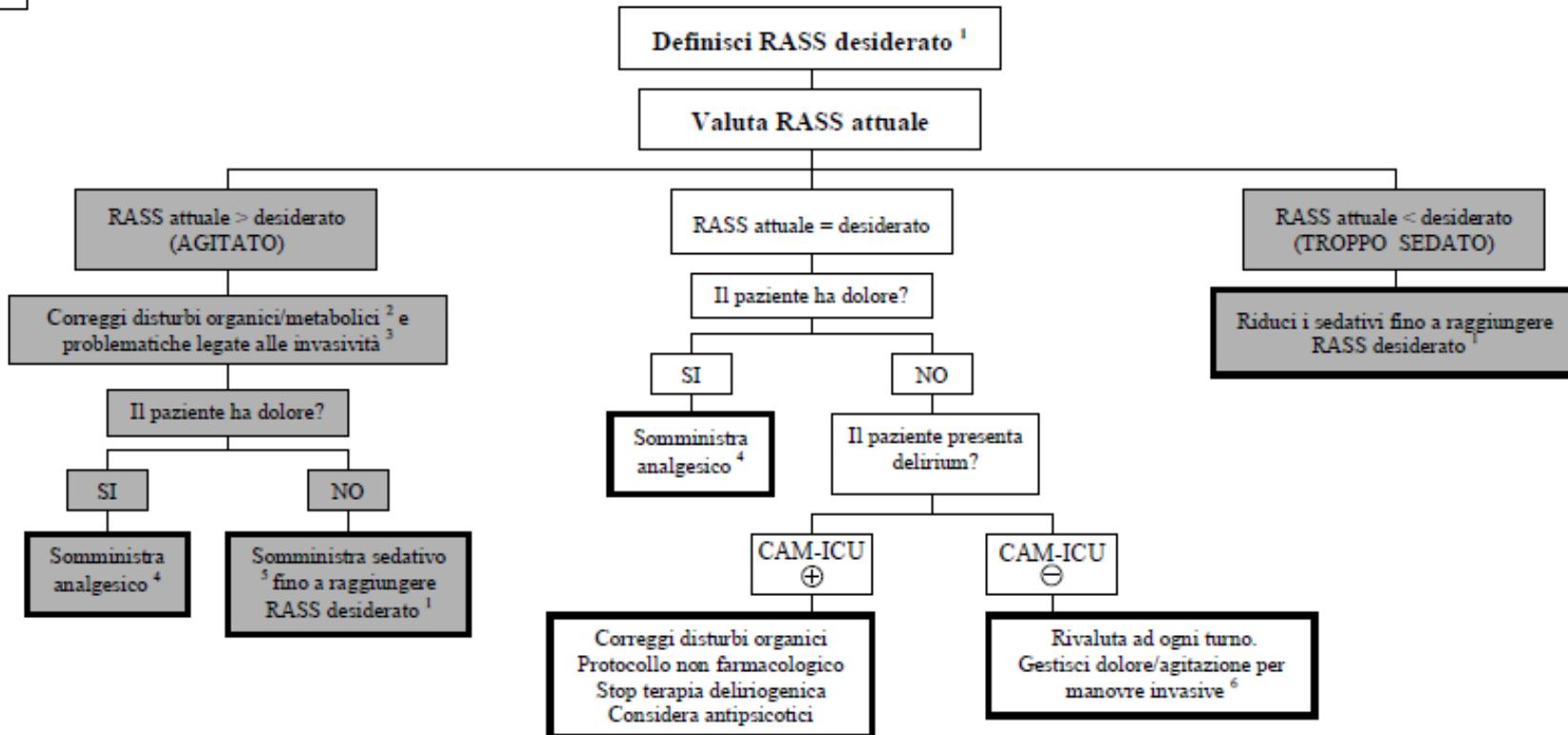
⁵ Sedazione endovenosa: Propofol (max 6 mg/kg*h) o Midazolam (max 0.2 mg/kg*h) a boli ed eventuale infusione continua: somministra sempre il minimo dosaggio efficace.

Sedazione enterale: Idrossizina (max 600 mg/die) e Lorazepam (max 16 mg/die): somministra sempre il minimo dosaggio efficace.

Melatonina 3 mg per 2 (ore 20 e 24) da ingresso fino a dimissione.

⁶ Valuta necessità di boli di analgesico e/o sedativo durante manovre invasive (posizionamento invasività, endoscopia, indagini diagnostiche, mobilizzazione paziente, ...).

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Domanda costante: si può rendere più superficiale il livello di sedazione e quindi ridurre/stoppare l'utilizzo di sedativi?

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Crit Care Med 2002; 30:119-141

Diagnostic and Statistical Manual of Mental Disorders – 5

Criteria for delirium

TABLE 1

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Adapted from American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (5th ed.). Arlington, VA: Author.

Includes:

- Sedation
- Neurologic dysfunction
- Cognitive dysfunction

Delirium and Outcomes

- Increased ICU Length of Stay (8 vs 5 days)
- Increased Hosp Length of Stay (21 vs. 11 days)
- Increased time on the Ventilator (9 vs 4 days)
- Higher costs (\$22,000 vs \$13,000 in ICU costs)
- Estimated \$4 to \$16 **billion** associated U.S. costs
- 3-fold increased risk of death
- Every delirium day increased by 35%
“ ICU accelerated dementia ”

Ely EW, *Intensive CareMed*, 2001

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Lin SM, *Crit Care Med*, 2004

Milbrandt E, *Crit Care Med*, 2004

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Delirium and mortality

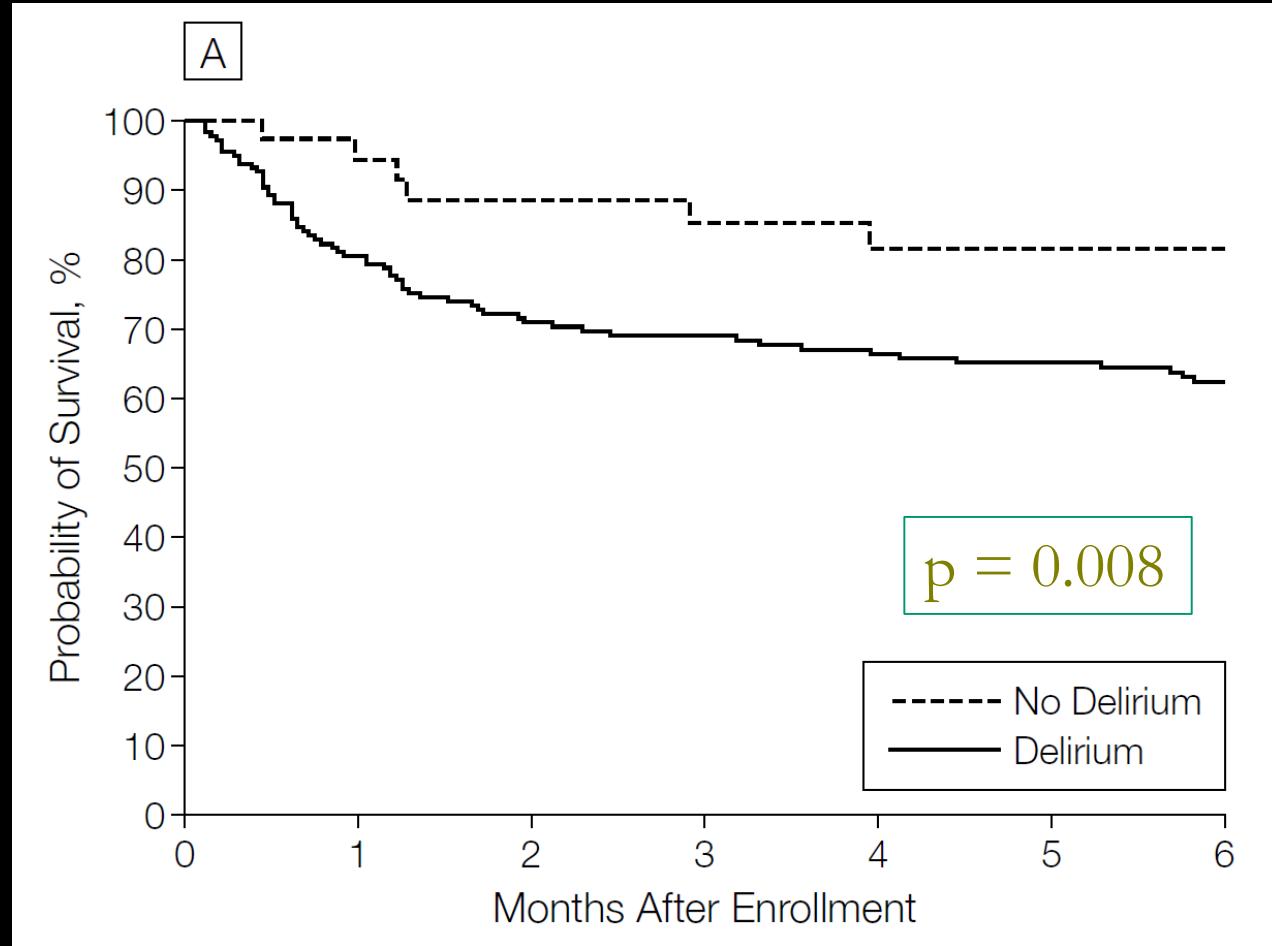
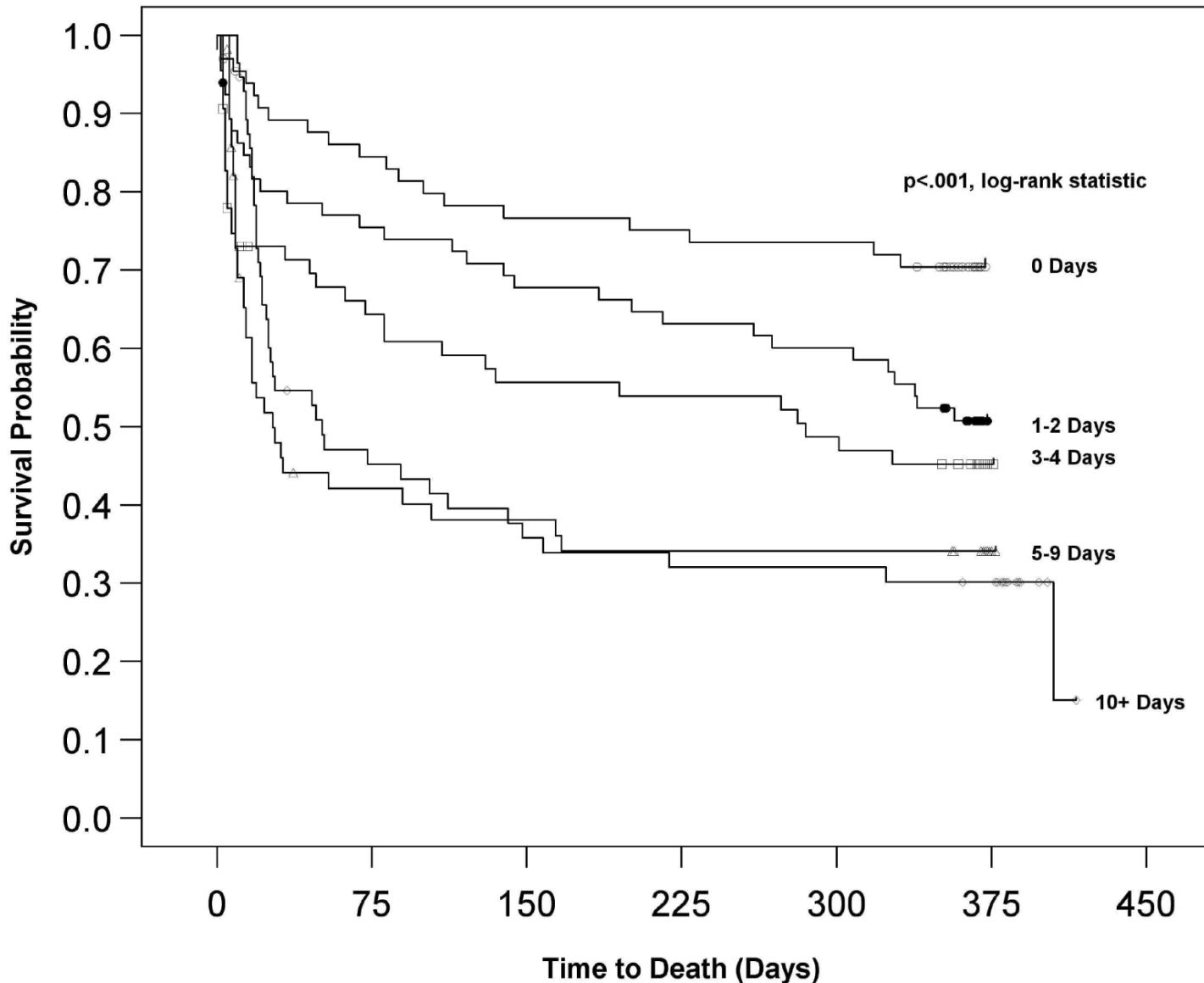
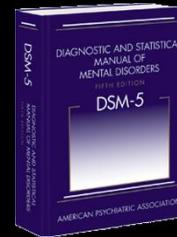


Figure 2. Kaplan-Meier Survival Curves for an ICU Delirium Days Predictor



DSM-5: diagnostic criteria for delirium



Criterion A There is a disturbance in attention and awareness.

Delirium develops over a short period of time, typically hours to days. There is a change in baseline attention and awareness. It fluctuates throughout the day.

Criterion C There is also another disturbance in cognition, such as impaired memory, orientation, language, and perception.

The disturbances in (A.) and (C.) are not better explained by another pre-existing, established, or evolving neurocognitive disorder.

Criterion E There is evidence of the delirium is due to a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies.



Delirium is often ‘invisible’ (unless you look for it)

Different clinical manifestations:

- Vast majority in ICU is hypoactive “quiet” subtype (35%) or mixed (64%)
- Very little (1%) is the pure hyperactive subtype

Older age is a strong predictor of hypoactive

Onset: ICU Day 2 (+/-1.7)

How long: 4.2 (+/-1.7) days

Ely EW et al. JAMA 2001;2710
Peterson J et al. JAGS 2006;54:479-84
Bergeron N, ICM 2001;27:859-64

Ely EW et al. Crit Care Med 2001; 9:1370-1379
McNicoll L et al. JAGS 2003;51:591-98
Ouimet S, ICM 2007;33:1007-1013

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- Very little (1%) is the pure hyperactive subtype

Older age is a strong predictor of hypoactive

Onset: ICU Day 2 (+/-1.7)

How long: 4.2 (+/-1.7) days

Ely EW et al. JAMA 2001;2710
Peterson J et al. JAGS 2006;54:479-84
Bergeron N, ICM 2001;27:859-64

Ely EW et al. Crit Care Med 2001; 9:1370-1379
McNicoll L et al. JAGS 2003;51:591-98
Ouimet S, ICM 2007;33:1007-1013

Qual è la mia
frequenza cardiaca ?

Masimo rainbow SET

97

76

140
50
BPM

APOD



42

PVI

13

SpOC ml/dl

10.1

SpHb g/dl



Assessment of ICU Patients

Patient Comfort		
Pain	Sedation	Delirium
<ul style="list-style-type: none">• 0-10 ScaleVAS-Pain<ul style="list-style-type: none">• BPS•PAINAD	Sedation Assessment Scales (RASS, SAS, MAAS, ...)	CAM-ICU IC-DSC

Jacobi J et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult.
Crit Care Med 2002; 30:119-141

Misura comportamentale del dolore nei pazienti ricoverati in Terapia Intensiva

BEHAVIORAL PAIN SCALE (BPS)

BPS per pazienti intubati

	1	2	3	4
Espressione facciale				
A				
	rilassato	fronte aggrottata	occhi chiusi	dignitante
Movimenti degli arti superiori				
B				
	immobili	piegati	contratti	retratti
	Se indeciso: controlla il tono muscolare mobilizzando passivamente l'arto superiore			
Adattamento alla ventilazione meccanica				
C				
	adattato	tossisce	asincrono	non ventilabile

BPS-NI per pazienti non intubati

	1	2	3	4
Espressione facciale				
	rilassato	fronte aggrottata	occhi chiusi	dignitante
Movimenti degli arti superiori				
	immobili	piegati	contratti	retratti
	Se indeciso: controlla il tono muscolare mobilizzando passivamente l'arto superiore			
Vocalizzazione				
	non emette lamenti di dolore	si lamenta <3 volte/min e per <3 sec	si lamenta >3 volte/min o per >3 sec	emette urla o lamenti verbali o trattiene il respiro

A + **B** + **C** = **VALORE TOTALE BPS o BPS-NI** da 3 (assente) a 12 (massimo), misura le manifestazioni comportamentali del dolore.

Tratto da: Chanques G. et al., Intensive Care Medicine 2009, Vol. 35, 2060-2067
Tradotto in italiano da G. Mistraletti e S. Barelo

The Richmond Agitation - Sedation Scale (RASS)

+ 4	Combattivo	Chiaramente combattivo, violento, potenziale pericolo per se stesso o per lo staff
+ 3	Molto agitato	Aggressivo, rischio evidente di rimozione invasività
+ 2	Agitato	Frequenti movimenti afinalistici, disadattamento alla ventilazione meccanica
+ 1	Irrequieto	Ansioso ma senza movimenti aggressivi e vigorosi
0	Sveglio e tranquillo	Comprende i periodi di sonno fisiologico



Sessler CN, Gosnell MS, Grap MJ, et al.

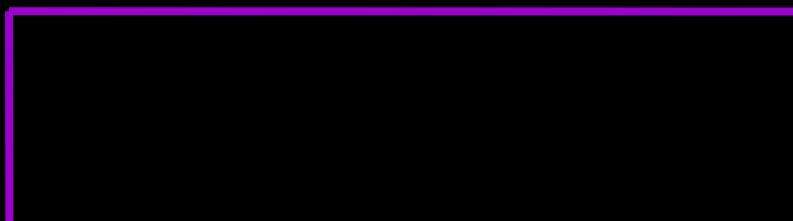
The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients

Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338-44.

The Richmond Agitation - Sedation Scale (RASS)

+ 4	Combattivo
+ 3	Molto agitato
+ 2	Agitato
+ 1	Irrequieto
0	Sveglio e tranquillo

- 1	Soporoso	Non completamente sveglio, apre gli occhi allo stimolo verbale, mantiene il contatto visivo > 10 secondi
- 2	Lievemente sedato	Brevi risvegli allo stimolo verbale, contatto visivo < 10 secondi
- 3	Moderatamente sedato	Movimenti o apertura degli occhi allo stimolo verbale (ma senza contatto visivo)



Sessler CN, Gosnell MS, Grap MJ, et al.

The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients

Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338-44.

The Richmond Agitation - Sedation Scale (RASS)

+ 4	Combattivo
+ 3	Molto agitato
+ 2	Agitato
+ 1	Irrequieto
0	Sveglio e tranquillo

- 1	Soporoso
- 2	Lievemente sedato
- 3	Moderatamente sedato

- 4	Sedazione profonda
- 5	Non risvegliabile

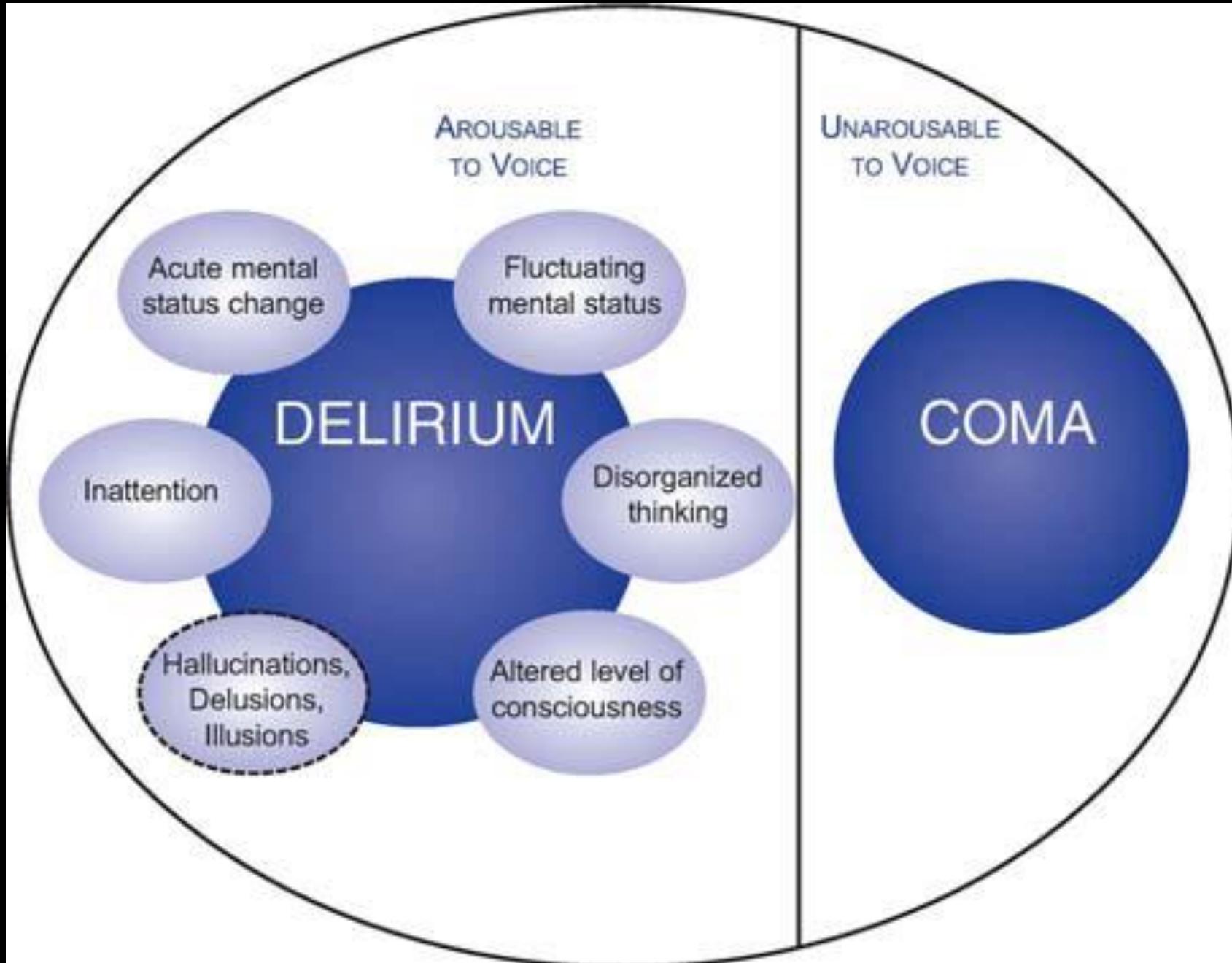
Non risposta allo stimolo verbale,
movimenti o apertura occhi alla stimolazione tattile/dolorosa

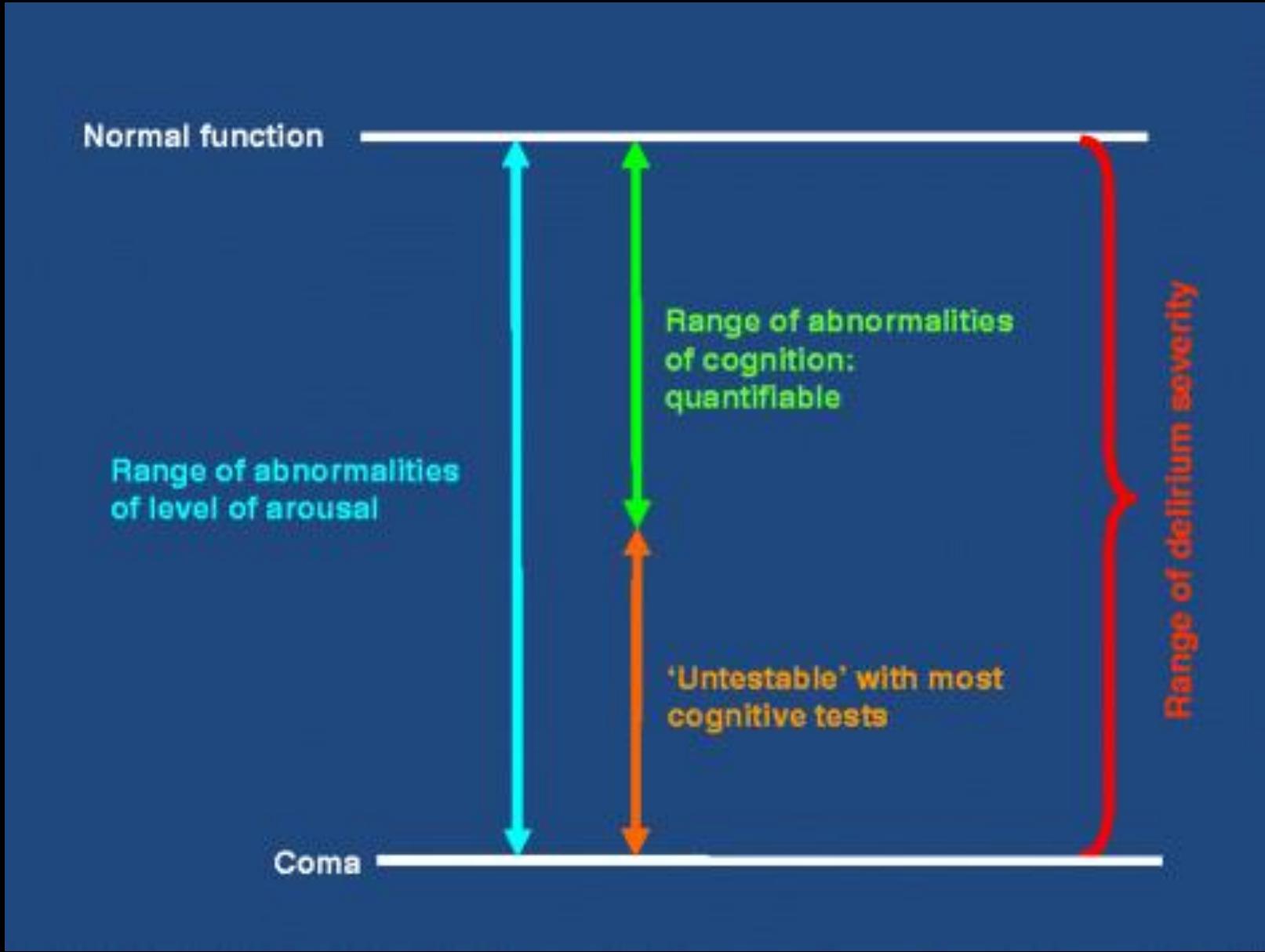
Nessuna risposta alla stimolazione tattile/dolorosa

Sessler CN, Gosnell MS, Grap MJ, et al.

The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients

Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338-44.





Delirium Scales

CARING FOR THE
CRITICALLY ILL PATIENT

Delirium in Mechanically Ventilated Patients

Validity and Reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

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DELIRIUM IS A DISTURBANCE OF consciousness characterized by an acute onset and fluctuating course of impaired cognitive functioning so that a patient's ability to receive, process, store, and recall information is strikingly impaired. It is associated with poor outcomes in hospitalized patients, including increased length of stay, the need for subsequent institutionalization, and higher mortality rates.¹⁻⁵ Although the frequency of delirium varies from 15% to 50% among general medical or surgical patients,^{1,6-11} these rates apply to patients who are not in the intensive care unit (ICU), and few data exist concerning delirium in the ICU.¹²⁻¹⁶

Mechanically ventilated ICU pa-

Context: Delirium is a common problem in the intensive care unit (ICU). Accurate diagnosis is limited by the difficulty of communicating with mechanically ventilated patients and by lack of a validated delirium instrument for use in the ICU.

Objectives: To validate a delirium assessment instrument that uses standardized non-verbal assessments for mechanically ventilated patients and to determine the occurrence rate of delirium in such patients.

Design and Setting: Prospective cohort study testing the Confusion Assessment Method for ICU Patients (CAM-ICU) in the adult medical and coronary ICUs of a US university-based medical center.

Participants: A total of 111 consecutive patients who were mechanically ventilated were enrolled from February 1, 2000, to July 15, 2000, of whom 96 (86.5%) were evaluable for the development of delirium and 15 (13.5%) were excluded because they remained comatose throughout the investigation.

Main Outcome Measures: Occurrence rate of delirium and sensitivity, specificity, and interrater reliability of delirium assessments using the CAM-ICU, made daily by 2 critical care study nurses, compared with assessments by delirium experts using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria.

Results: A total of 471 daily paired evaluations were completed. Compared with the reference standard for diagnosing delirium, 2 study nurses using the CAM-ICU had sensitivities of 100% and 93%, specificities of 98% and 100%, and high interrater reliability ($\kappa=0.96$; 95% confidence interval, 0.92-0.99). Interrater reliability measures across subgroup comparisons showed κ values of 0.92 for those aged 65 years or older, 0.99 for those with suspected dementia, or 0.94 for those with Acute Physiology and Chronic Health Evaluation II scores at or above the median value of 23 (all $P<.001$). Comparing sensitivity and specificity between patient subgroups according to age, suspected dementia, or severity of illness showed no significant differences. The mean (SD) CAM-ICU administration time was 2 (1) minutes. Reference standard diagnoses of delirium, stupor, and coma occurred in 25.2%, 21.3%, and 28.5% of all observations, respectively. Delirium occurred in 80 (83.3%) patients during their ICU stay for a mean (SD) of 2.4 (1.6) days. Delirium was even present in 39.5% of alert or easily aroused patient observations by the reference standard and persisted in 10.4% of patients at hospital discharge.

Conclusions: Delirium, a complication not currently monitored in the ICU setting, is extremely common in mechanically ventilated patients. The CAM-ICU appears to be rapid, valid, and reliable for diagnosing delirium in the ICU setting and may be a useful instrument for both clinical and research purposes.

JAMA. 2001;286:2703-2710

www.jama.com

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ORIGINAL

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Intensive Care Delirium Screening Checklist: evaluation of a new screening tool

Abstract **Objective:** Delirium in the intensive care unit is poorly defined. Clinical evaluation is difficult in the setting of unstable, often intubated patients. A screening tool may improve the detection of delirium.

Method: We created a screening checklist of eight items based on DSM criteria and features of delirium: altered level of consciousness, inattention, disorientation, hallucination or delusion, psychomotor agitation or retardation, inappropriate mood or speech, sleep/wake cycle disturbance, and symptom fluctuation. During 3 months, all patients admitted to a busy medical/surgical intensive care unit were evaluated, and the scale score was compared to a psychiatric evaluation.

Results: In 93 patients studied, 15 developed delirium. Fourteen (93%) of them had a score of 4 points or more. This score was also present in 15 (19%) of patients without delirium, 14 of whom had a known psychiatric illness, dementia, a structural neurological abnormality or encephalopathy. A ROC analysis was used to determine the sensitivity and specificity of the screening tool. The area under the ROC

curve is 0.9017. Predicted sensitivity is 99% and specificity is 64%.

Conclusion: This study suggests that the Intensive Care Delirium Screening Checklist can easily be applied by a clinician or a nurse in a busy critical care setting to screen all patients even when communication is compromised. The tool can be utilized quickly and helps to identify delirious patients. Earlier diagnosis may lead to earlier intervention and better patient care.

Keywords: Delirium · Intensive care unit · Screening · Detection · Checklist · Rating scale

Abbreviations: ICU intensive care unit · DSM diagnostic and statistical manual of mental disorders · ROC receiver operator characteristic · APACHE acute physiologic and chronic health evaluation

CAM-ICU

Ely EW, JAMA 2001

ICDSC

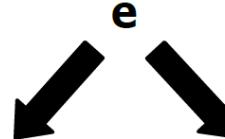
Bergeron N, Intensive Care Med 2001

CAM-ICU: Confusion Assessment Method in ICU

Punto 1: Alterazione acuta o fluttuazione
dello stato mentale

e

Punto 2: Disattenzione



Punto 3: Alterato livello di coscienza

oppure

Punto 4: Pensiero disorganizzato

= presenza di DELIRIUM

CAM-ICU: Scheda di lavoro

Punto 1: Alterazione Acuta o Fluttuazione dello Stato Mentale	Punteggio	Segna se presente
<p>Il paziente si presenta in modo diverso dal suo stato mentale di base OPPURE Il paziente ha presentato fluttuazioni dello stato mentale nelle ultime 24 ore come evidenziato da una variazione in una scala di sedazione (i.e., RASS), di stato di coscienza (GCS), o in un precedente assessment sul delirium?</p>	Se almeno una risposta è SI →	<input type="checkbox"/>
Punto 2: Disattenzione		
<p>Test 'Lettere' (in alternativa consulta il manuale per il test 'Immagini') Indicazioni. Dire al paziente: "<i>Sto per leggerle una serie di 10 lettere. Mi stringa la mano quando dico la lettera A.</i>" Leggere le lettere dalla seguente lista con un tono di voce normale e costante ad intervalli di 3 secondi.</p> <p style="text-align: center;">S A V E A H A A R T</p> <p>Viene controllato un errore quando il paziente non stringe la mano sulla lettera "A", o quando la stringe in risposta alle altre lettere</p>	Numero di errori > 2 →	<input type="checkbox"/>
Punto 3: Alterato Livello di Coscienza		
Il paziente è agitato, sedato o incosciente?	RASS ≠ 0 →	<input type="checkbox"/>
Punto 4: Pensiero Disorganizzato		
<p>Domande a cui si può rispondere solo Si/No, come ad esempio:</p> <ol style="list-style-type: none"> 1. Un sasso galleggia nell'acqua? 2. Ci sono pesci nel mare? 3. Un chilo pesa più di due chili? 4. Si può usare il martello per piantare un chiodo? <p>Errore: quando il paziente risponde in maniera scorretta alla domanda.</p> <p>Ordine semplice 5. Dire al paziente: "<i>Mi mostri queste dita</i>" (mostrare 2 dita); <i>"Ora faccia lo stesso con l'altra mano"</i> (senza mostrarle) se il paziente non riesce a muovere entrambe le braccia dire: <i>"Aggiunga un altro dito"</i></p> <p>Errore: quando il paziente non è in grado di completare l'intero esercizio.</p>	Numero totale di errori > 1 →	<input type="checkbox"/>

Punto 1 	Almeno uno  fra punto 3 e 4	Soddisfazione dei criteri →	<input type="checkbox"/> CAM-ICU Positivo (presenza di Delirium)
Punto 2 		Criteri non soddisfatti →	<input type="checkbox"/> CAM-ICU Negativo (assenza di Delirium)

Confusion Assessment Method (CAM-ICU) - DIAGRAMMA DI FLUSSO

1. Alterazione acuta o fluttuazione dello Stato Mentale

Il paziente si presenta in modo diverso dal suo stato mentale di base?
OPPURE
Il paziente ha presentato fluttuazioni dello stato mentale nelle ultime 24h?

NO

CAM-ICU negativo
NO DELIRIUM

SI

2. Disattenzione

"Mi stringa la mano quando sente la lettera A".
Leggere la seguente lista di lettere: **S A V E A H A A R T**

0-2
errori

CAM-ICU negativo
NO DELIRIUM

ERRORE: non stringe quando pronunci "A" o stringe sulle altre lettere.
Se impossibile eseguire Test delle Lettere → Test delle Immagini

> 2 ERRORI

3. Alterato livello di coscienza

Valutazione RASS attuale

RASS
 $\neq 0$

CAM-ICU positivo
DELIRIUM presente

RASS = 0

4. Pensiero Disorganizzato

1. Un sasso galleggia nell'acqua?
2. Ci sono pesci nel mare?
3. Un chilo pesa più di due chili?
4. Si può usare il martello per piantare un chiodo?

> 1 errore

0-1 errori

CAM-ICU negativo
NO DELIRIUM

Ordine semplice: "Mi mostri queste dita" (mostrare 2 dita)

"Ora faccia lo stesso con l'altra mano" (senza mostrarle)

Se il paziente non riesce a muovere entrambe le braccia dire: "Aggiunga un altro dito"

The Intensive Care Delirium Screening Checklist

PATIENT EVALUATION	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
Altered level of consciousness* (A-E)					
If A or B do not complete patient evaluation for the period					
Inattention					
Disorientation					
Hallucination - delusion – psychosis					
Psychomotor agitation or retardation					
Inappropriate speech or mood					
Sleep/wake cycle disturbance					
Symptom fluctuation					
TOTAL SCORE (0-8)					
Score	none	none	1	0	1
<u>Level of consciousness*</u> :	A: no response	B: response to intense and repeated stimulation (loud voice and pain)	C: response to mild or moderate stimulation	D: normal wakefulness	E: exaggerated response to normal stimulation
SCORING SYSTEM :					
The scale is completed based on information collected from each entire 8-hour shift or from the previous 24 hours. Obvious manifestation of an item = 1 point. No manifestation of an item or no assessment possible = 0 point. The score of each item is entered in the corresponding empty box and is 0 or 1.					
<p>1. <u>Altered level of consciousness</u>: A) No response or B) the need for vigorous stimulation in order to obtain any response signified a severe alteration in the level of consciousness precluding evaluation. If there is coma (A) or stupor (B) most of the time period then a dash (-) is entered and there is no further evaluation during that period. C) Drowsiness or requirement of a mild to moderate stimulation for a response implies an altered level of consciousness and scores 1 point. D) Wakefulness or sleeping state that could easily be aroused is considered normal and scores no point. E) Hypervigilance is rated as an abnormal level of consciousness and scores 1 point.</p>					
<p>2. <u>Inattention</u>: Difficulty in following a conversation or instructions. Easily distracted by external stimuli. Difficulty in shifting focuses. Any of these scores 1 point.</p>					
<p>3. <u>Disorientation</u>: Any obvious mistake in time, place or person scores 1 point.</p>					
<p>4. <u>Hallucination, delusion or psychosis</u>: The unequivocal clinical manifestation of hallucination or of behaviour probably due to hallucination (e.g. trying to catch a non-existent object) or delusion. Gross impairment in reality testing. Any of these scores 1 point.</p>					
<p>5. <u>Psychomotor agitation or retardation</u>: Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential dangerousness (e.g. pulling out iv lines, hitting staff). Hypoactivity or clinically noticeable psychomotor slowing. Any of these scores 1 point.</p>					
<p>6. <u>Inappropriate speech or mood</u>: Inappropriate, disorganized or incoherent speech. Inappropriate display of emotion related to events or situation. Any of these scores 1 point.</p>					
<p>7. <u>Sleep/wake cycle disturbance</u>: Sleeping less than 4 hours or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment). Sleeping during most of the day. Any of these scores 1 point.</p>					
<p>8. <u>Symptom fluctuation</u>: Fluctuation of the manifestation of any item or symptom over 24 hours (e.g. from one shift to another) scores 1 point.</p>					

Fig.1 The Intensive Care Delirium Screening Checklist

Intensive Care Delirium Screening Checklist (ICDSC)

VALUTAZIONE DEL PAZIENTE :		Data															
Alterazione stato di coscienza (A-E) *			M	P	N	M	P	N	M	P	N	M	P	N	M	P	N
se A o B, non proseguire la valutazione del paziente in quel periodo																	
Disattenzione		M	P	N	M	P	N	M	P	N	M	P	N	M	P	N	
Disorientamento		M	P	N	M	P	N	M	P	N	M	P	N	M	P	N	
Allucinazione o psicosi		M	P	N	M	P	N	M	P	N	M	P	N	M	P	N	
Agitazione psicomotoria o rallentamento		M	P	N	M	P	N	M	P	N	M	P	N	M	P	N	
Alterazione del linguaggio o dell'umore		M	P	N	M	P	N	M	P	N	M	P	N	M	P	N	
Disturbo del ciclo sonno/veglia		M	P	N	M	P	N	M	P	N	M	P	N	M	P	N	
Fluttuazione dei sintomi		M	P	N	M	P	N	M	P	N	M	P	N	M	P	N	
PUNTEGGIO TOTALE (0 – 8)																	

* Stato di coscienza:

- A: nessuna risposta
- B: risposta solo a stimolo intenso e ripetuto
- C: risposta a stimolo da lieve a moderato
- D: normale veglia
- E: risposta esagerata a stimolo normale

Punteggio

- | | |
|---------|--|
| nessuno | |
| nessuno | |
| 1 | |
| 0 | |
| 1 | |

Diagnosi di Delirium se ICDSC ≥ 4. Delirium subclinico se ICDSC fra 1 e 3

SISTEMA DI ASSEGNAZIONE DEL PUNTEGGIO :

La scala viene completata in base alle informazioni ottenute durante ciascun turno di 8 ore, oppure riferito alle 24 ore precedenti.

Manifestazioni evidenti di un fattore = 1 punto. Assenza di alterazione di quel fattore o impossibilità a rilevarlo = 0 punti.

Il punteggio di ciascun fattore viene registrato nella casella corrispondente al turno presente (M = mattino, P = pomeriggio, N = notte), e può essere 0 o 1.

1. Alterazione stato di coscienza:

- A) Nessuna risposta, oppure B) Necessità di stimolazione intensa per ottenere una qualsiasi risposta, rappresentano una severa alterazione dello stato di coscienza che preclude la valutazione. Essendo presente coma (A) o stupor (B) per la maggior parte del periodo osservato, si inserisce un trattino (-) e non si prosegue nell'ulteriore valutazione durante quel periodo.
- C) Sopore o necessità di stimolo da lieve a moderato per ottenere una risposta implica un'alterazione dello stato di coscienza. Viene assegnato 1 punto.
- D) La veglia o il sonno fisiologico dal quale si può prontamente essere svegliati è considerato normale, non viene quindi assegnato nessun punto.
- E) Lo stato di irrequietezza o agitazione vengono registrati come alterazioni del livello di coscienza. Viene assegnato 1 punto.

2. Disattenzione: difficoltà nel seguire una conversazione o ad eseguire ordini semplici. Facile distrazione a causa di stimoli esterni. Difficoltà nello spostamento di attenzione. La presenza di una qualsiasi di queste voci determina l'assegnazione di 1 punto.

3. Disorientamento: qualsiasi palese valutazione errata di tempo, spazio o persona. Viene assegnato 1 punto.

4. Allucinazione o psicosi: manifestazione clinica inequivocabile di allucinazioni o comportamento probabilmente indotto da allucinazioni (ex: tentativo di afferrare un oggetto non esistente). Alterazione grossolana di percezione della realtà. Per qualsiasi di queste voci viene assegnato 1 punto.

5. Agitazione psicomotoria o rallentamento: iperattività che richiede l'uso di sedativi aggiuntivi o di mezzi di contenzione per evitare potenziali danni (ex: rimozione invasività, aggressioni allo staff). Ipoattività o rallentamento psicomotorio clinicamente evidente. Viene assegnato 1 punto.

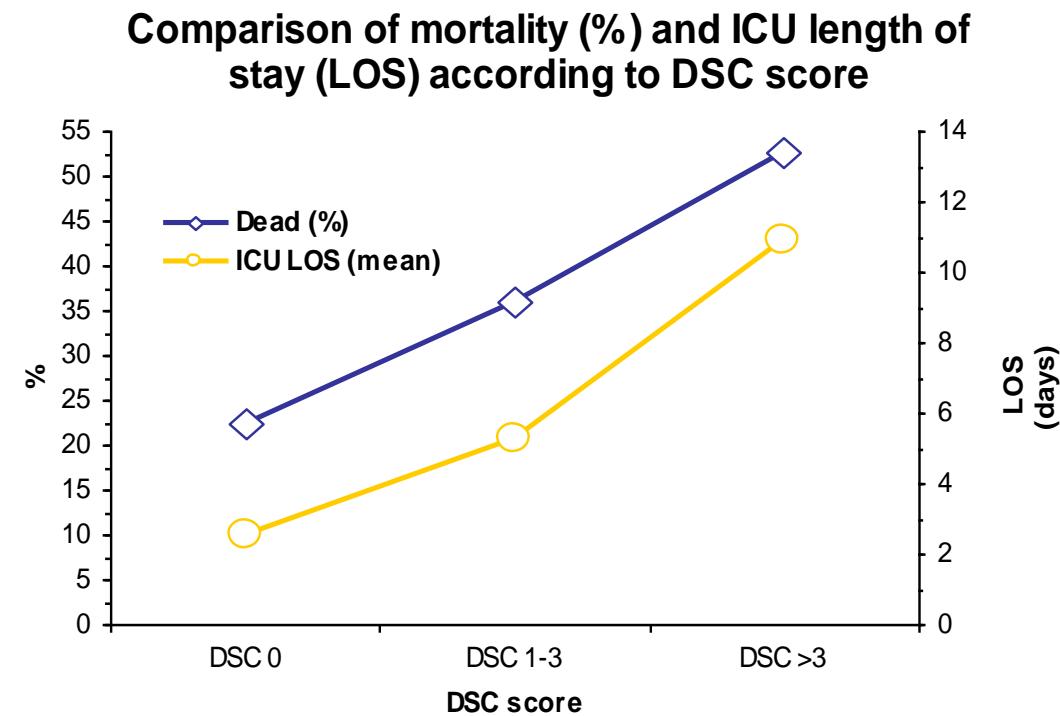
6. Alterazione del linguaggio o dell'umore: discorso inappropriate, disorganizzato o incoerente. Manifestazione inappropriate di emozioni in relazione agli eventi o alla situazione. Per qualsiasi di queste voci viene assegnato 1 punto.

7. Disturbo del ciclo sonno/veglia: periodo di sonno inferiore alle 4 ore o risvegli frequenti durante la notte (non vanno considerati i periodi di veglia causati dallo staff medico o dall'ambiente rumoroso). Sonno prolungato durante il di. Per qualsiasi di queste voci viene assegnato 1 punto.

8. Fluttuazione dei sintomi: fluttuazione (nelle precedenti 24h) della presenza di uno dei fattori indagati. Viene assegnato 1 punto.

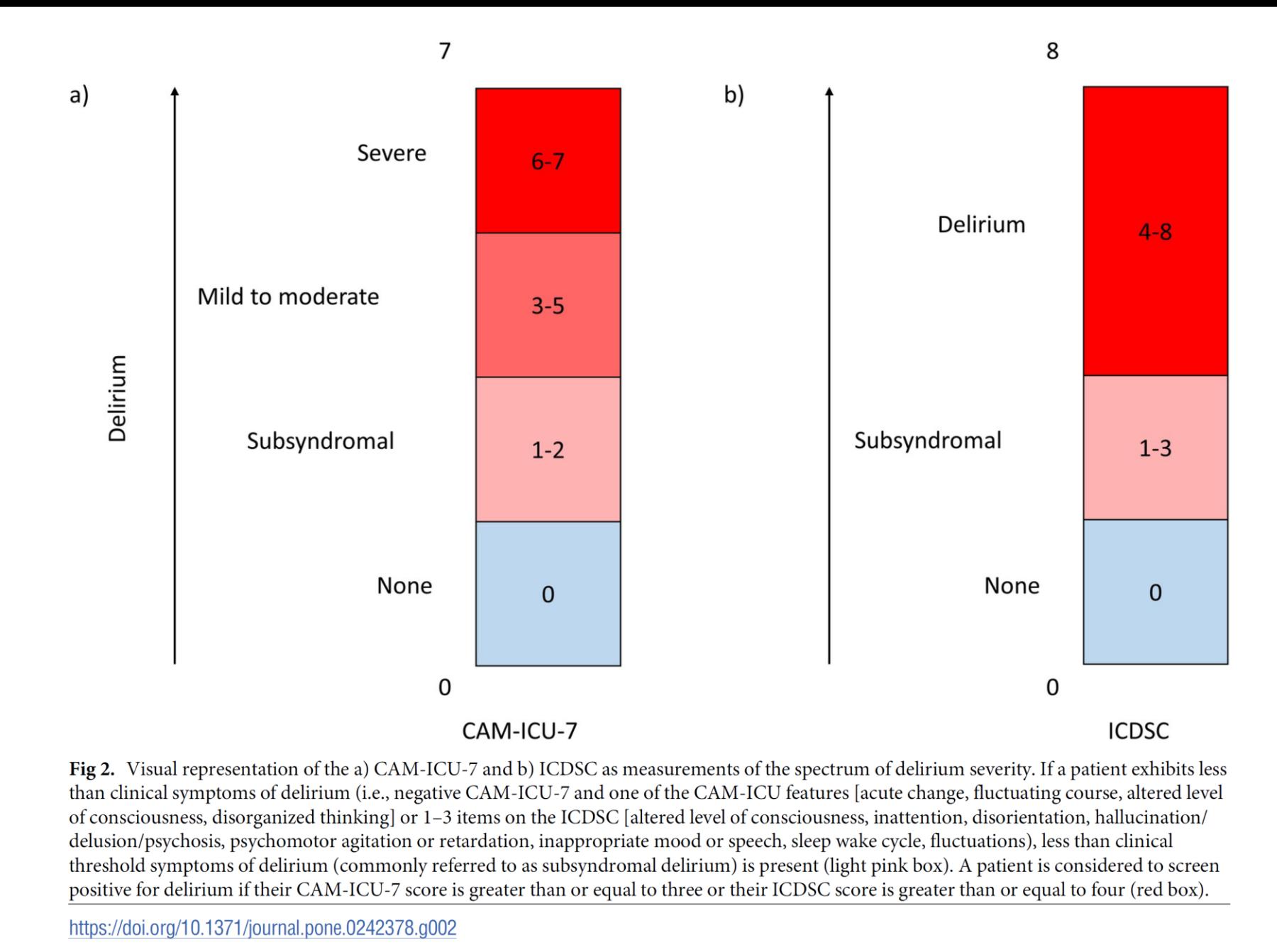
Sébastien Ouimet
Richard Riker
Nicolas Bergeon
Mariève Cossette
Brian Kavanagh
Yoanna Skrobik

Subsyndromal delirium in the ICU: evidence for a disease spectrum



CAM-ICU-7: stratification of delirium severity

CAM-ICU		
Items	Grading	Score
<p>1. Acute Onset or Fluctuation of Mental Status Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?</p>	0 absent 1 present	
<p>2. Inattention Say to the patient, "<i>I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand.</i>" Read letters from the following letter list in a normal tone 3 seconds apart. <u>SAVEAHAART</u> (Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")</p>	0 absent (correct ≥ 8) 1 for inattention (correct 4-7) 2 for severe inattention (correct 0-3)	
<p>3. Altered Level of Consciousness Present if the Actual RASS score is anything other than alert and calm (zero)</p>	0 absent (RASS 0) 1 for altered level (RASS 1, -1) 2 for severe altered level (RASS $>1, <-1$)	
<p>4. Disorganized Thinking <u>Yes/No Questions</u> 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. <u>Command:</u> Say to patient "Hold up this many fingers" (Hold two fingers in front of patient). "Now do the same with the other hand" (Do not repeat number of fingers) An error is counted if patient is unable to complete the entire command.</p>	0 absent (correct ≥ 4) 1 for disorganized thinking (correct 2, 3) 2 for severe disorganized thinking (correct 0, 1)	
Total Score		



Come trattare
farmacologicamente
il Delirium
in Terapia Intensiva

ORIGINAL ARTICLE

Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

T.D. Girard, M.C. Exline, S.S. Carson, C.L. Hough, P. Rock, M.N. Gong, I.S. Douglas, A. Malhotra, R.L. Owens, D.J. Feinstein, B. Khan, M.A. Pisani, R.C. Hyzy, G.A. Schmidt, W.D. Schweickert, R.D. Hite, D.L. Bowton, A.L. Masica, J.L. Thompson, R. Chandrasekhar, B.T. Pun, C. Strength, L.M. Boehm, J.C. Jackson, P.P. Pandharipande, N.E. Brummel, C.G. Hughes, M.B. Patel, J.L. Stollings, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the MIND-USA Investigators*

ABSTRACT

BACKGROUND

There are conflicting data on the effects of antipsychotic medications on delirium in patients in the intensive care unit (ICU).

METHODS

In a randomized, double-blind, placebo-controlled trial, we assigned patients with acute respiratory failure or shock and hypoactive or hyperactive delirium to receive intravenous boluses of haloperidol (maximum dose, 20 mg daily), ziprasidone (maximum dose, 40 mg daily), or placebo. The volume and dose of a trial drug or placebo was halved or doubled at 12-hour intervals on the basis of the presence or absence of delirium, as detected with the use of the Confusion Assessment Method for the ICU, and of side effects of the intervention. The primary end point was the number of days alive without delirium or coma during the 14-day intervention period. Secondary end points included 30-day and 90-day survival, time to freedom from mechanical ventilation, and time to ICU and hospital discharge. Safety end points included extrapyramidal symptoms and excessive sedation.

RESULTS

Written informed consent was obtained from 1183 patients or their authorized repre-

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Ely at the Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center at Vanderbilt University, 2525 West End Ave., Suite 450, Nashville, TN 37203, or at wes.ely@vumc.org.

*A complete list of the Modifying the Impact of ICU-Associated Neurological Dysfunction—USA (MIND-USA) Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 22, 2018, and updated on November 2, 2018, at NEJM.org.

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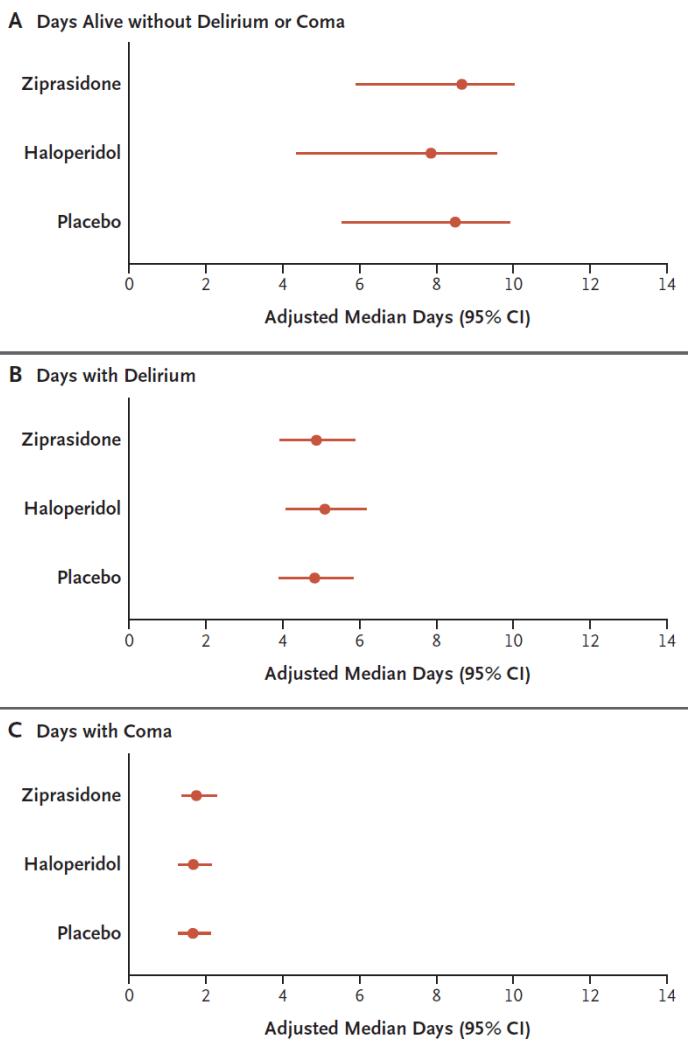


Figure 2. Effects of Haloperidol, Ziprasidone, and Placebo on Days Alive without Delirium or Coma, Days with Delirium, and Days with Coma.

In analyses that were adjusted for age, preexisting cognitive impairment, Clinical Frailty Score and Charlson Comorbidity Index score at baseline, and modified Sequential Organ Failure Assessment score and Richmond Agitation–Sedation Scale score at randomization, there were no significant differences between the trial groups with respect to the primary end point (days alive without delirium or coma) and with respect to the secondary end points of mental status (durations of delirium and coma).

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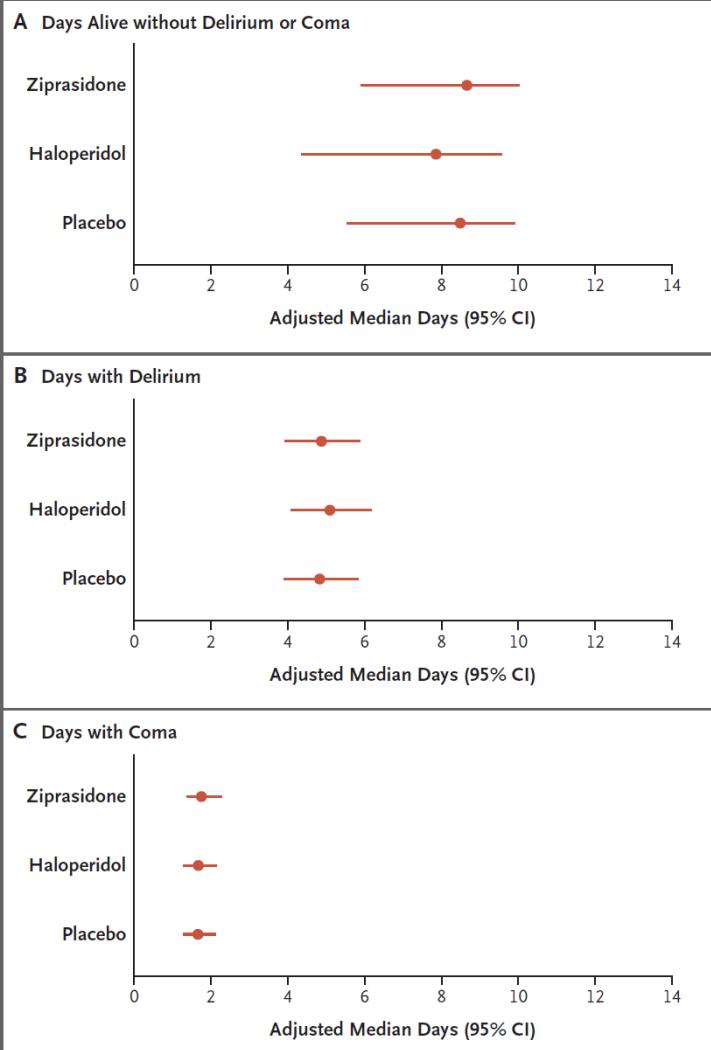


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I.S.
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ACKGROU

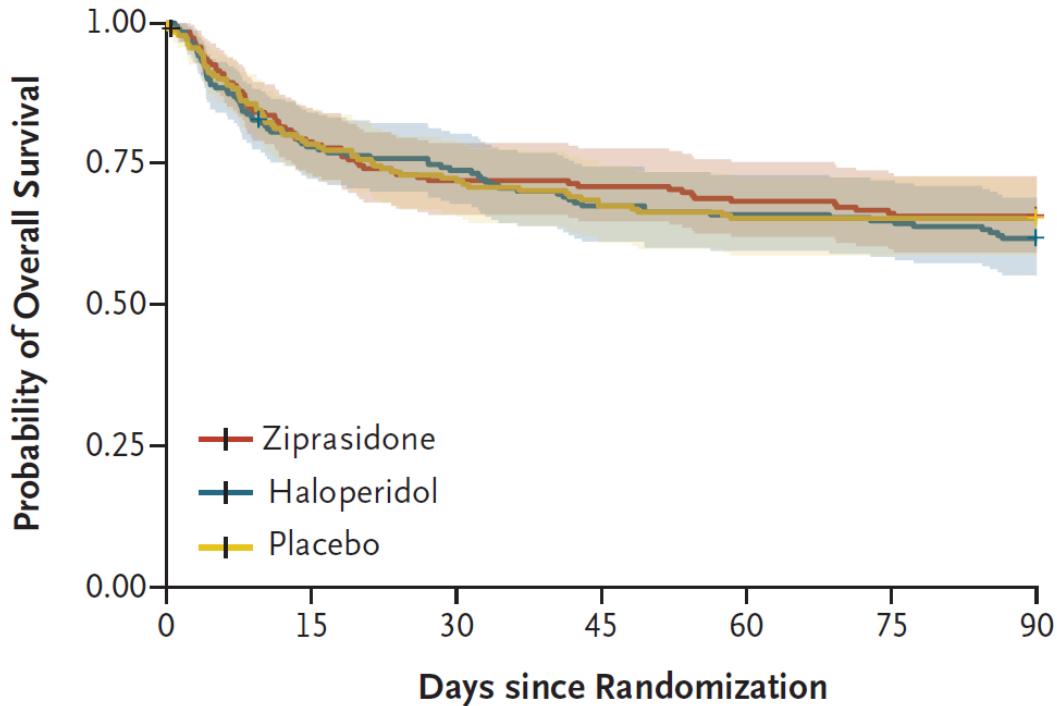
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ESULTS

Written in



No. at Risk (cumulative no. of deaths)

	190 (0)	150 (40)	137 (53)	135 (55)	130 (60)	126 (64)	125 (65)
Ziprasidone	190 (0)	150 (40)	137 (53)	135 (55)	130 (60)	126 (64)	125 (65)
Haloperidol	192 (0)	149 (42)	141 (50)	129 (62)	126 (65)	124 (67)	118 (73)
Placebo	184 (0)	143 (39)	132 (50)	123 (59)	119 (63)	119 (63)	119 (63)



Cochrane
Library

Cochrane Database of Systematic Reviews

Pharmacological interventions for the treatment of delirium in critically ill adults (Review)

Burry L, Hutton B, Williamson DR, Mehta S, Adhikari NKJ, Cheng W, Ely EW, Egerod I, Fergusson DA, Rose L. Pharmacological interventions for the treatment of delirium in critically ill adults.

Cochrane Database of Systematic Reviews 2019, Issue 9. Art. No.: CD011749.

DOI: [10.1002/14651858.CD011749.pub2](https://doi.org/10.1002/14651858.CD011749.pub2).

Authors' conclusions

We identified trials of varying quality that examined six different drug classes for treatment of delirium in critically ill adults. We found evidence that the alpha₂ agonist dexmedetomidine may shorten delirium duration, although this small effect (compared with placebo) was seen in pairwise analyses based on a single study and was not seen in the NMA results. Alpha₂ agonists also ranked best for duration of mechanical ventilation and length of ICU stay, whereas the CHE inhibitor rivastigmine was associated with longer ICU stay. We found no evidence of a difference between placebo and any drug in terms of delirium-free and coma-free days, days with coma, physical restraint use, length of stay, long-term cognitive outcomes, or mortality. No studies reported delirium relapse, resolution of symptoms, or quality of life. The ten ongoing studies and the six studies awaiting classification that we identified, once published and assessed, may alter the conclusions of the review.

ORIGINAL



Haloperidol, clonidine and resolution of delirium in critically ill patients: a prospective cohort study

Lisa Smit^{1*} , Sandra M. A. Dijkstra-Kersten², Irene J. Zaal², Mathieu van der Jagt¹ and Arjen J. C. Slooter²

Abstract

Purpose: Haloperidol and clonidine are commonly used to treat agitation in delirious intensive care unit (ICU) patients, but it is unclear whether these agents may shorten the duration of delirium. The objective of this study was to determine whether haloperidol, clonidine, or their combined administration to delirious ICU patients results in delirium resolution.

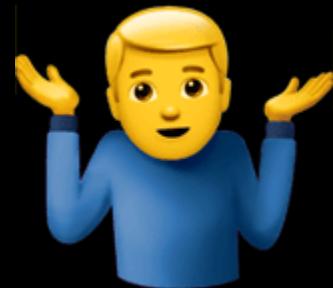
Methods: This was a cohort study on a mixed ICU, excluding patients with a primary neurological disorder. The main outcome was the probability of delirium resolution, using propensity score matching and Markov multinomial logistic regression models for daily transitions. Secondary outcomes were delirium duration, number of delirium days, ventilation days, length of stay in the ICU and hospital, and ICU mortality.

Results: A total of 3614 patients were included (1165 delirious [32%]; 2449 non-delirious [68%]). Delirium occurred on 4708 (18.9%) of 24,906 days. The probability of delirium resolution was lower in delirious patients who received haloperidol (OR 0.47, 95% CI 0.39–0.57), clonidine (OR 0.78, 95% CI 0.63–0.97), or both (OR 0.45, 95% CI 0.36–0.56) compared to untreated delirious patients. Delirious patients who received haloperidol, clonidine, or both had generally longer delirium duration, more delirium and ventilation days, and spent more time in the ICU and in hospital than untreated delirious patients. These agents had no effect on ICU mortality.

Conclusion: Haloperidol and clonidine use in delirious ICU patients may be associated with reduced probability of delirium resolution. This finding, however, merits further investigation given inherent limitations of this observational analysis.

Keywords: Delirium, Critical care, Intensive care unit, Haloperidol, Clonidine

La strategia per trattare
il delirium **NON** è farmacologica



A VOLTE NELLA VITA TUTTO FILA LISCIO



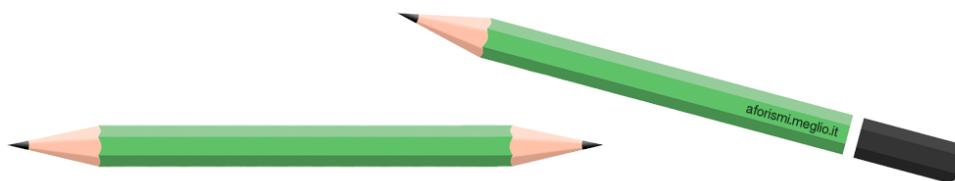
aforismi.meglio.it

E A VOLTE ACCADONO IMPREVISTI.



aforismi.meglio.it

LA COSA IMPORTANTE E' SAPER REAGIRE



aforismi.meglio.it

TRASFORMANDO I PROBLEMI IN OPPORTUNITA'

Strategies to prevent ICU delirium

- 1) Measure it !
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 - Underlying infection (sepsis), maintain normotermia
 - Correct hypoxia
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The screenshot shows the homepage of the icudelirium.org website. At the top left is the Vanderbilt University Medical Center logo. At the top right is the United States Department of Veterans Affairs logo. The main header features the website's name "icudelirium.org" and a tagline "RESEARCH DESIGNED TO TURN MIRRORS INTO WINDOWS". Below the header is a navigation bar with links for HOME, DELIRIUM, SEDATION, OUTCOMES, REFERENCES, and OUR GROUP. A sub-header below the navigation bar reads "ICU DELIRIUM AND COGNITIVE IMPAIRMENT STUDY GROUP". The main content area has two columns. The left column contains a photograph of a healthcare provider attending to a patient in an ICU setting and a descriptive text about delirium. The right column contains a search bar and a section titled "sedation" with a descriptive text. At the bottom, there are links for various study components and resources.

VANDERBILT UNIVERSITY
MEDICAL CENTER

UNITED STATES
DEPARTMENT OF VETERANS AFFAIRS

icudelirium.org

RESEARCH DESIGNED TO TURN
MIRRORS INTO WINDOWS

HOME DELIRIUM SEDATION OUTCOMES REFERENCES OUR GROUP

ICU DELIRIUM AND COGNITIVE IMPAIRMENT STUDY GROUP

delirium overview *and how to diagnose it*



Delirium is confusion that comes on very fast, sometimes in just a few hours. When someone becomes delirious, it means that they can not think clearly, have trouble paying attention and are not aware of what is going on around them. Sometimes they may even see or hear things that are not really there but seem very real to them.

[+]

Risk Factors Study Terminology and Mnemonics Assessment Implementation of CAM-ICU FAQ Patients and Family

Sedation Resources Wake Up and Breathe Study

   | Mappa del sito | www.sedaen.it |

[Home](#) [Chi siamo](#) [Formazione](#) [Letteratura](#) [Corsi ECM](#) [Agorà](#) cerca...

**“ Non esiste un protocollo di sedazione perfetto,
esiste il miglior trattamento
per quel paziente in quel momento. ”**

G. lapichino



[Home](#)

BENVENUTI su sedaICU !

SedaICU.it è un sito utile a **infermieri e medici di Terapia Intensiva**, per lavorare meglio. L'obiettivo è curare bene i pazienti critici, e così migliorare il loro outcome. Per ottenerlo, gli operatori devono avere occasioni di **formazione efficace**, che li renda più soddisfatti e più competenti. Su www.sedaicu.it troverai indicazioni per usare i farmaci sedativi in modo nuovo e per operare il [monitoraggio neurologico con strumenti validati](#).

Stiamo assistendo in Terapia Intensiva ad una profonda sfida culturale: pazienti svegli, parenti presenti, staff consapevole dei limiti e delle possibilità. Non è facile "cambiare testa", ma è il primo passo per stare meglio. Tutti.

[Link veloci](#)

ORIGINAL ARTICLE

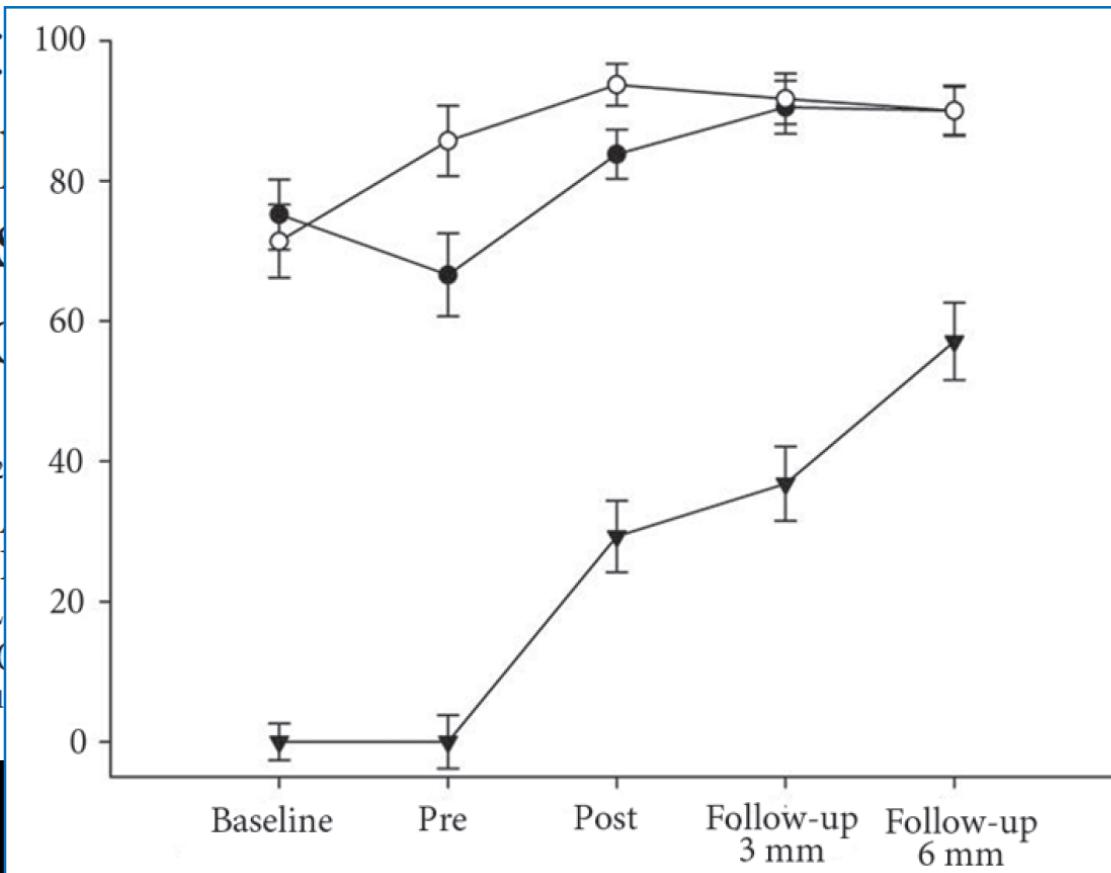
Neurological assessment with validated tools in general ICU: multicenter, randomized, before and after, pragmatic study to evaluate the effectiveness of an e-learning platform for continuous medical education

Giovanni MISTRALLETTI^{1, 2 *}, Michele UMBRELLO², Stefania ANANIA²,
Elisa ANDRIGHI², Alessandra DI CARLO², Federica MARTINETTI², Serena BARELLO²,
Giovanni SABBATINI², Paolo FORMENTI², Tommaso MARAFFI¹, Francesco MARRAZZO¹,
Alessandra PALO³, Giacomo BELLANI⁴, Riccarda RUSSO⁵, Silvia FRANCESCONI⁶,
Federico VALDAMBRINI⁷, Marco CIGADA⁸, Francesca RICCARDI⁹, Egidio A. MOJA¹⁰,
Gaetano IAPICHINO^{1, 2} on behalf of the SedaICU investigators

ORIGINAL ARTICLE

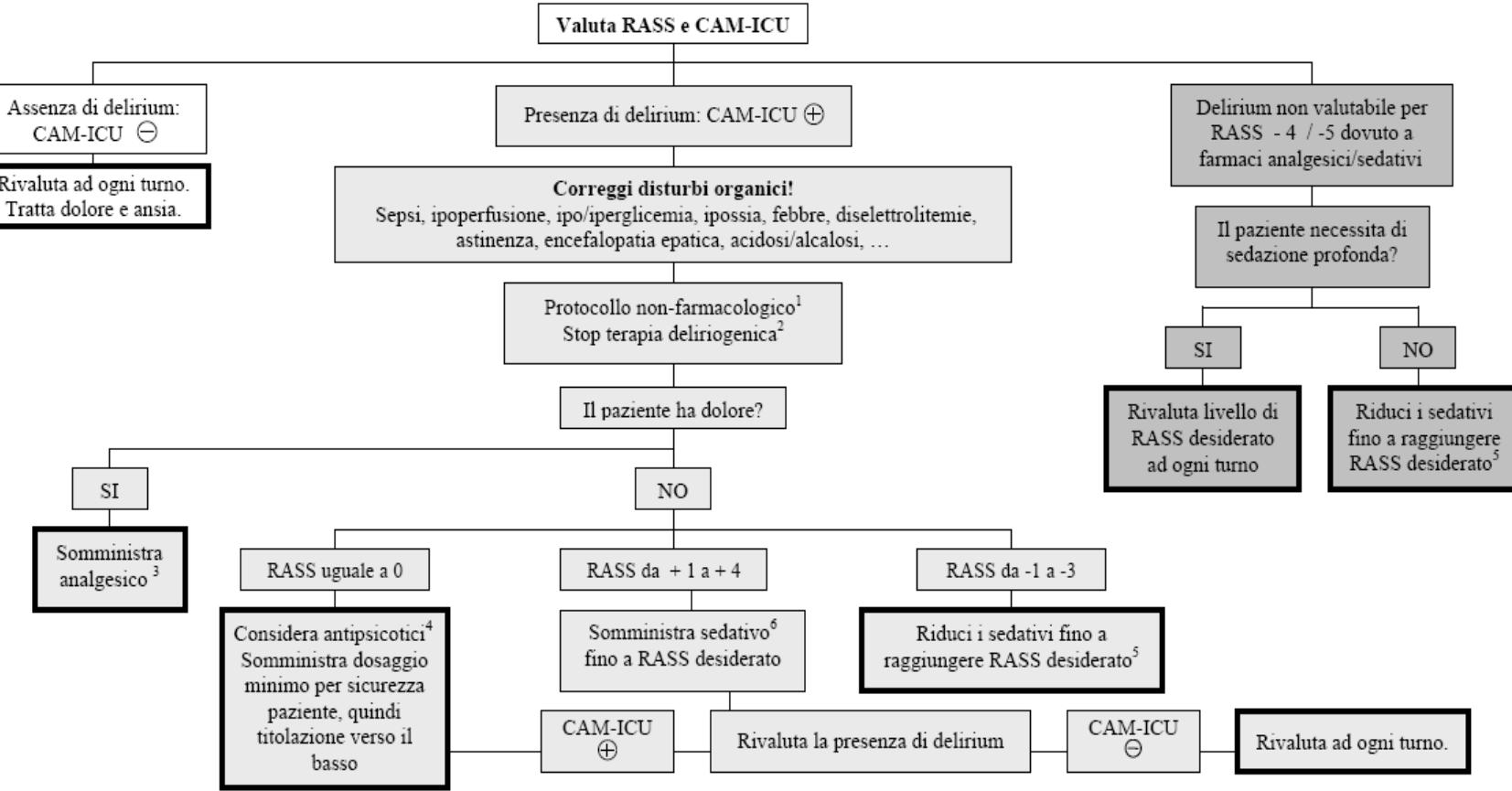
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Giovanni MISTRALLETI ^{1, 2}
Elisa ANDRIGHI ², Alessandra DI C...
Giovanni SABBATINI ², Paolo FORMI...
Alessandra PALO ³, Giacomo BEL...
Federico VALDAMBRINI ⁷, Marco C...
Gaetano IAPICHINO ¹



Misurarlo permette di individuarlo
...tempestivamente!

GESTIONE DEL DELIRIUM IN TERAPIA INTENSIVA



¹Protocollo non-farmacologico

² Considera interruzione/sostituzione di terapia deliriogenica: benzodiazepine, oppiacei, antidepressivi triciclici, propofol, anticolinergici, (metoclopramide, inibitori della pompa protonica, prometazina, difenidramina), altri neurolettici.

Orientamento

- Utilizzo supporti visivi e uditivi personali.
- Incoraggia la comunicazione chiamando il paziente per nome.
- Disponibilità di oggetti personali del paziente.
- Coerenza di intervento dello staff medico/infermieristico.
- Impiego di TV/musica durante il giorno.

Ambiente

- Luci spente di notte, accese durante il giorno; meglio se il paziente vede la luce del sole.
- Disincita il sonno diurno.
- Mobilizzazione del paziente e fisioterapia durante il giorno.
- Controlla l'eccesso di rumore (staff, strumentazione, visitatori) durante la notte.
- Evita procedure infermieristiche notturne.

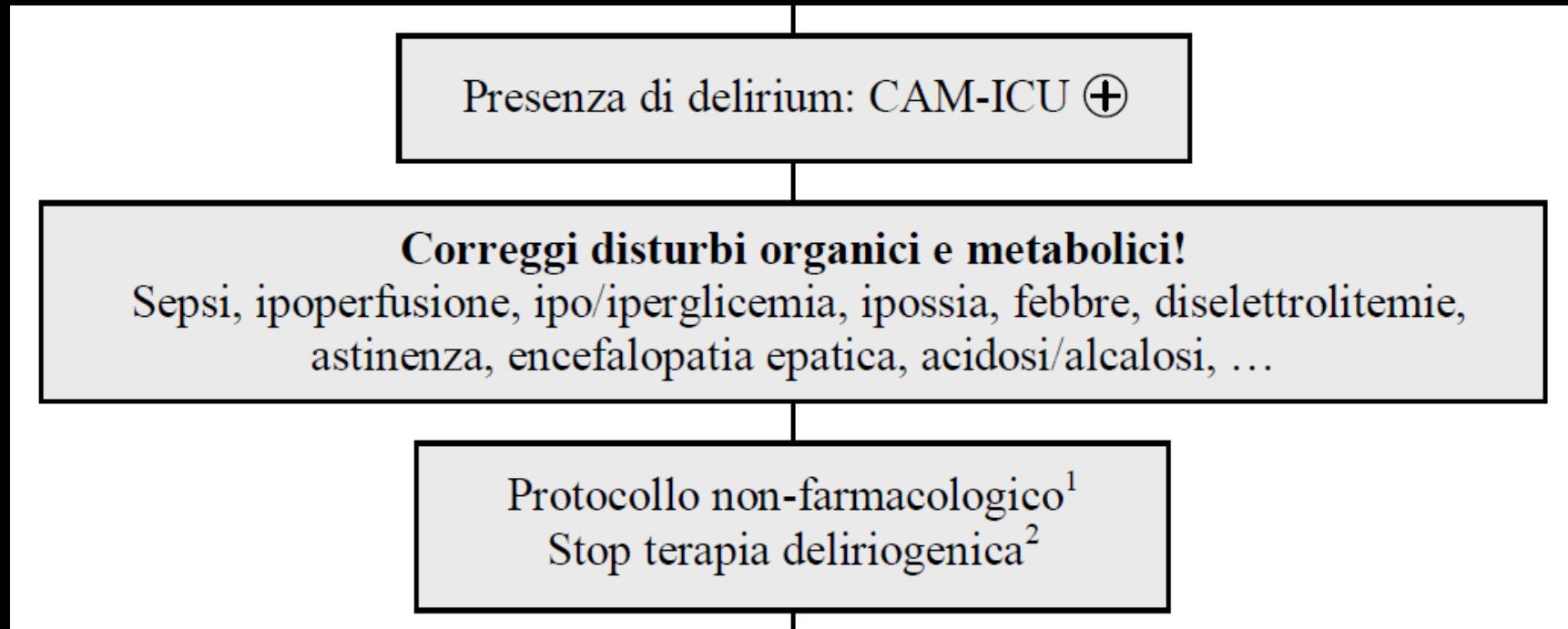
³ Un adeguato controllo del dolore può ridurre il delirio. Preferisci somministrazione a boli. Stima con strumenti validati (VNR o BPS).

⁴ Durante svezzamento dai sedativi, considera aloperidolo 0.5 - 5 mg per os (0.5-1 mg se età > 65 anni) ogni 8 ore. Dose massima: 20 mg/die. Interrompere per iperplessia, allungamento intervallo QT, rigidità muscolare.
Considera l'utilizzo di antipsicotici atipici: olanzapina, clozapina, quetiapina, risperidone, ziprasidone, aripiprazolo.

⁵ RASS sempre 'desiderato' = 0/-1 (paziente ben adattato nonostante patologia e invasività). Se necessario: RASS desiderato fra - 2 e - 4.

⁶ *Sedazione endovenosa:* Propofol (max 6 mg/kg-h) o Midazolam (max 0.2 mg/kg-h) a boli ed eventuale infusione continua: somministra sempre il minimo dosaggio efficace.
Sedazione enterale: Idrossizina (max 600 mg /die) e Lorazepam (max 16 mg / die): somministra sempre il minimo dosaggio efficace.
Melatonina 3 mg per 2 (ore 20 e 24) da ingresso fino a dimissione.

Nel caso di delirium...



...prima di tutto bisogna correggere le cause sottostanti...

... iniziare usando accorgimenti non farmacologici ...

¹ Protocollo non-farmacologico

Orientamento

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Controlla l'eccesso di rumore (staff, strumentazione, visitatori) durante la notte.

Evitare procedure medico/infermieristiche notturne

...ed interrompendo la terapia deliriogenica !

² Considera interruzione/sostituzione di terapia deliriogenica: benzodiazepine, oppiacei, antidepressivi triciclici, propofol, anticolinergici, (metoclopramide, inibitori della pompa protonica, prometazina, difenidramina), altri neurolettici.

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ORIGINAL ARTICLE

Acute Kidney Injury as a Risk Factor for Delirium and Coma during Critical Illness

Edward D. Siew^{1,2,3,4}, William H. Fissell^{1,2}, Christina M. Tripp⁵, Jeffrey D. Blume⁵, Matthew D. Wilson², Amanda J. Clark⁶, Andrew J. Vincz¹, E. Wesley Ely^{2,4,7,8,9}, Pratik P. Pandharipande^{10,11}, and Timothy D. Girard¹²

¹Division of Nephrology and Hypertension and ⁷Division of Allergy, Pulmonary, and Critical Care Medicine, ²Department of Medicine, ³Vanderbilt Center for Kidney Disease, ⁵Department of Biostatistics, ⁶Department of Pediatrics, ⁸Center for Health Services Research, and ¹⁰Division of Anesthesiology Critical Care Medicine, Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee; ⁴Geriatric Research, Education and Clinical Center Service, ⁹Medical Service, and ¹¹Anesthesia Service, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, Tennessee; and ¹²Clinical Research, Investigation, and Systems Modeling of Acute Illness Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

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Am J Respir Crit Care Med Vol 195, Iss 12, pp 1597–1607, Jun 15, 2017

ORIGINAL ARTIC

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Edward D. Siew^{1,2,3,4}, William H. Fissell^{1,2}
Amanda J. Clark⁶, Andrew J. Vincz¹, E. W.

¹Division of Nephrology and Hypertension and ⁷Medicine, ³Vanderbilt Center for Kidney Disease Research, and ¹⁰Division of Anesthesiology Critical Care, Nashville, Tennessee; ⁴Geriatric Research, Education, and Department of Veterans Affairs Medical Center, Investigation, and Systems Modeling of Acute Illness, Pittsburgh, Pennsylvania

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Am J Respir Crit Care

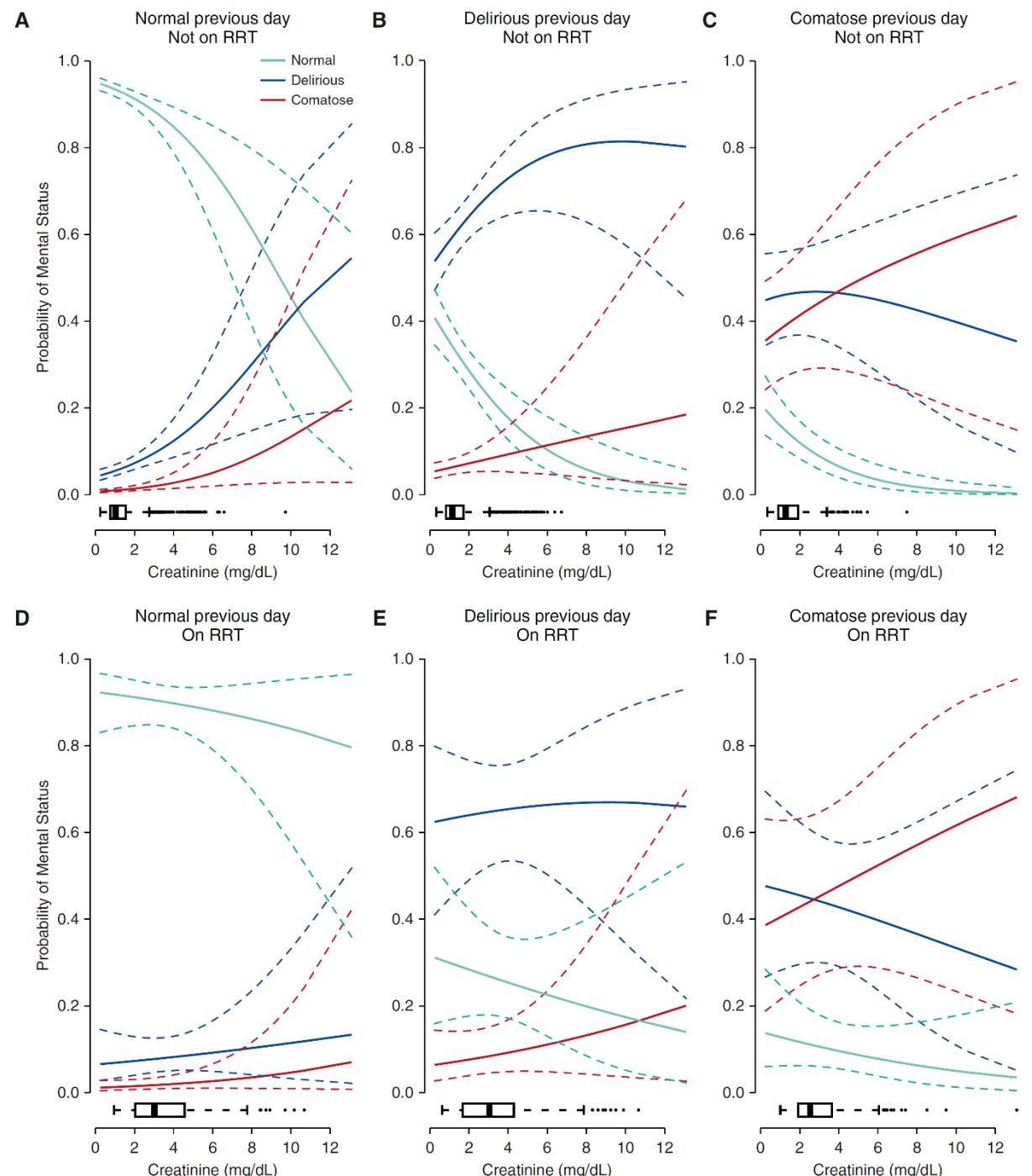


Table 3 – A useful mnemonic for remembering possible causes of delirium

I	Infection
W	Withdrawal
A	Acute metabolic
T	Traumatic injury
C	CNS lesion
H	Hypoxia
D	Deficiency of vitamins
E	Endocrine
A	Acute vascular
T	Toxins (including medications)
H	Heavy metals

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STUDY PROTOCOL

Open Access

A study protocol for a randomized controlled trial of family-partnered delirium prevention, detection, and management in critically ill adults: the ACTIVATE study



Kirsten M. Fiest^{1,2,3*} ID, Karla D. Krewulak¹, Bonnie G. Sept¹, Krista L. Spence¹, Judy E. Davidson⁴, E. Wesley Ely⁵, Andrea Soo¹ and Henry T. Stelfox^{1,2,3}

Abstract

Background: Delirium is very common in critically ill patients admitted to the intensive care unit (ICU) and results in negative long-term outcomes. Family members are also at risk of long-term complications, including depression and anxiety. Family members are frequently at the bedside and want to be engaged; they know the patient best and may notice subtle changes prior to the care team. By engaging family members in delirium care, we may be able to improve both patient and family outcomes by identifying delirium sooner and capacitating family members in care.

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Cause predisponenti

Table 1. Predisposing and precipitating risk factors associated with ICU delirium

Predisposing Factors					
Genetics	Demographics		Chronic Comorbidities		
APOE4 (31)	Age (29, 33)			Alcohol (30) Cognitive impairment (16, 30) Hypertension (13)	
Precipitating Factors					
Acute Physiology	Biochemical	Acute Diagnosis	Procedures	Medications	Environment
APACHE II score (29, 32)	Tryptophan (29)	Anxiety (32)	Number of intravenous infusions (30)	Opioids (13, 29, 33)	Isolation (30)
Arterial pH (16)	Tyrosine (29)	Coma (32)	Number of tubes and catheters (13, 30, 34)	Benzodiazepines (16, 33)	Daylight (13, 30)
Bilirubin (13)		Medical admission (30)		Dopamine (82)	Family visits (13, 30)
Creatinine (16)				Epidural use (13)	
Pain level (32)				Antipsychotics (30)	
				Propofol (33)	

Cause precipitanti

Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients

Pratik Pandharipande, M.D., M.S.C.I.,* Ayumi Shintani, Ph.D., M.P.H.,† Josh Peterson, M.D., M.P.H.,‡

Brenda Truman Pun, R.N., M.S.N., A.C.N.P.,§ Grant R. Wilkinson, Ph.D., D.Sc.,|| Robert S. Dittus, M.D., M.P.H.,#

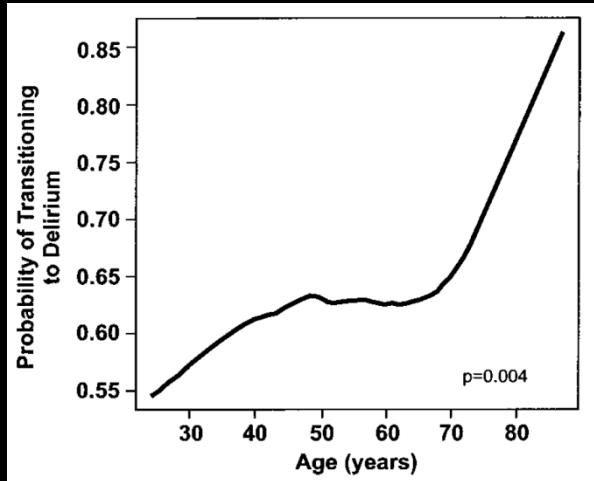
Gordon R. Bernard, M.D.,** E. Wesley Ely, M.D., M.P.H.††

Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients

Pratik Pandharipande, M.D., M.S.C.I.,* Ayumi Shintani, Ph.D., M.P.H.,† Josh Peterson, M.D., M.P.H.,‡

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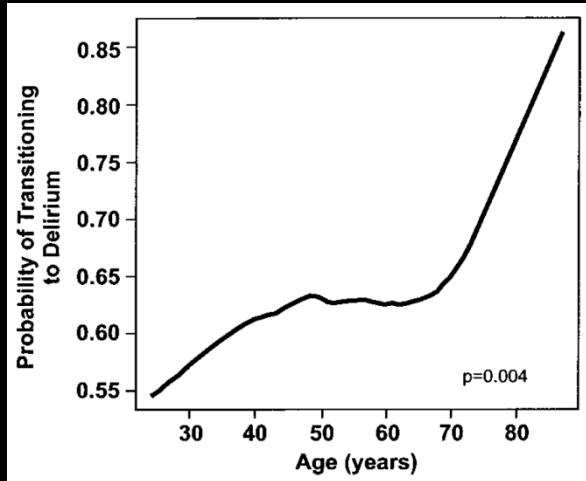
age

Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients

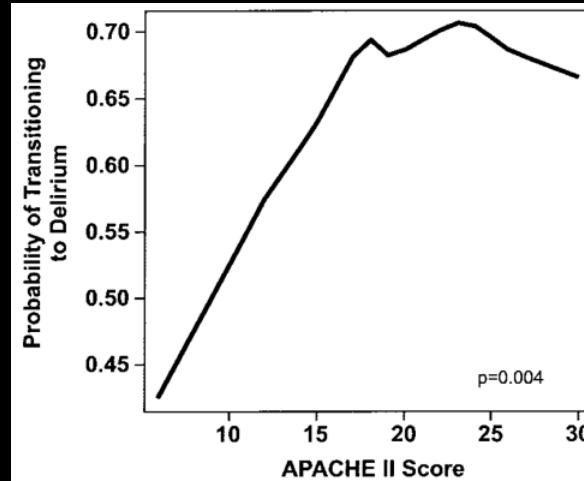
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age



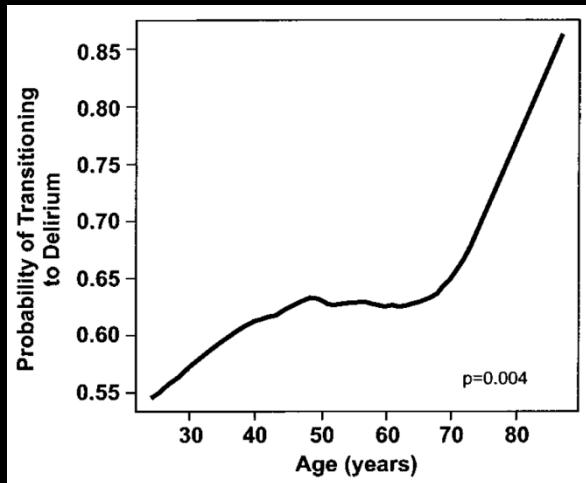
severity

Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients

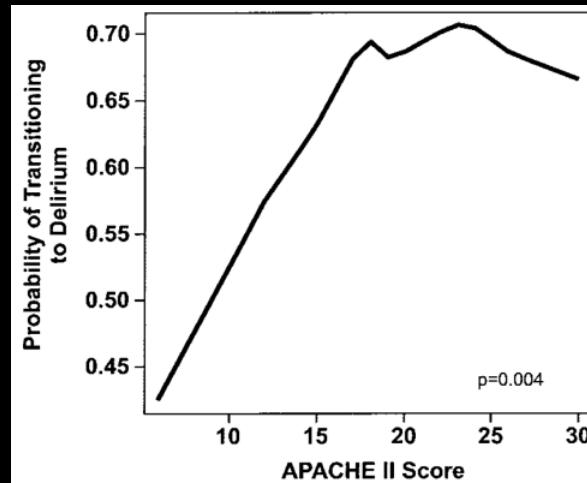
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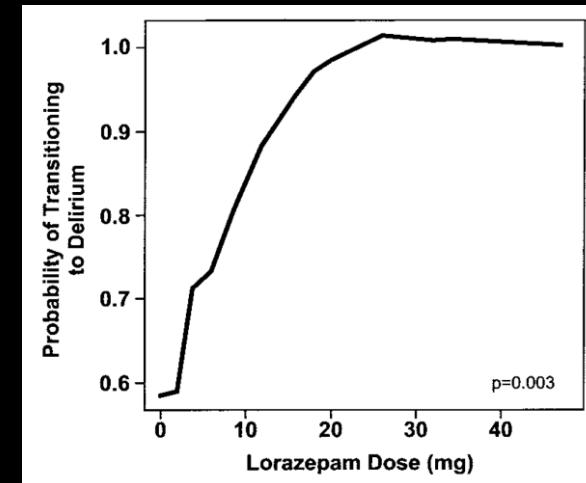
Gordon R. Bernard, M.D.,** E. Wesley Ely, M.D., M.P.H.††



age



severity



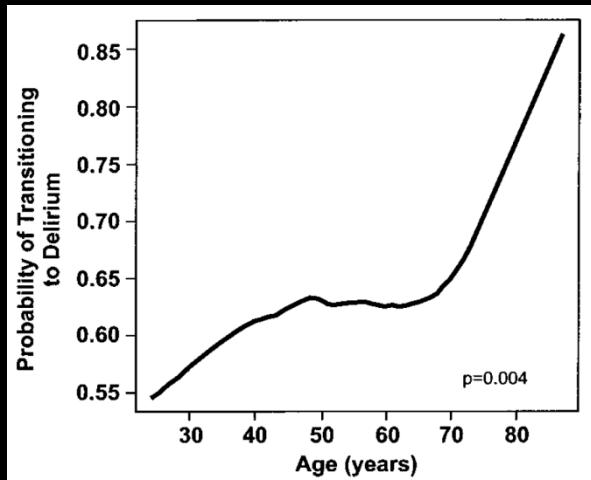
sedatives

Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients

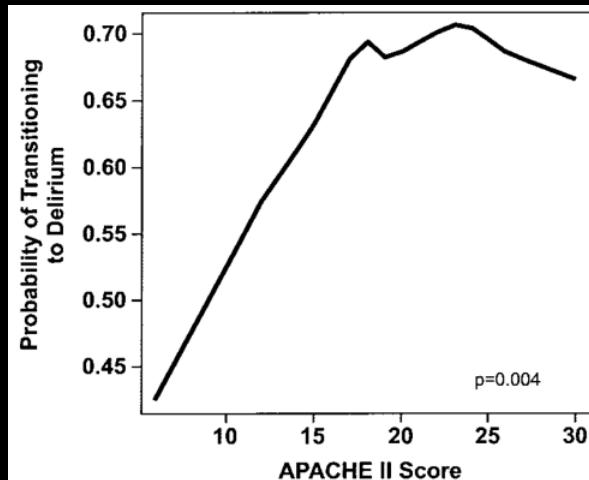
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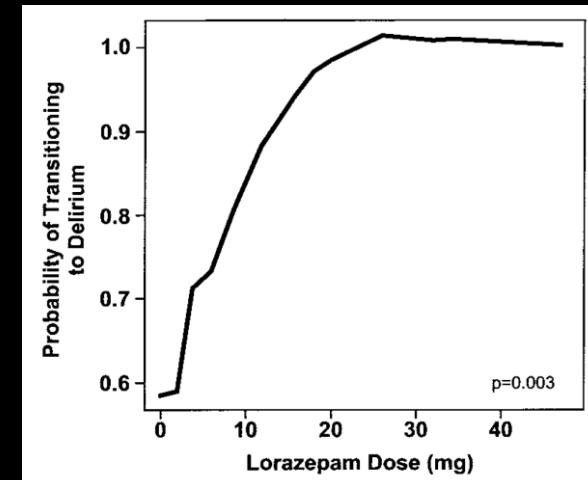
Gordon R. Bernard, M.D.,** E. Wesley Ely, M.D., M.P.H.††



age



severity



sedatives

...only
lorazepam?

Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients

Pratik Pandharipande, M.D., M.S.C.I.,* Ayumi Shintani, Ph.D., M.P.H.,† Josh Peterson, M.D., M.P.H.,‡

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Gordon R. Bernard, M.D.,** E. Wesley Ely, M.D., M.P.H.††

Table 2. Multivariable Analysis of Sedative and Analgesic Medications as Risk Factors for Transitioning to Delirium/Coma or Delirium Only*

Medication	Transitioning to Delirium Only Odds Ratio (95% CI)	P Value
Lorazepam	1.2 (1.1–1.4)	0.003
Midazolam	1.7 (0.9–3.2)	0.09
Fentanyl	1.2 (1.0–1.5)	0.09
Morphine	1.1 (0.9–1.2)	0.24
Propofol	1.2 (0.9–1.7)	0.18

lorazepam?

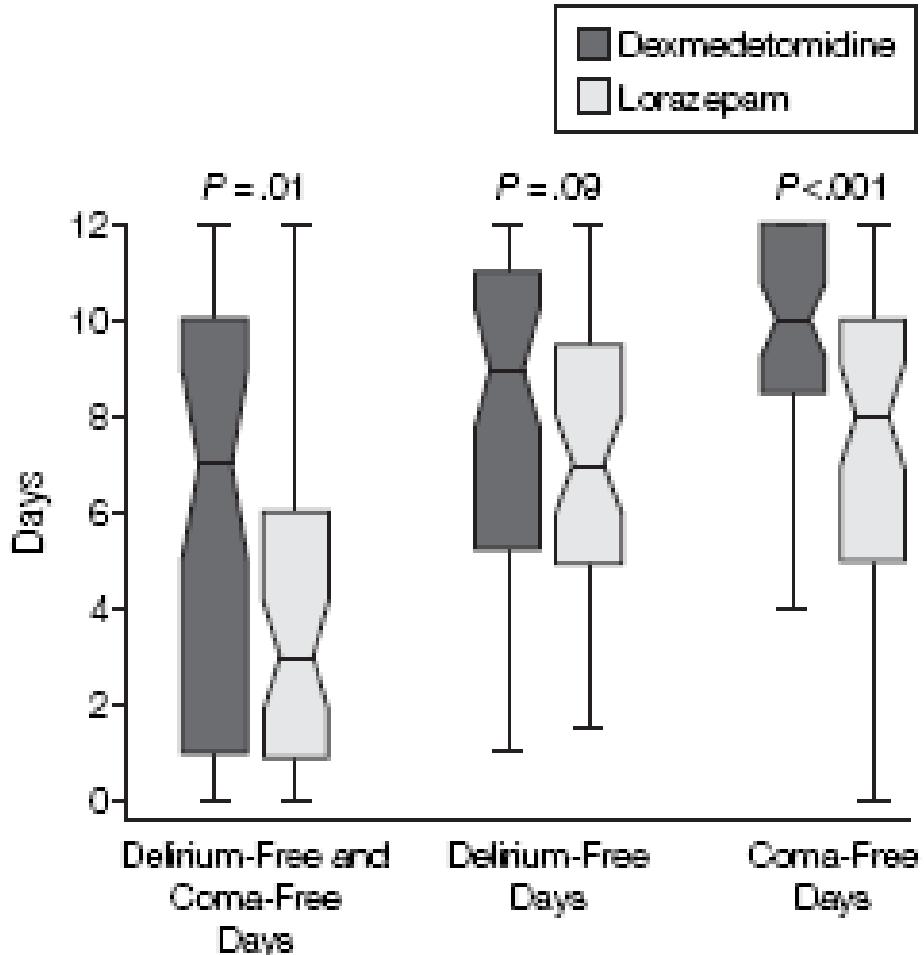
Dexmedetomidine vs Lorazepam

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

The MENDS Randomized
Controlled Trial

Pandharipande P, *JAMA* 2007

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



Pharmacological prophylaxis?

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

The REDUCE Randomized Clinical Trial

Mark van den Boogaard, PhD; Arjen J. C. Slooter, MD, PhD; Roger J. M. Brüggemann, PharmD, PhD; Lisette Schoonhoven, PhD; Albertus Beishuizen, MD, PhD; J. Wytze Vermeijden, MD, PhD; Danie Pretorius, MD; Jan de Koning, MD; Koen S. Simons, MD; Paul J. W. Dennesen, MD, PhD; Peter H. J. Van der Voort, MD, PhD; Saskia Houterman, PhD; J. G. van der Hoeven, MD, PhD; Peter Pickkers, MD, PhD; for the REDUCE Study Investigators

JAMA. 2018;319(7):680-690. doi:[10.1001/jama.2018.0160](https://doi.org/10.1001/jama.2018.0160)

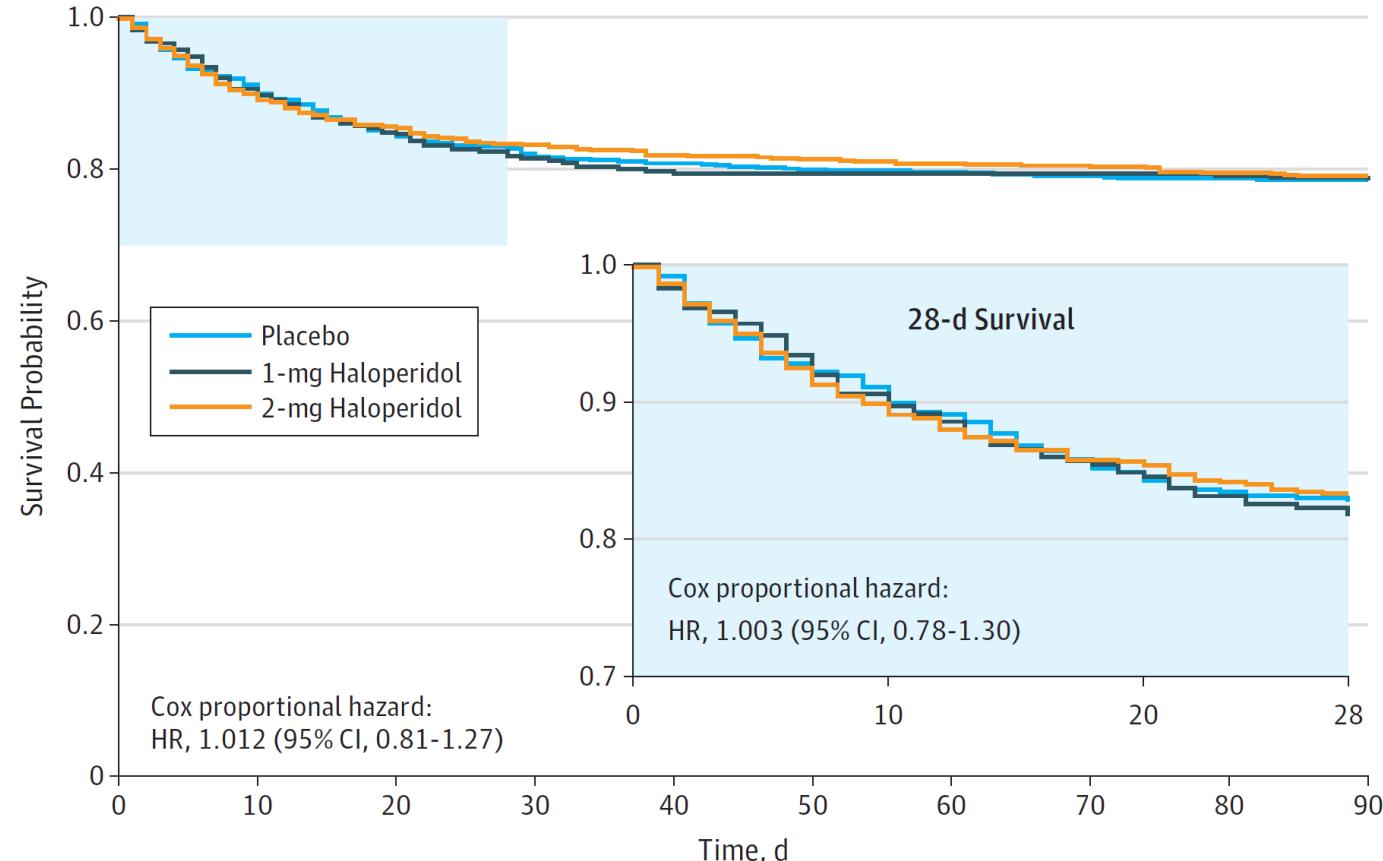
Effect of Haloperidol on Survival Among Critically Ill Adults

With
The R

Mark van de
Albertus Be
Paul J. W. D
Peter Pickke

JAM

Figure 2. Survival Analysis at 28 and 90 Days



No. at risk

Placebo	707	644	600	580	571	565	563	559	557	556
1-mg Haloperidol	350	317	297	285	279	278	278	278	277	276
2-mg Haloperidol	732	658	627	609	599	595	591	589	582	579

Pharmacological prophylaxis?

No, thanks.

Prevention by protocols?

MONITORAGGIO NEUROLOGICO

		infermieri					
medici		Mattino	Pome	Notte			
	Dolore (num + lett)						
	Ansia						
	Contenzione	si	no	si	no	si	no
	RASS						
	Sonno (ore)						
	Agitazione (ore)						
	CAM-ICU (Delirium)	+	-	+	-	+	-
	Valutazione tp. sedativa	I	A	E	I	A	E

BPS
da 3 (minimo)
a 12 (massimo)

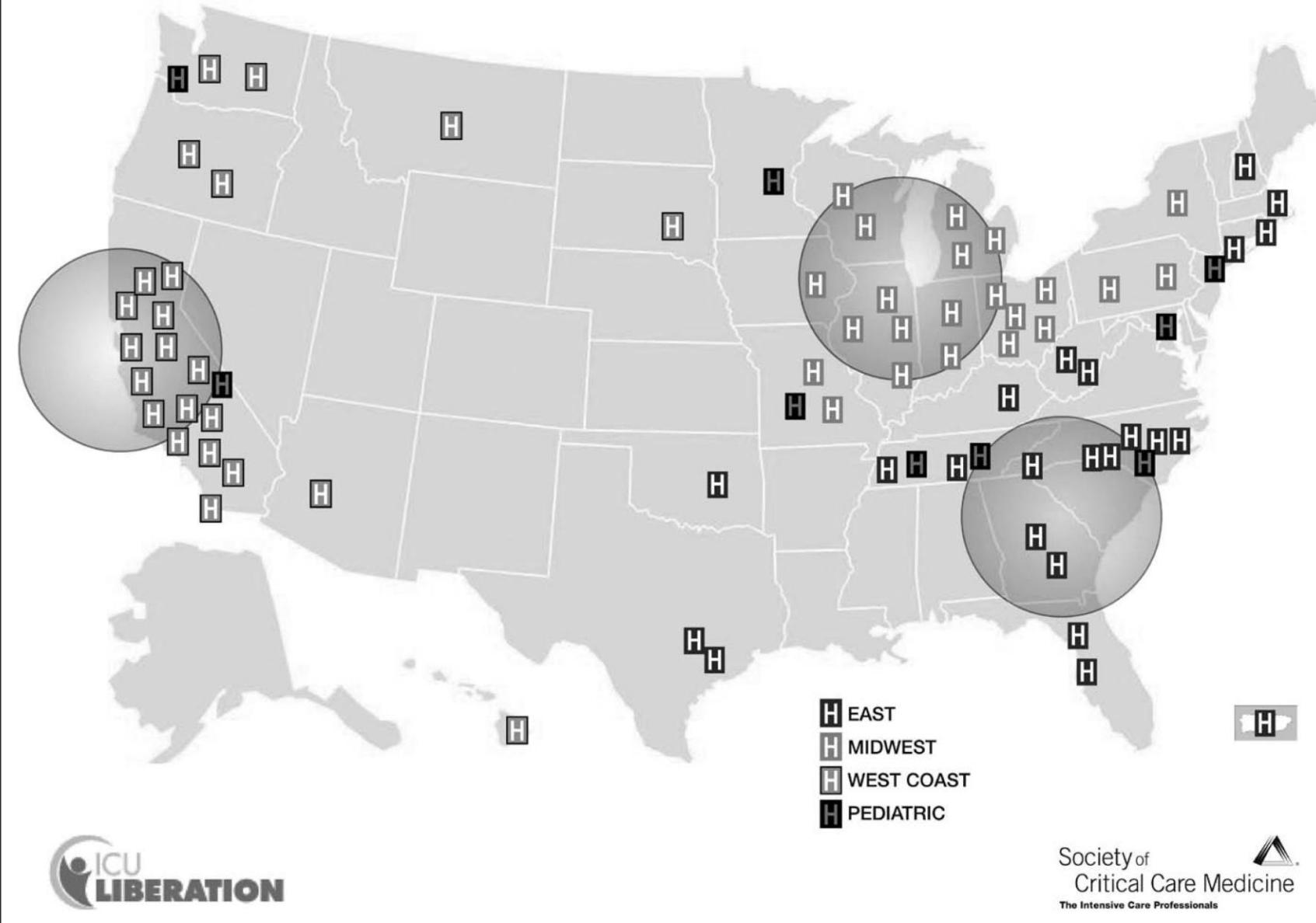
VNR
da 0 (minimo)
a 10 (massimo)

da - 5 (minimo)
a + 4 (massimo)

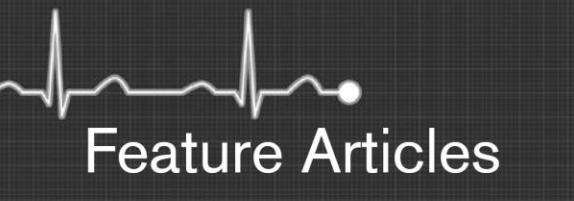
I - insufficiente
A - adeguata
E - eccessiva

- A** ssess for and manage pain
- B** oth spontaneous awakening and breathing trials
- C** hoice of sedation and analgesia
- D** elirium: assess, prevent and manage
- E** arly mobility and exercise
- F** amily engagement and empowerment

ICU Liberation Hospitals and Regions



WEly, Crit Care Med 2017



Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults

Brenda T. Pun, DNP, RN, FCCM¹; Michele C. Balas, PhD, RN, CCRN-K, FCCM, FAAN^{2,3}; Mary Ann Barnes-Daly, MS, RN, CCRN-K, DC⁴; Jennifer L. Thompson, MPH⁵; J. Matthew Aldrich, MD⁶; Juliana Barr, MD, FCCM^{7,8}; Diane Byrum MSN, RN, CCRN-K, CCNS, FCCM⁹; Shannon S. Carson, MD¹⁰; John W. Devlin, PharmD, FCCM¹¹; Heidi J. Engel, PT, DPT¹²; Cheryl L. Esbrook, OTR/L, BCPR¹³; Ken D. Hargett, MHA, FAARC, FCCM¹⁴; Lori Harmon, RRT, MBA, CPHQ¹⁵; Christina Hielsberg, MA¹⁵; James C. Jackson, PsyD¹; Tamra L. Kelly, BS, RRT, MHA⁴; Vishakha Kumar, MD, MBA¹⁵; Lawson Millner, RRT¹⁶; Alexandra Morse, PharmD⁴; Christiane S. Perme, PT, CCS, FCCM¹⁴; Patricia J. Posa, BSN, MSA, CCRN-K¹⁷; Kathleen A. Puntillo, PhD, RN, FCCM, FAAN¹⁸; William D. Schweickert, MD¹⁹; Joanna L. Stollings, PharmD, FCCM²⁰; Alai Tan, PhD²; Lucy D'Agostino McGowan, PhD²¹; E. Wesley Ely, MD, MPH, FCCM^{1,22}

Objective: Decades-old, common ICU practices including deep sedation, immobilization, and limited family access are being challenged. We endeavoured to evaluate the relationship between ABCDEF bundle performance and patient-centered outcomes in critical care.

Design: Prospective, multicenter, cohort study from a national quality improvement collaborative.

Setting: 68 academic, community, and federal ICUs collected data during a 20-month period.

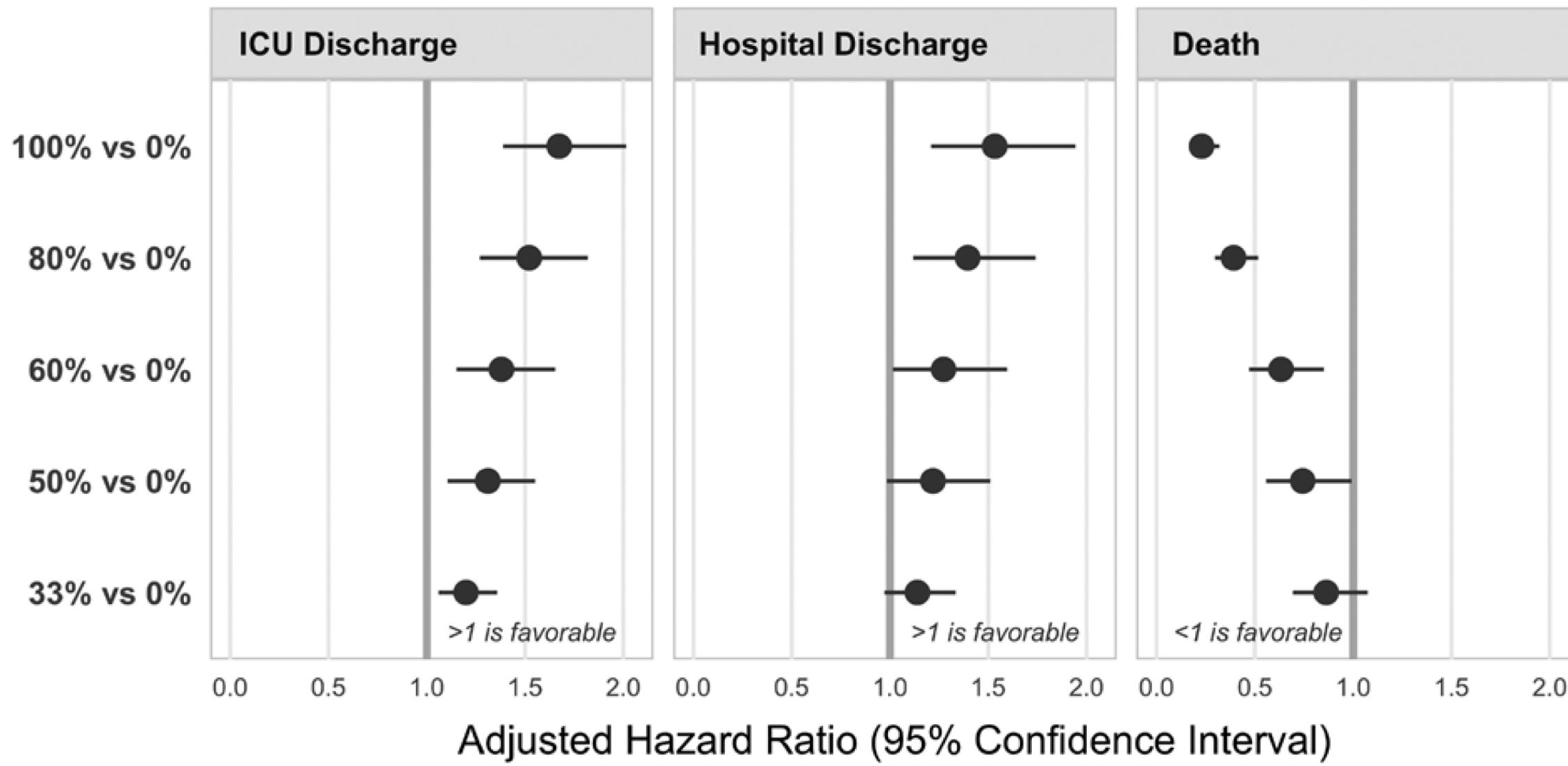
Patients: 15,226 adults with at least one ICU day.

Interventions: We defined ABCDEF bundle performance (our main exposure) in two ways: 1) complete performance (patient received every eligible bundle element on any given day) and 2) proportional performance (percentage of eligible bundle elements performed on any given day). We explored the association between complete and proportional ABCDEF bundle performance and three sets of outcomes: patient-related (mortality, ICU and hospital discharge), symptom-related (mechanical ventilation, coma, delirium, pain, restraint use), and system-related (ICU readmission, discharge destination). All models were adjusted for a minimum of 18 a priori determined potential confounders.

TABLE 2. Outcomes for Patients With Complete (vs Incomplete) ABCDEF Bundle Performance: Data are Adjusted Hazard Ratios and Adjusted Odds Ratios

Outcomes	Complete Bundle Performance	p Value
Patient-Related Outcomes	Adjusted Hazard Ratio (95% CI)	
ICU discharge ^a	1.17 (1.05–1.30)	< 0.004
Hospital discharge ^b	1.19 (1.01–1.40)	< 0.033
Death ^c	0.32 (0.17–0.62)	< 0.001
Symptom-Related Outcomes^d	AOR (95%CI)	
Mechanical ventilation	0.28 (0.22–0.36)	< 0.0001
Coma	0.35 (0.22–0.56)	< 0.0001
Delirium	0.60 (0.49–0.72)	< 0.0001
Significant pain	1.03 (0.88–1.21)	0.7000
Physical restraints	0.37 (0.30–0.46)	< 0.0001
System-Related Outcomes	AOR (95%CI)	
ICU readmission ^e	0.54 (0.37–0.79)	< 0.001
Discharge destination ^f	0.64 (0.51–0.80)	< 0.001

Proportion of ABCDEF Bundle Elements Performed



- A** ssess for and manage pain
- B** oth spontaneous awakening and breathing trials
- C** hoice of sedation and analgesia
- D** elirium: assess, prevent and manage
- E** arly mobility and exercise
- F** amily engagement and empowerment

The ABCDEF How ICU Lib

E. Wesley Ely, MD, M



ICU Liberation: ABCDEF Bundle



Symptoms Pain, Agitation, Delirium Guidelines	Monitoring Tools	Care ABCDEF Bundle	Done
Pain	Critical-Care Pain Observation Tool (CPOT) NRS Numeric Rating Scale BPS Behavioral Pain Scale	A: Assess, Prevent and Manage Pain B: Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT) C: Choice of Analgesia and Sedation D: Delirium: Assess, Prevent and Manage E: Early Mobility and Exercise F: Family Engagement and Empowerment	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Agitation	Richmond Agitation-Sedation Scale (RASS) Sedation-Agitation Scale (SAS)		
Delirium	Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) Intensive Care Delirium Screening Checklist (ICDSC)		



bundle



Care	Done
ABCDEF Bundle	
Assess, Prevent and Manage Pain	<input type="checkbox"/>
Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT)	<input type="checkbox"/>
Choice of Analgesia and Sedation	<input type="checkbox"/>
Delirium: Assess, Prevent and Manage	<input type="checkbox"/>
Early Mobility and Exercise	<input type="checkbox"/>
Family Engagement and Empowerment	<input checked="" type="checkbox"/> <input type="checkbox"/>

Pharmacological prophylaxis?

No, thanks.

Prevention by protocols?

Yes !!!

RESEARCH

Open Access



CrossMark

Risk factors for new-onset delirium in patients with bloodstream infections: independent and quantitative effect of catheters and drainages—a four-year cohort study

Tolga Dittrich¹, Sarah Tschudin-Sutter², Andreas F. Widmer², Stephan Rüegg³, Stephan Marsch⁴ and Raoul Sutter^{3,4*}

RESEARCH

Risk factors in patients independent of catheter study

Tolga Dittrich¹ and Raoul Suttorp²

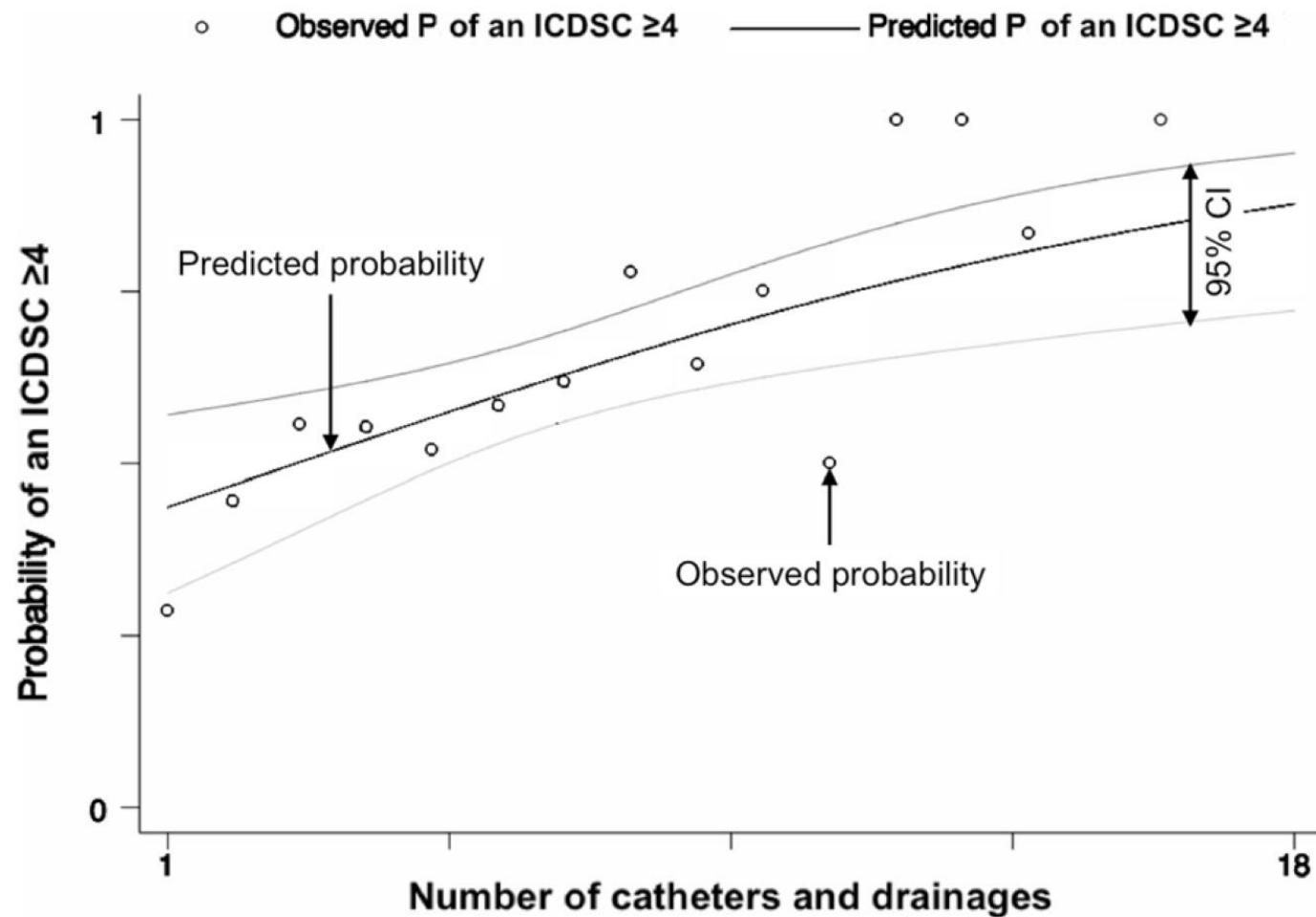


Fig. 2 Probability of an ICDSC ≥ 4 during bloodstream infections in relation to the number of catheters and drainages. ICDSC Intensive Care Delirium Screening Checklist, CI confidence interval

RESEARCH

Risk factors for delirium in patients with bloodstream infections

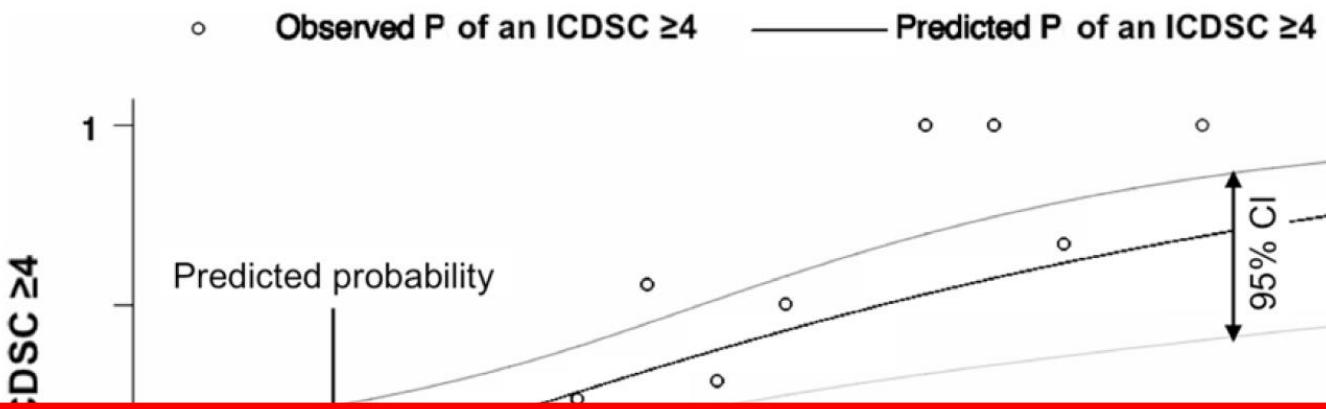


Table 4 Uni- and multivariable logistic regression analyses of predictors for an ICDSC ≥ 4 during bloodstream infections ($n = 240$)

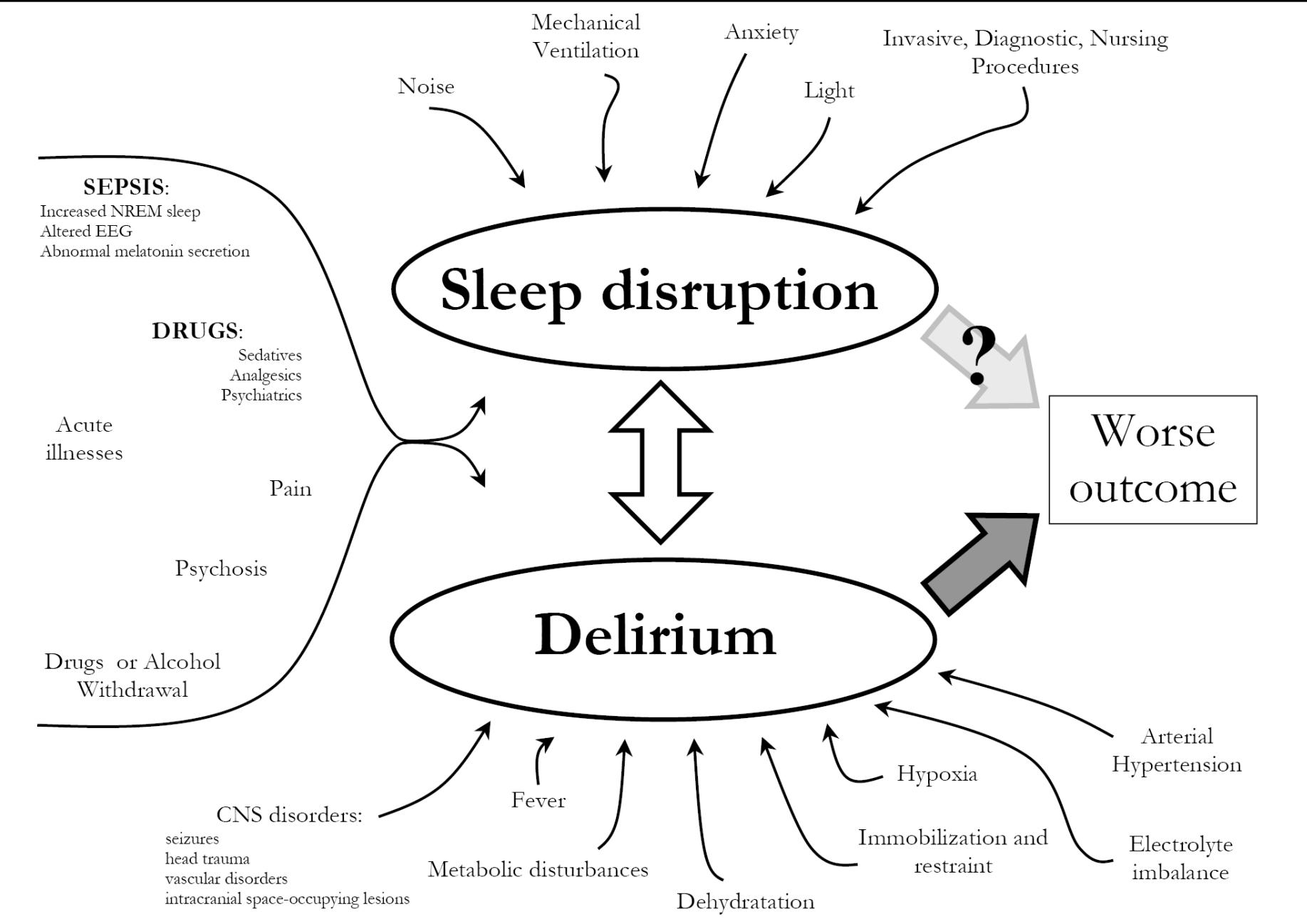
Predictors for ICDSC ≥ 4 during BSI	Univariable			Multivariable* (stepwise model selection by Akaike information criterion)		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.04	1.02–1.06	<0.001	1.04	1.02–1.06	<0.001
Male gender	2.00	1.14–3.42	0.015	2.26	1.17–4.36	0.015
SAPS II	1.01	0.99–1.03	0.063	–	–	–
SAS	1.20	1.01–1.42	0.041	1.18	0.96–1.45	0.117
SOFA score	1.06	1.00–1.14	0.059	–	–	–
Dementia and/or leukoencephalopathy	2.23	0.79–6.31	0.130	–	–	–
Albumin at admission (for every increasing mg/L)	0.96	0.92–0.99	0.016	–	–	–
Number of catheters and drainages (for every additional catheter)	1.14	1.05–1.24	0.002	1.14	1.04–1.25	0.004

BSI bloodstream infections, ICDSC Intensive Care Delirium Screening Checklist, SAPS simplified acute physiology score, SAS Riker Sedation-Agitation Scale, SOFA score Sequential [Sepsis-related] Organ Failure Assessment Score

* Stepwise forward and backward selection including all variables presented in the table yielded identical results; italic p values are considered significant

Strategies to prevent ICU delirium

- 1) Measure it !
- 2) Treat reversible causes:
 - Underlying infection (sepsis), maintain normotermia
 - Correct hypoxia
 - Ensure adequate cerebral perfusion (CHF)
 - Correct metabolic disturbances (electrolites, blood glucose)
- 3) Frequent reorientation of patient by nurse and family
- 4) Analgesia and goal-directed **conscious** sedation
- 5) Weaning from mechanical ventilation as soon as possible
- 6) Early mobilization and physical therapy
- 7) Attention to optimizing sleep patterns





Abnormal Sleep, Circadian Rhythm Disruption, and Delirium in the ICU: Are They Related?

Marietou Daou^{1,2}, Irene Telias^{1,2,3,4}, Magdy Younes⁵, Laurent Brochard^{1,3,4} and M. Elizabeth Wilcox^{1,2*}

¹ Interdepartment Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada, ² Department of Medicine (Respirology), University Health Network, Toronto, ON, Canada, ³ Department of Medicine (Critical Care Medicine), St. Michael's Hospital, Toronto, ON, Canada, ⁴ Keenan Research Centre, Li Ka Shing Knowledge Institute, Toronto, ON, Canada, ⁵ Sleep Disorders Centre, Winnipeg, MB, Canada

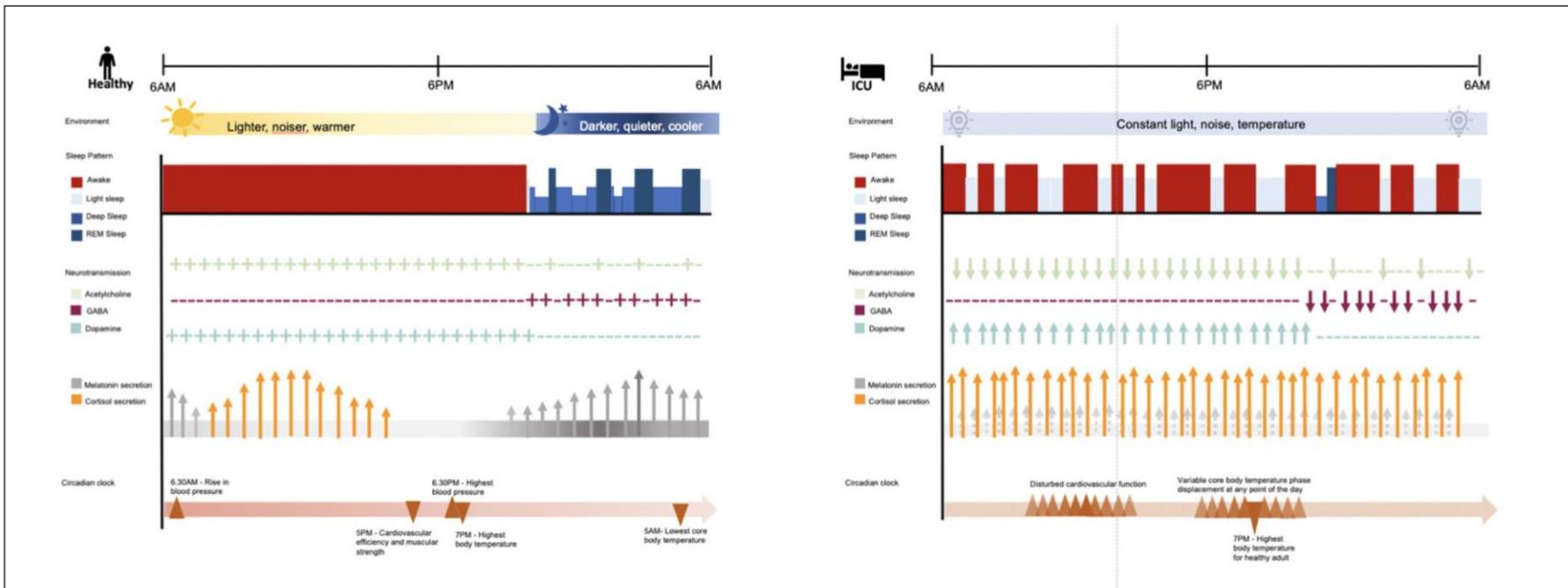


FIGURE 1 | Comparison of sleep and circadian rhythms in healthy adult and adult with critical illness in the ICU. In a healthy adult, the circadian clock is synced to the daily external cycle of changing light, sound, and temperature. The sleep stage of a healthy adult occurs during the night and is composed of 2–5% light sleep, 48–70% deep sleep, 20–25% rapid eye movement (REM) sleep. REM sleep reoccurs in cycles of 90–120 min. Acetylcholine is predominantly discharged during wakefulness and REM sleep; while GABAergic activity is predominant during deep sleep. Dopaminergic activity promotes alertness and reduces sleep. Melatonin secretion starts around 9.30 pm (dim light melatonin onset) and stops around 7.30 am, peaking around 3 am. Cortisol secretion starts in the early morning, peaks around 10 am in correspondence to the time of highest alertness, and keeps declining gradually throughout the day, and the night. Overall, these processes coordinate physiological functions including cardiovascular functions and temperature. In contrast, the intensive care unit (ICU) constant artificial environment disrupts the daily cycle of circadian functions. In the ICU critically ill patients, compared to healthy adults, present equal to normal sleep time in the course of 24 h but the majority of it consists of light sleep; 50% of sleep time is distributed during the day and disturbed by frequent arousals. For instance, benzodiazepine decrease sleep latency, slow wave sleep (SWS) and REM sleep duration and frequency; propofol suppresses SWS EEG bursts; opioids alter REM sleep; while, dexmedetomidine improve stage 2 and sleep efficiency by shifting 75% of sleep to nighttime. In ICU patients, the acute stress environment has been associated with decreased GABAergic and cholinergic transmission, and increased dopaminergic transmission, impaired melatonin secretion and increased cortisol production, along with displacement of physiological functions normally coordinated by the circadian clock. These disturbances have been associated with symptoms of delirium. ICU, intensive care unit; REM, rapid eye movement; GABA, gamma-aminobutyric acid.

SLEEP

SEDATION

Fully reversible

Spontaneous

Circadian

Essential
biological function

Cyclic
EEG stages
progression

Not reversible

Continuous
norepinephrine
secretion

Sleep with
altered
architecture

Muscle hypotonia

Temperature disregulation

Disconjugate eye movement

Respiration depression

BMJ Open Feasibility of melatonin for prevention of delirium in critically ill patients: a protocol for a multicentre, randomised, placebo-controlled study

Lisa Burry,¹ Damon Scales,² David Williamson,³ Jennifer Foster,⁴ Sangeeta Mehta,⁵ Melanie Guenette,⁶ Eddy Fan,⁷ Michael Detsky,^{8,9} Azar Azad,¹⁰ Francis Bernard,^{11,12} Louise Rose¹³

Martinez et al. *Trials* (2017) 18:4
DOI 10.1186/s13063-016-1751-0

Trials

STUDY PROTOCOL

Open Access



Prophylactic Melatonin for Delirium in Intensive Care (Pro-MEDIC): study protocol for a randomised controlled trial

F. Eduardo Martinez^{1*} , Matthew Anstey^{2,3,4}, Andrew Ford⁵, Brigit Roberts⁶, Miranda Hardie⁷, Robert Palmer⁶, Lynn Choo⁷, David Hillman^{8,9}, Michael Hensley¹⁰, Erin Kelty¹¹, Kevin Murray¹², Bhajan Singh^{13,14,15} and Bradley Wibrow^{16,17}

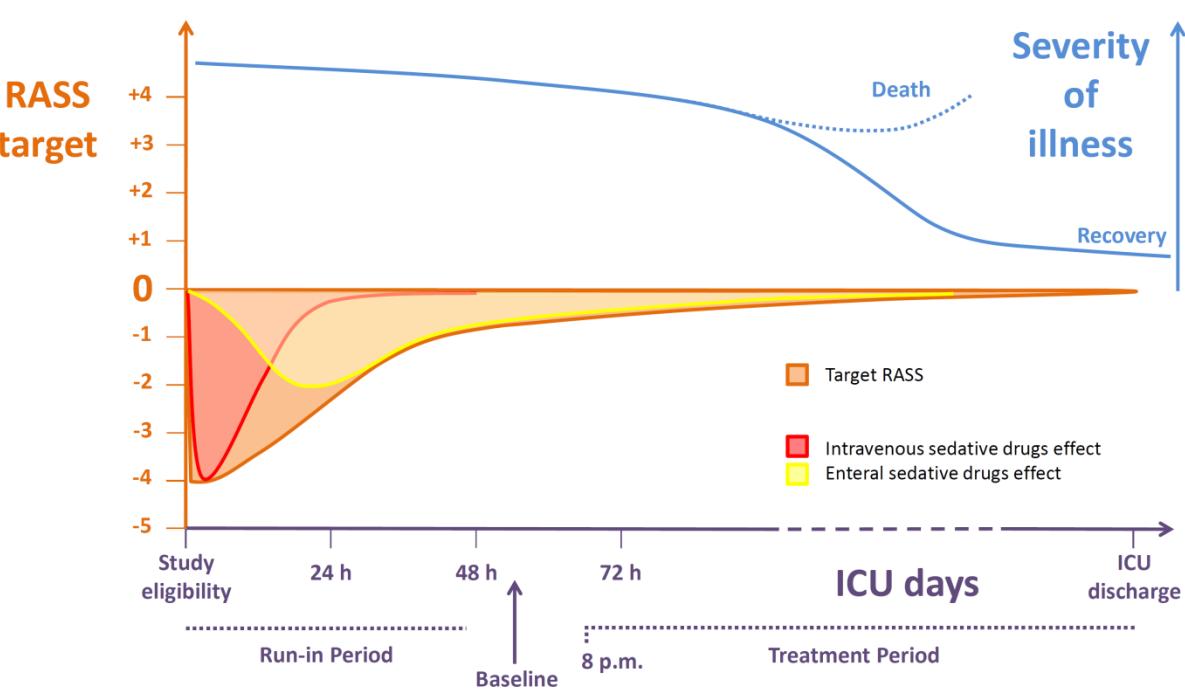


ORIGINAL ARTICLE

Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial

G. MISTRALETTI ^{1, 2}, M. UMBRELLO ², G. SABBATINI ¹, S. MIORI ¹, M. TAVERNA ¹
B. CERRI ², E. S. MANTOVANI ², P. FORMENTI ², P. SPANU ², A. D'AGOSTINO ³
S. SALINI ⁴, A. MORABITO ^{5, 6}, F. FRASCHINI ⁷, R. J. REITER ⁸, G. IAPICHINO ^{1, 2}

¹Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy; ²U.O. Anestesia e Rianimazione, A. O. San Paolo-Polo Universitario, Milan, Italy; ³Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy; ⁴Dipartimento di Economia, Management e Metodi Quantitativi Università



Reasons for sedation

Invasive procedures and clinical stabilization

Use of sedative drugs for «patients adaptation» to critical illnesses (anxiety/agitation, oxygen consumption decrease, compliance with mechanical ventilation, ...)

Drugs provided by local guidelines

Propofol or Midazolam i.v.

Hydroxizine (max 600mg/die) via NGT/NJT

Lorazepam (max 16mg/die) via NGT/NJT

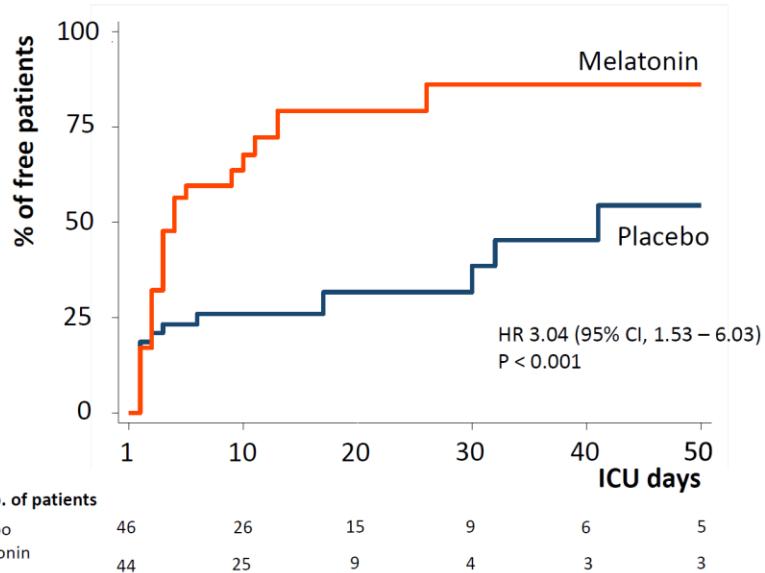
Melatonin (6mg/die) via NGT/NJT

Double-blind RCT

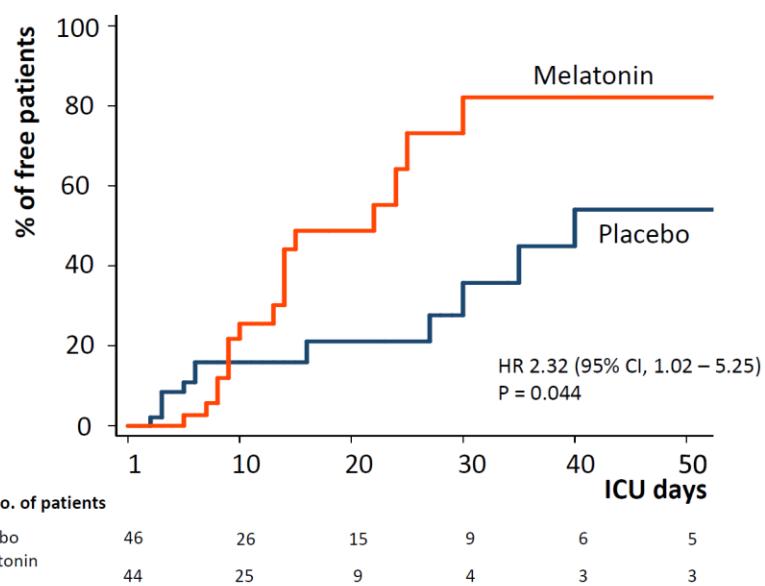
from 3rd ICU day to ICU discharge day

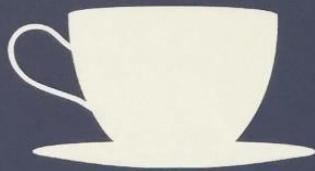
Placebo via NGT/NJT

A Primary outcome: weaning from sedative and analgesic drugs



B Secondary outcome: weaning from mechanical ventilation

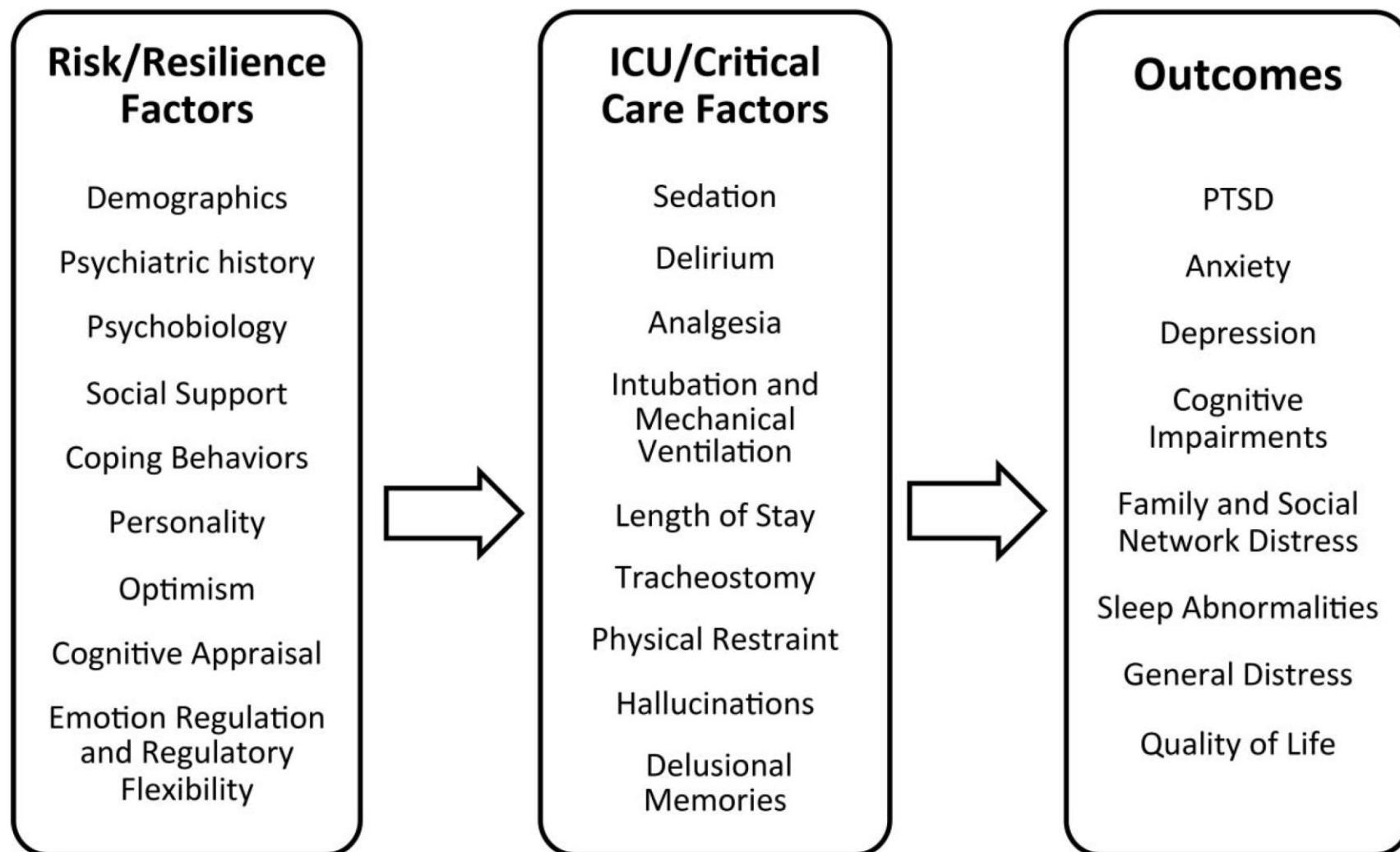




KEEP CALM
USE LESS
AND
TRUST IN
PHYSIOLOGY



... facendo una
«medicina di precisione»,
personalizzata,
in Terapia Intensiva.



icudelirium.org

RESEARCH DESIGNED TO TURN
MIRRORS INTO WINDOWS

HOME

DELIRIUM

SEDATION

OUTCOMES

REFERENCES

OUR GROUP

ICU DELIRIUM AND COGNITIVE IMPAIRMENT STUDY GROUP



A new frontier in critical care:
saving the injured brain.

E. Wesley Ely, 2008



Il nostro obiettivo
non può essere solo
aggiungere giorni alla vita.

Dobbiamo mettere
vita in quei giorni.

Grazie dell'attenzione



giovanni.mistraletti@unimi.it

Relazione su: “**sedazione, curarizzazione e monitoraggio**”

1) Quali scale per la misura di sedazione e agitazione hanno migliori proprietà psicometriche?

- a. Scala di Ramsay
- b. RASS e SAS**
- c. Glasgow Coma Scale
- d. CAM-ICU

2) Quali farmaci hanno un effetto protettivo sullo sviluppo di delirium in Terapia Intensiva?

- a. uso analgesico della ketamina al posto degli oppiacei
- b. aloperidolo al posto degli antipsicotici atipici
- c. sedativi non benzodiazepinici al posto delle benzodiazepine**
- d. anestetici inalatori al posto del propofol

3) Quali sono le strategie efficaci nel ridurre la prevalenza e la durata del delirium in Terapia Intensiva?

- a. utilizzare precocemente e mantenere nel tempo un target di sedazione cosciente
- b. implementare programmi di fisioterapia e mobilizzazione del paziente
- c. favorire l'ingresso dei familiari e impostare terapie condivise
- d. tutte le risposte precedenti sono corrette**

Le risposte giuste sono evidenziate in grassetto: 1)b, 2)c, 3)d.



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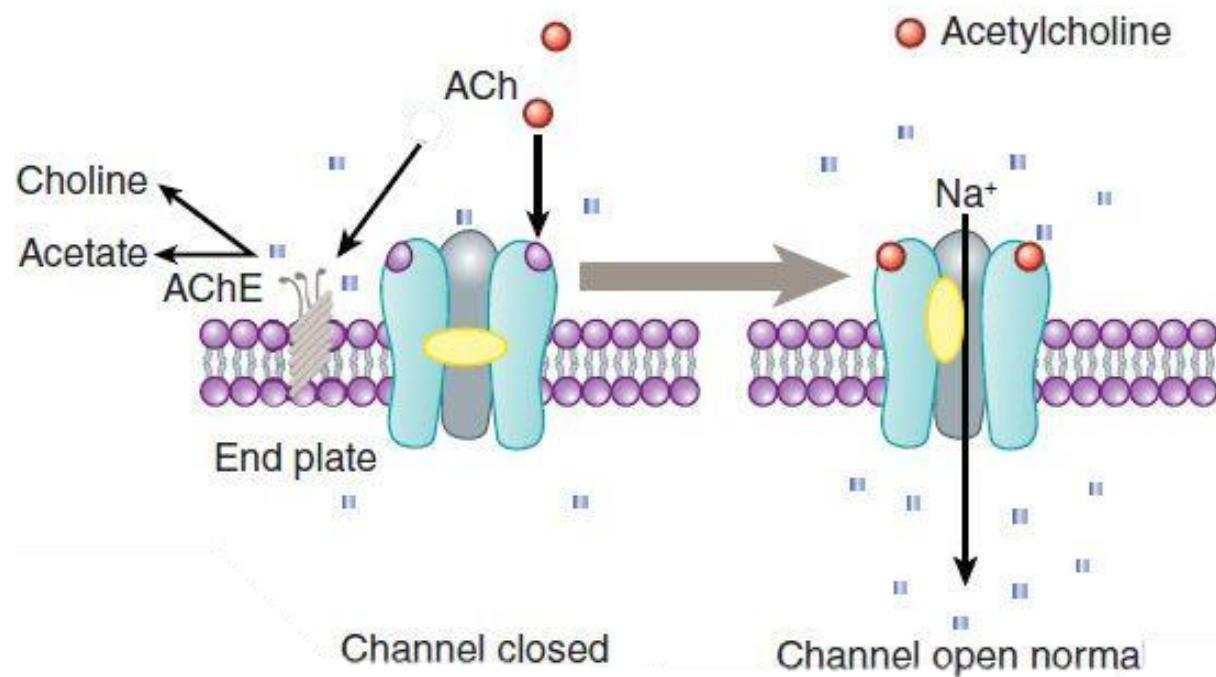
Neuromuscular Blocking Agents in Critically Ill Patients

01/10/21

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Normal Neuromuscular Function

- Acetylcholine then diffuses across the synaptic cleft to activate nicotinic receptors (N_M) located on the motor end plate
- The binding of two acetylcholine molecules to receptors on the $\alpha\beta$ and $\delta\alpha$ subunits causes opening of the channel.
- The subsequent movement of sodium and potassium through the channel is associated with a graded depolarization of the end plate membrane



Classification and Mechanism of Action

- Neuromuscular blocking agents (NMBAs) paralyze skeletal muscles by blocking the transmission of nerve impulses at the myoneural junction.

- DEPOLARIZING NMBAs:

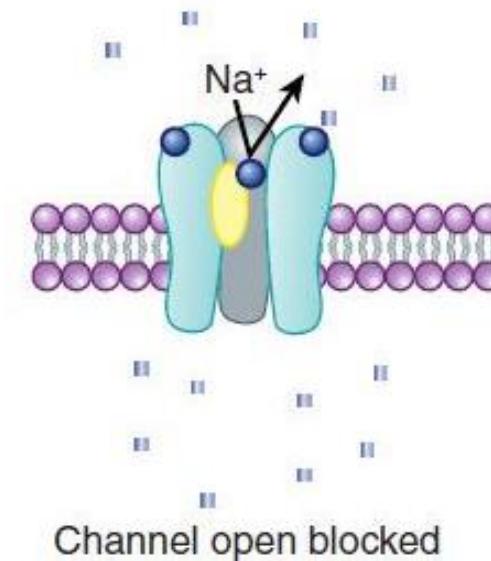
bind to cholinergic receptors on the motor endplate, causing depolarization of the endplate membrane.

The NMBAs prevents the normal closure of the channel gate and the blocker may move rapidly in and out of the pore.

Depolarizing blockers may desensitize the end plate by occupying the receptor and causing persistent depolarization.

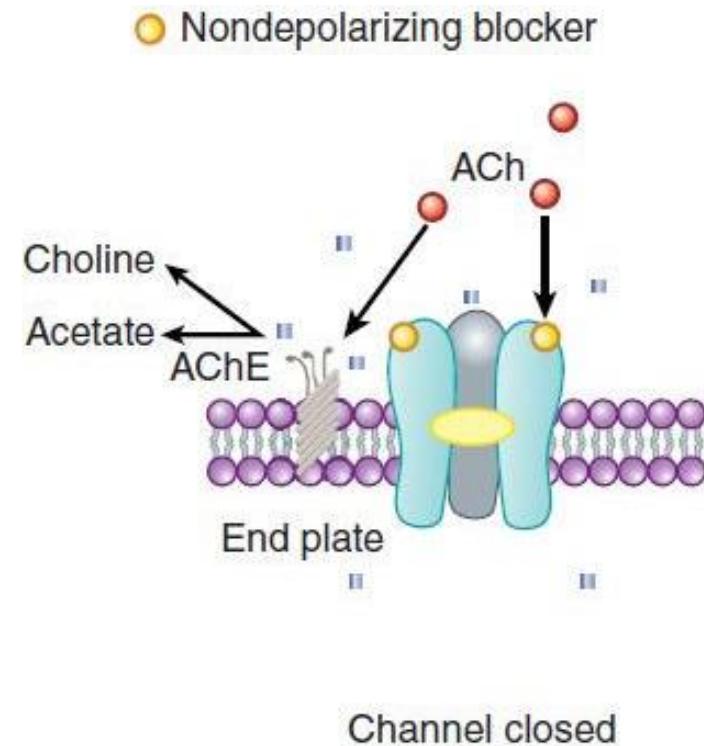
- E.g. Succinylcholine

● Depolarizing blocker



Classification and Mechanism of Action

- Neuromuscular blocking agents (NMBAs) paralyze skeletal muscles by blocking the transmission of nerve impulses at the myoneural junction.
- NON-DEPOLARIZING NMBAs:
competitive inhibition of the ACh receptor on the motor endplate.
prevents the conformational change in the receptor or physically obstructs the ion channels
 - aminosteroid compounds
(e.g. pancuronium, vecuronium, rocuronium)
 - benzylisoquinolinium compounds
(e.g. atracurium, cisatracurium, mivacurium).



Properties of neuromuscular blocking agents

Table 1. Neuromuscular blocking agents

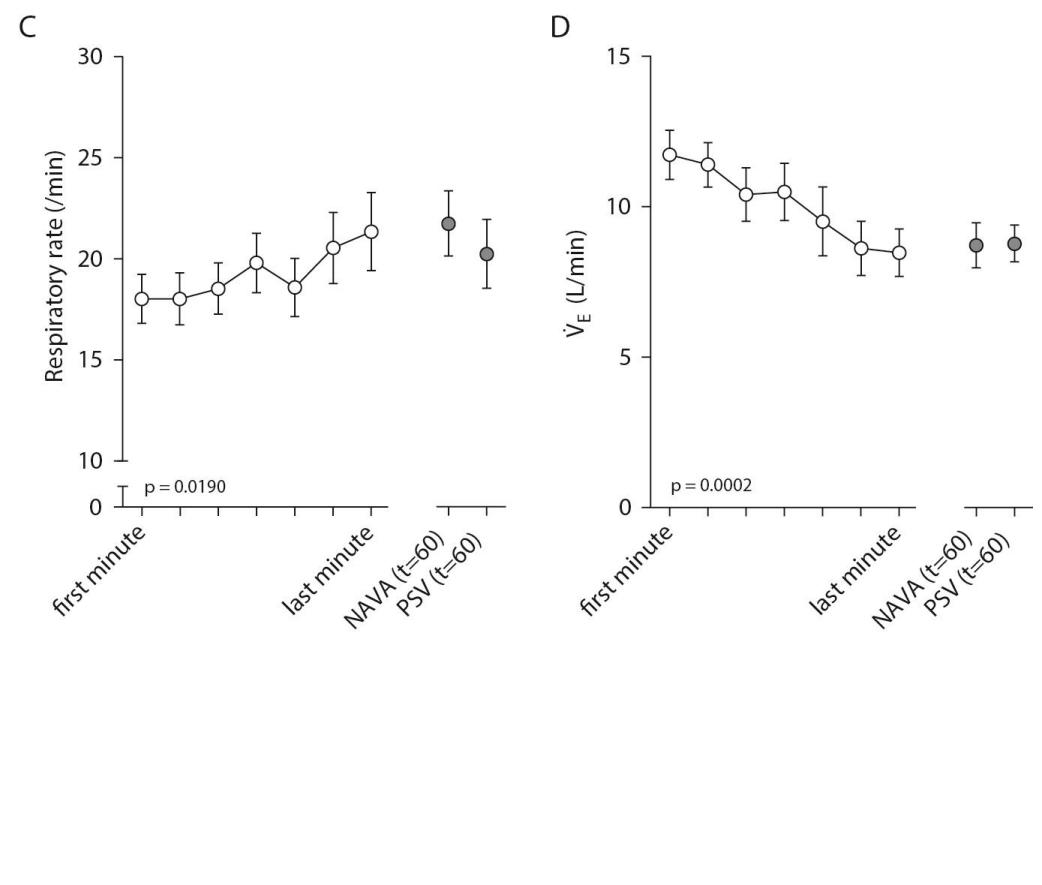
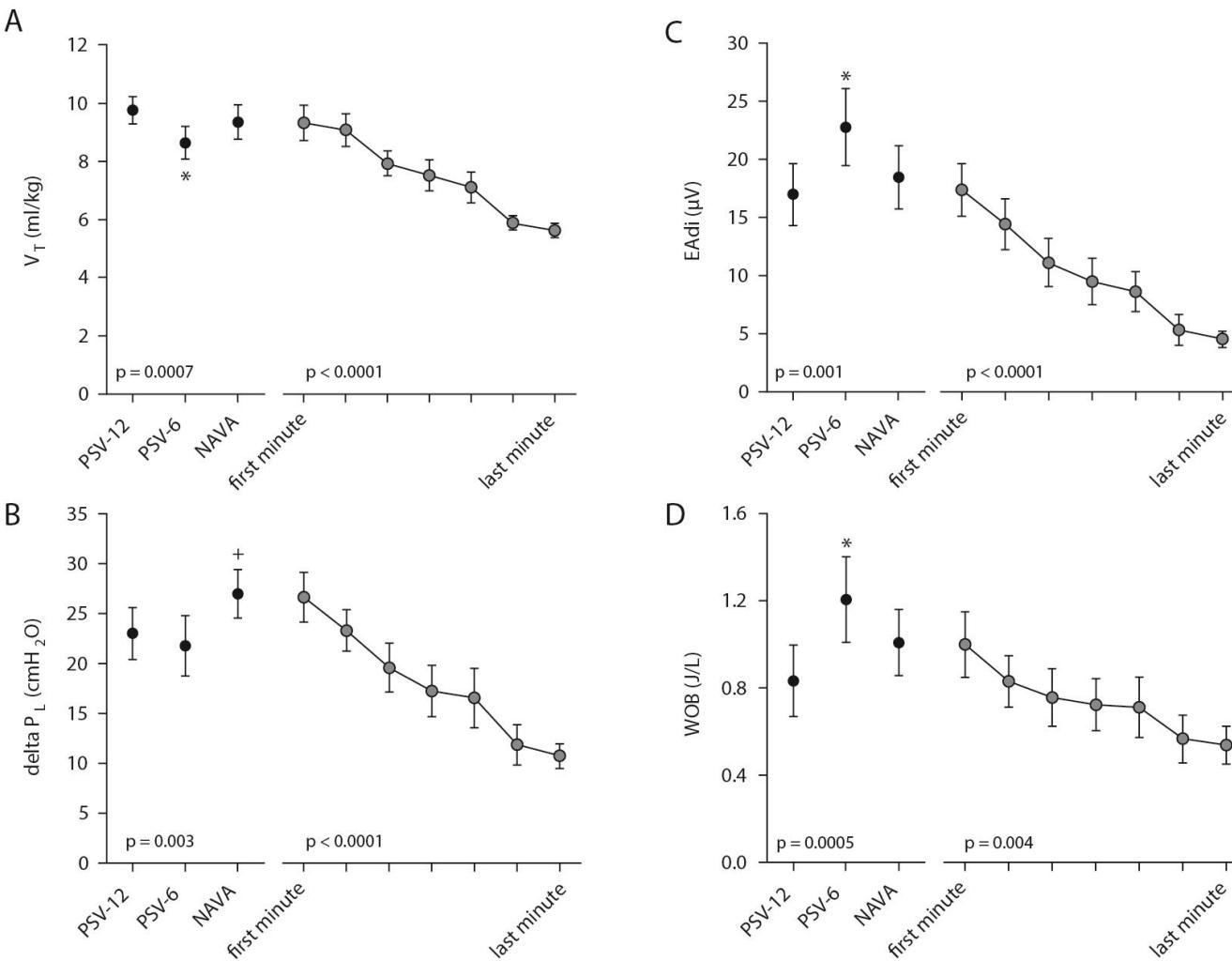
		Start of effect (min)	End of effect (min)	Dose (bolus) (mg kg⁻¹)	Dose (infusion) (mcg kg⁻¹ min⁻¹)	Elimination	Side effect
Pancuronium	Long effect	2-3	60-100	0.05-0.1	0.8-1.7	45%-70% renal, 15% hepatic	Vagal blockade, sympathetic stimulation
Vecuronium	Moderate effect	3-4	20-35	0.08-0.1	0.8-1.7	10%-50% renal, 35%-50% hepatic	Vagal blockade in high dose
Rocuronium	Moderate effect	1-2	20-35 (60-80 with high induction dose)	0.6-1 (1-1.2 for high induction)	8-12	33% renal, <75% hepatic	Vagal blockade in high dose
Atracurium	Moderate effect	3-5	20-35	0.4-0.5	5-20	5%-10% renal, Hoffman elimination	Histamine release, minimal ganglionic blockade
Cisatracurium	Moderate effect	2-3	30-60	0.1-0.2	1-3	5%-10% renal, Hoffman elimination	None
Succinylcholine	Short effect	<1	5-10	1 (higher doses in children)	Mostly no infusion use	Plasma cholinesterase	Minimal histamine release, muscarinic stimulation (bradycardia)



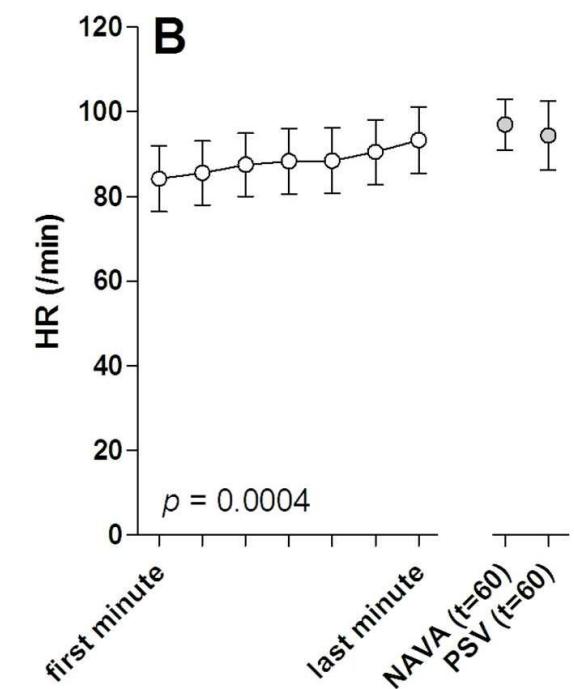
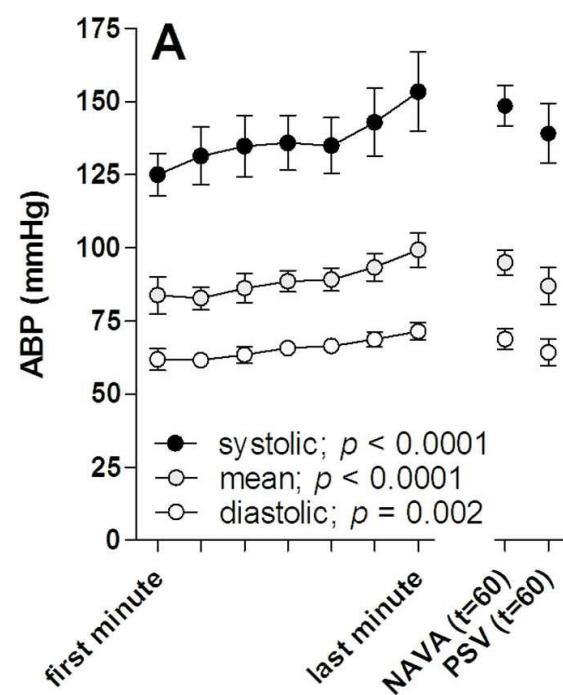
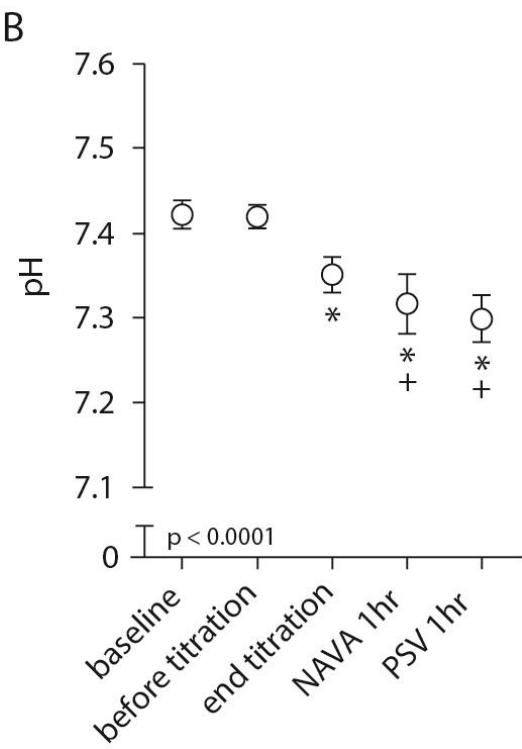
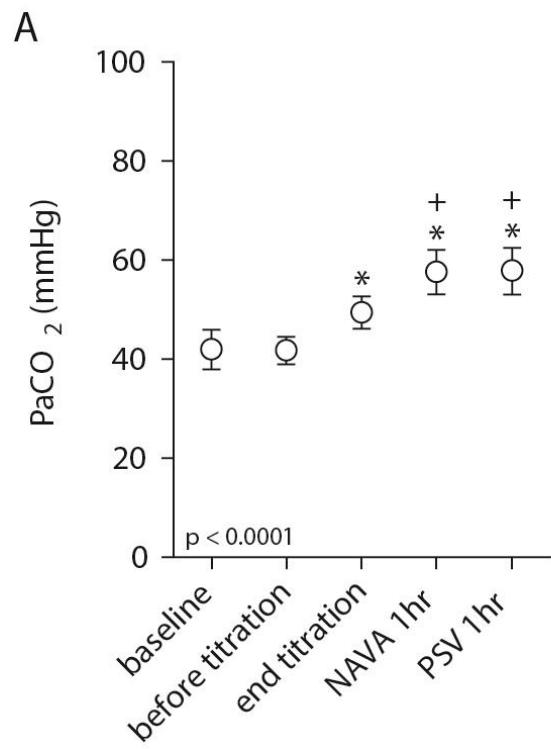
Main indications for the use of neuromuscular blocking agents in the ICU

- NMBAs are **not** first line agents for managing undesired movement, agitation, or ventilator asynchrony, since they do not have sedative, amnestic or analgesic properties.
- The use of NMBAs in patients with severe hypoxemia (ARDS) or status asthmaticus facilitate mechanical ventilation, decrease oxygen consumption, increase chest wall compliance, prevent respiratory asynchronies (double triggering), and facilitate permissive hypercapnia
- The use of NMBAs in patients with ARDS has remained unclear since data are conflicting. (ACURASYS 2010 vs. ROSE 2019 trials)

Partial Neuromuscular Blockade in Sedated Patients with High Tidal Volumes



But with some drawbacks...



Main indications for the use of neuromuscular blocking agents in the ICU

- To facilitate short procedures under general anesthesia (endotracheal intubation, emergent intubation, rapid sequence intubation, bronchoscopy, gastrointestinal endoscopy, specialized radiologic procedures)
- To abolish shivering response (therapeutic hypothermia following cardiac arrest)
- To decrease oxygen consumption during cardiogenic shock
- To prevent unwanted motor movement such as respiratory distress, and coughing on tracheal suction in patients with increased intracranial pressure or massive hemoptysis
- To facilitate treatment of medical conditions associated with increased muscular activity: tetanus, neuroleptic malignant syndrome

Which NMBAs to choose in ICU?

The choice between agents in the ICU depends on:

1. the indication: timing.
2. the patient's comorbidities: renal failure, liver failure, and hyperkalemia, etc.



Cisatracurium: continuous infusions, metabolism is unrelated to renal or hepatic function (Hoffman's reaction), decreased incidence of ICU acquired weakness.

Rocuronium: endotracheal intubation in the ICU, rapid onset and intermediate duration of action, fast reversal (Sugammadex).

Succinylcholine: endotracheal intubation in the ICU, rapid onset and short duration of action.

Contraindications to succinylcholine (e.g. hyperkalemia, burns, stroke, susceptibility to malignant hyperthermia, denervation)

Factors Affecting the response to NMBAs

Neuromuscular disease: miastenia gravis (cholinergic crisis, resistant to depolarizing agents, very sensitive to nondepolarizing NMBAs)
denervation (upregulation of nicotinic acetylcholine receptors (nAChRs))

Burns: burn injury upregulates extrajunctional nAChRs beginning within 24 hours of injury.

Elderly: the effects of steroidal NMBAs are prolonged due to decreased volume of distribution, changes in circulatory physiology, decreased regional renal and hepatic blood flow, and anatomic changes at the neuromuscular junction (NMJ)

Factors Affecting the response to NMBAs

Hepatic and renal disease: increase aminosteroid compounds half-life

Drug interactions: drugs that potentiate the action of NMBAs, local anesthetics, aminoglycosides, polymyxine B, tetracycline., magnesium, calcium channel blockers, beta-adrenergic blockers, immunosuppressive agents (cyclophosphamide, cyclosporine). dantrolene, diuretics, Lithium carbonate...

Hypothermia: prolonged response to nondepolarizing NMBAs. The effect is proportional to the degree of hypothermia. Neuromuscular monitoring is still reliable and can help guide neuromuscular blockade management in the hypothermic patient.

Factors Affecting the response to NMBAs

Electrolyte disturbances

- Hypermagnesemia, hypokalemia: potentiates the effects of NMBAs
- Hypercalcemia: reduces response to the administration of nondepolarizing NMBAs

Acidosis ($\text{pH} < 7.3$): both metabolic or respiratory in origin, can prolong the effects of NMBAs, by increasing NMBA affinity for postjunctional nAChRs.

Alkalosis ($\text{pH} > 7.51$): can shorten the duration of neuromuscular blockade produced by nondepolarizing muscle relaxants, but will not affect the duration of action of depolarizing muscle relaxants

Neuromuscular blockers and safety concerns

ICU-acquired weakness:

- Muscles weakness, long-term sequelae of critical illness, affects roughly 2/3 of ICU survivors
- Associated with prolonged mechanical ventilation, and prolonged ICU and hospital lengths of stay, use of pressors, hypoalbuminemia.
- The risk of persistent paralysis is higher in patients with hepatic or renal dysfunction
- Prolonged blockade of the neuromuscular junction may cause muscle atrophy, particularly in the presence of fluorinated corticosteroids (dexamethasone), ischaemia, acidosis or electrolyte disturbances, aminoglycosides
- A trial of cisatracurium for ARDS found no evidence of an increased risk of acute quadriplegic myopathy, although a high proportion of patients also received corticosteroids
(Papazian, N Engl J Med 2010; 363:1107-1116)



ICU-acquired weakness: prevention strategy

- Not combine fluorinated corticosteroids and long lasting non-depolarising NMBAs
- Duration of neuromuscular blockade should be as short as possible (ideally less than 48 h). Aim to daily sedation and paralysis interruption and tailoring.
- Maintain normal glucose, pH and electrolytes levels
- Avoid aminoglycosides administration
- Prompt passive and active mobilization, and access to a rehabilitation program



Neuromuscular blockers and safety concerns

Awareness:

- Awareness with recall results from the absence of or incomplete sedation with NMBAs.
- Paralysis with a preserved conscience exposes the patient to psychological trauma and medico-legal procedures.
- In ICU survivors, the prevalence of post-ICU PTSD is 10–39% at hospital discharge. In survivors of ARDS, a systematic review found a prevalence of psychiatrically diagnosed PTSD in 44% at hospital discharge.

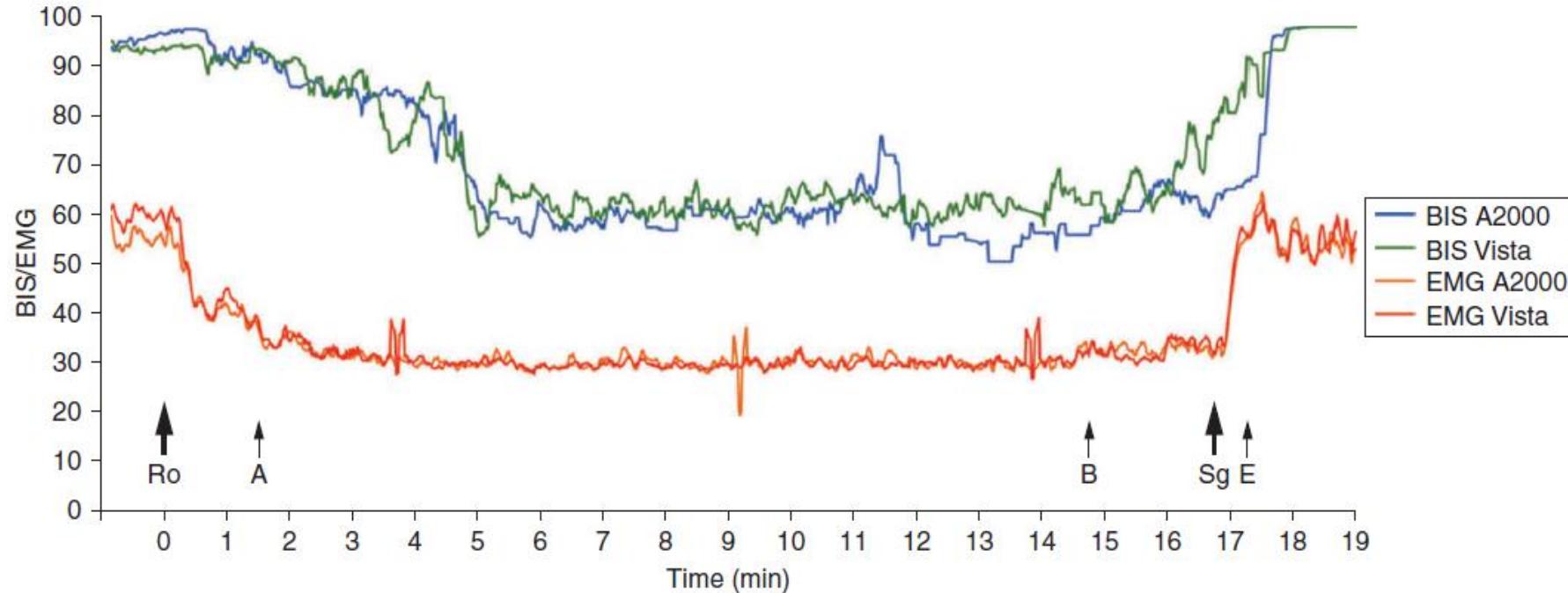




From the guidelines

- Patients receiving NMBAs should be assessed both clinically and by TOF monitoring (Grade of recommendation B), with a goal of adjusting the degree of neuromuscular blockade to achieve one or two twitches.
(Grade of recommendation C)
- Before initiating neuromuscular blockade, patients should be medicated with sedative and analgesic drugs to provide adequate sedation and analgesia in accordance with the physician's clinical judgment to optimize therapy.
(Grade of recommendation C)

What about the BIS?

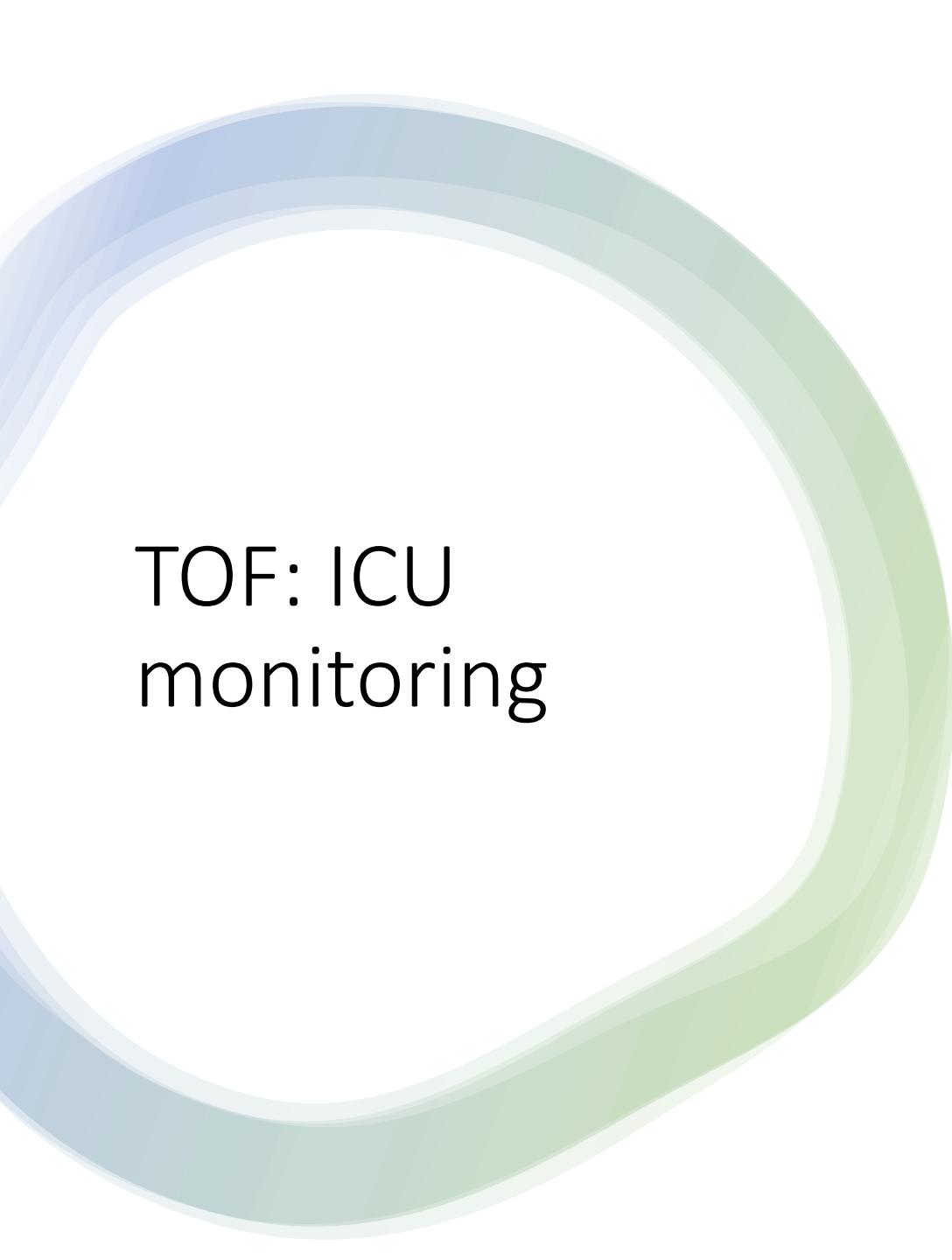


“These results suggest that the BIS monitor requires muscle activity, in addition to an awake EEG, in order to generate values indicating that the subject is awake. Consequently, BIS may be an unreliable indicator of awareness in patients who have received neuromuscular blocking drugs.”

Neuromuscular blockers: ICU monitoring

Monitoring the depth of neuromuscular blockade aims to:

- ensure that objectives for muscle relaxation are reached in an anesthetized patient (one or two twitches)
- the use of the lowest effective dose of NMBAs dose is used (limit the development of ICU-acquired weakness)
- avoid deleterious residual neuromuscular blockade after extubation
- avoid awareness



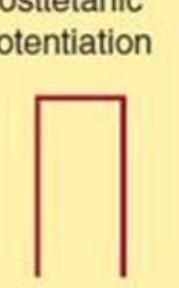
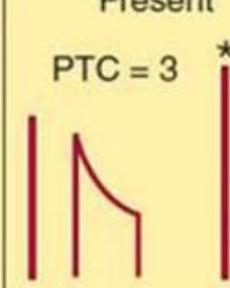
TOF: ICU monitoring

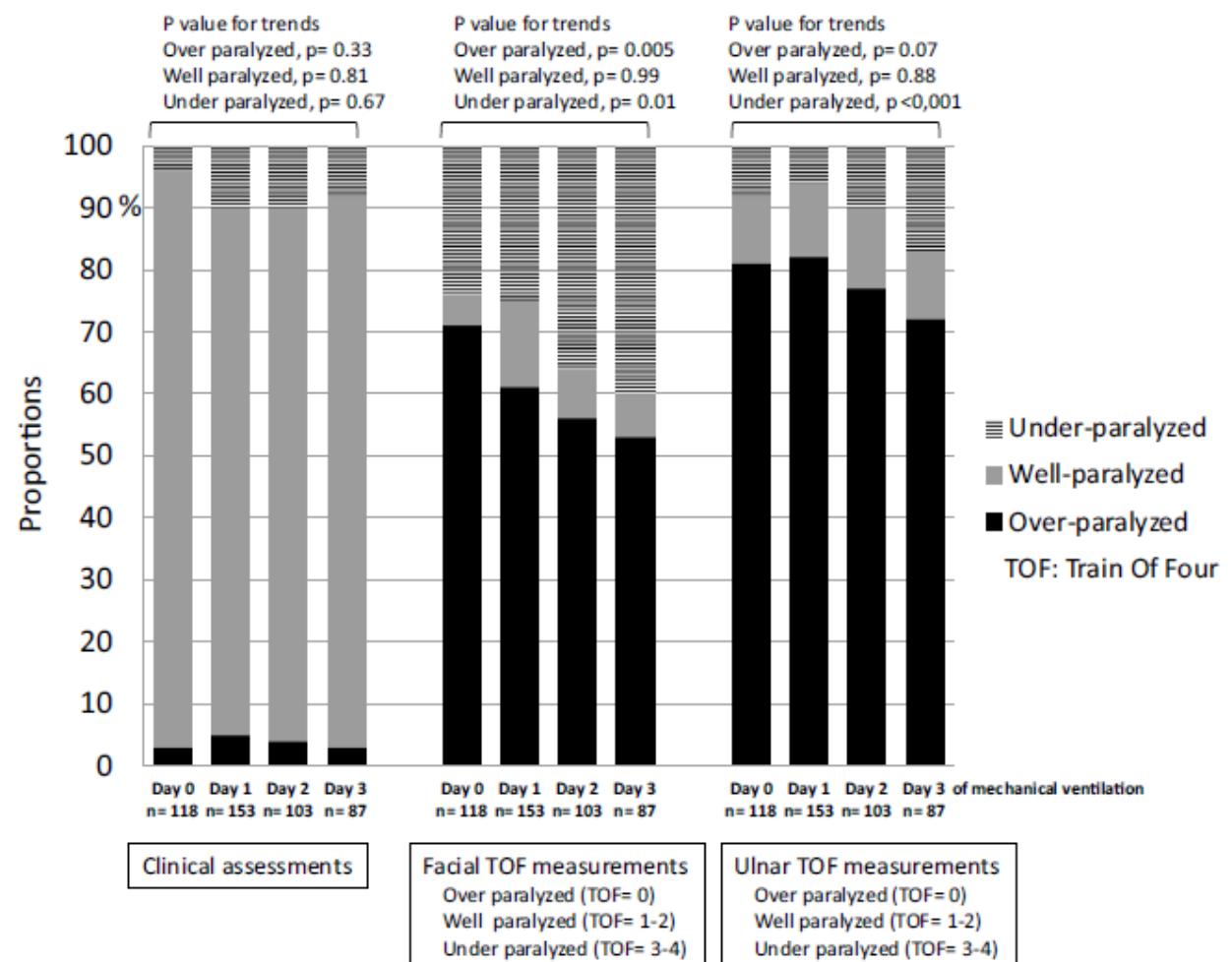
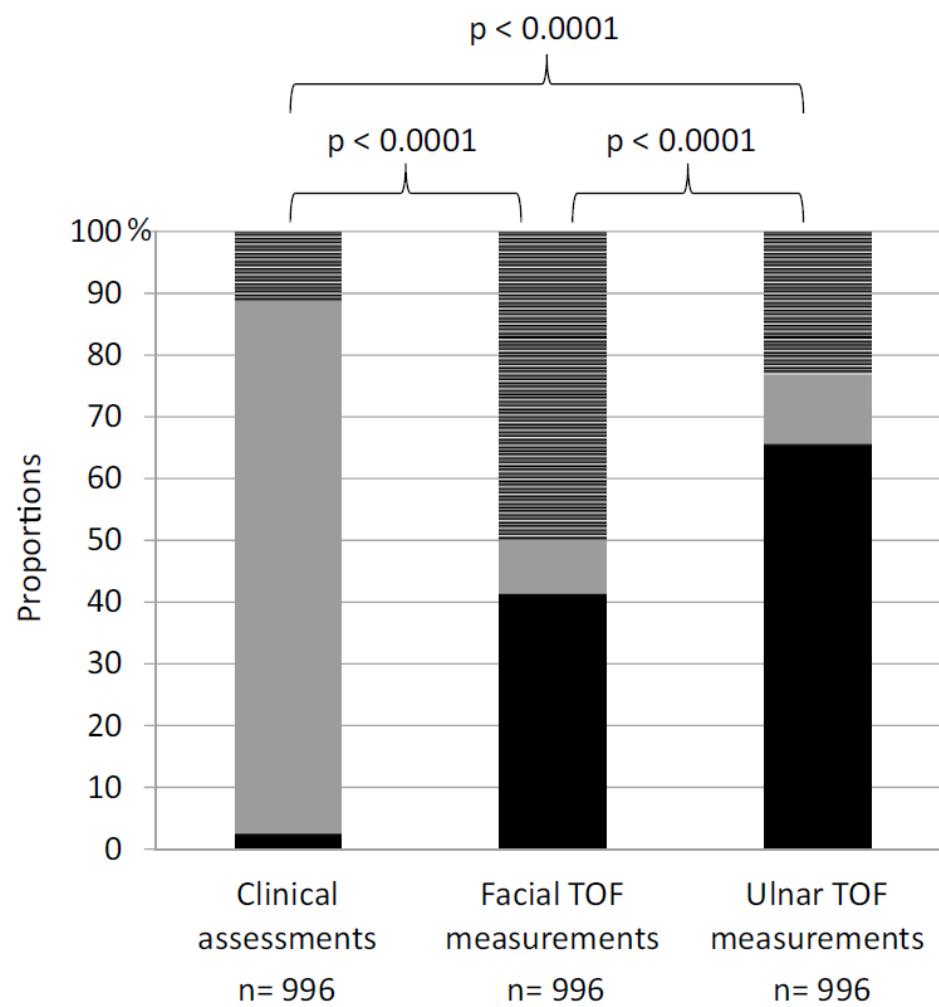
In addition to monitoring for adequate sedation and analgesia, the depth of neuromuscular blockade should be assessed by:

- repeated clinical monitoring :
 - skeletal muscle movement, respiratory efforts, detection of patient–ventilator asynchronies
- qualitative evaluation:
 - TOF, however, be aware of the low correlation of blockade measured clinically and peripherally compared with the paralysis of the diaphragm
 - The evaluation of the decline in the twitch response can be performed by comparing the strength (TOF ratio) of the fourth twitch to that of the first twitch.

The measurement of the TOF can be impaired by hypothermia, peripheral oedema, or incorrect positioning of electrodes

TOF: ICU monitoring

No Drug	Nondepolarizing Block	Depolarizing Block	
		Phase I	Phase II
Train-of-four	TOF-R = 1.0	Fade 	Constant but diminished TOF-R = 1.0 
Double burst		Fade 	No fade 
Posttetanic potentiation	PTC = > 6	Present PTC = 3 	Absent 



Take home messages

- NMBAs are not first-line agents for managing undesired movement, agitation, or ventilator asynchrony since they do not have sedative, amnestic, or analgesic properties.
- Before initiating neuromuscular blockade, provide adequate sedation and analgesia
- Daily interruption of paralysis is required for awareness monitoring
- Daily assessment of paralysis using TOF, early interruption of NMBAs, and the use of cisatracurium reduce the incidence of ICU-acquired weakness

