

# DELIRIUM IN ICU: Prevention and Management

Milind Baldi

# Contents

- Introduction
- Risk factors
- Assessment
- Prevention
- Management

# Introduction

- Delirium is a syndrome characterized by acute cerebral dysfunction with a change in baseline mental status, inattention, and either disorganized thinking or altered level of consciousness.

# Introduction

- The prevalence of delirium in ICU cohort studies has been reported as low as 20–30% and as high as 70–80% or more.
- Incidence and prevalence rate of delirium were 24.4% and 53.6% respectively

Best Pract Res Clin Anaesthesiol. 2012 Sep; 26(3): 277–287.  
Gen Hosp Psych 2012 Nov-Dec;34(6):639-46

## Patient Vulnerability Factors

Younger,  
no dementia,  
low comorbidity  
burden

Low

Older, dementia,  
high comorbidity  
burden

High

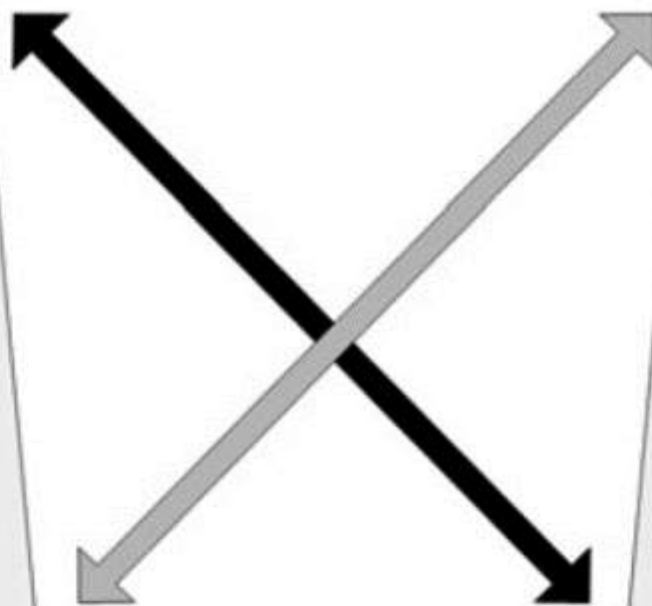
## Precipitating Factors

Urinary tract  
infection

Low

Severe sepsis

High



# Diagnosis

- a standard clinical evaluation does not have an adequate accuracy for the diagnosis

# Clinical manifestations

## ○ Cognitive Symptoms

- disorientation,
- inability to sustain attention,
- impaired short-term memory,
- reduced level of consciousness

## ○ Behavioral Symptoms

- sleep-wake cycle disturbance,
- irritability,
- hallucinations
- delusions

# Delirium Scales

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DOI 10.1007/s001340100069

## ORIGINAL

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

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#### Introduction

Behavioral disturbances in patients admitted to the intensive care unit (ICU) are common and have been associated with increased morbidity [1, 2] and mortality

**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

[3]. Delirium occurring in the ICU setting is a poorly described and studied entity, which encompasses a range of behavioral and neuropsychiatric disorders during critical illness. To date, no systematic disorder classification attempt exists. Much of what is described in stan-

## 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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**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 ( $\kappa = 0.94$ , 95% confidence interval, 0.92–0.99). Interrater reliability measures across subgroup comparisons showed  $\kappa$  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 (80.1%) 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 patients, 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.

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RESEARCH

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# The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies

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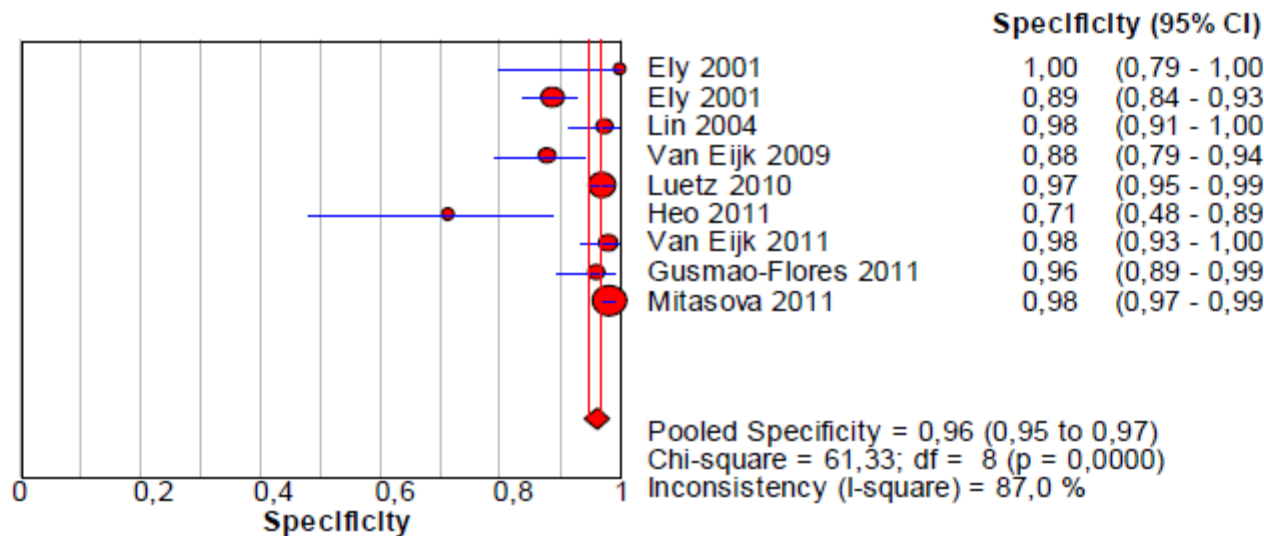
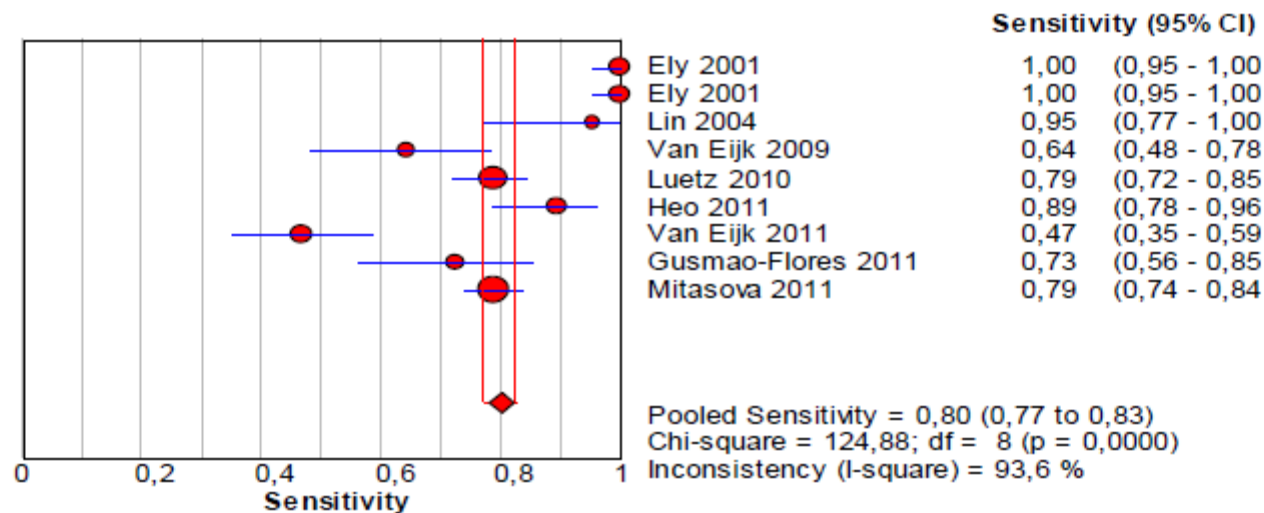


Figure 3 Forest plot of the pooled values of sensitivity and specificity of the CAM-ICU.

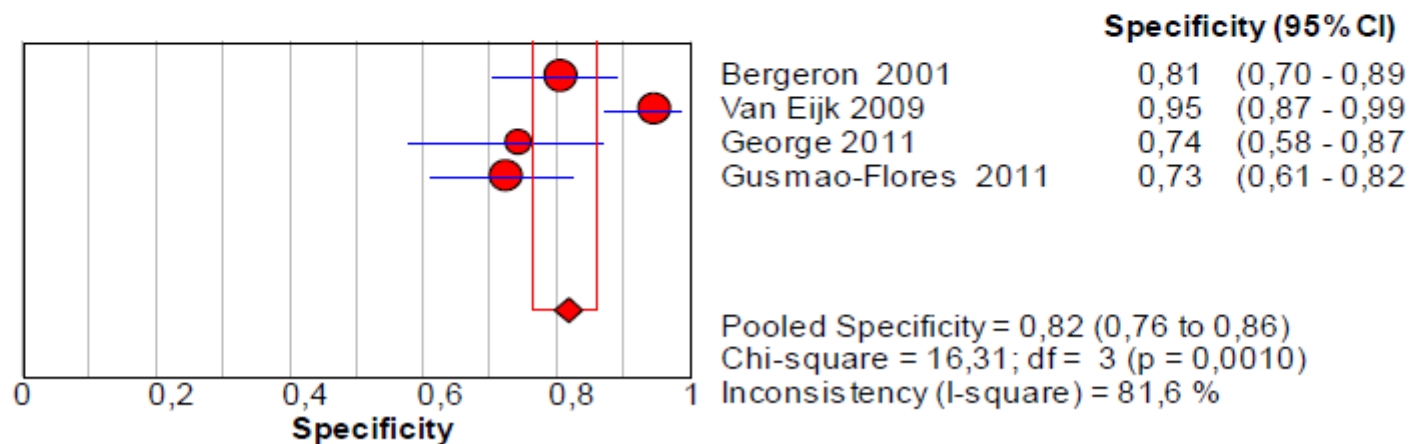
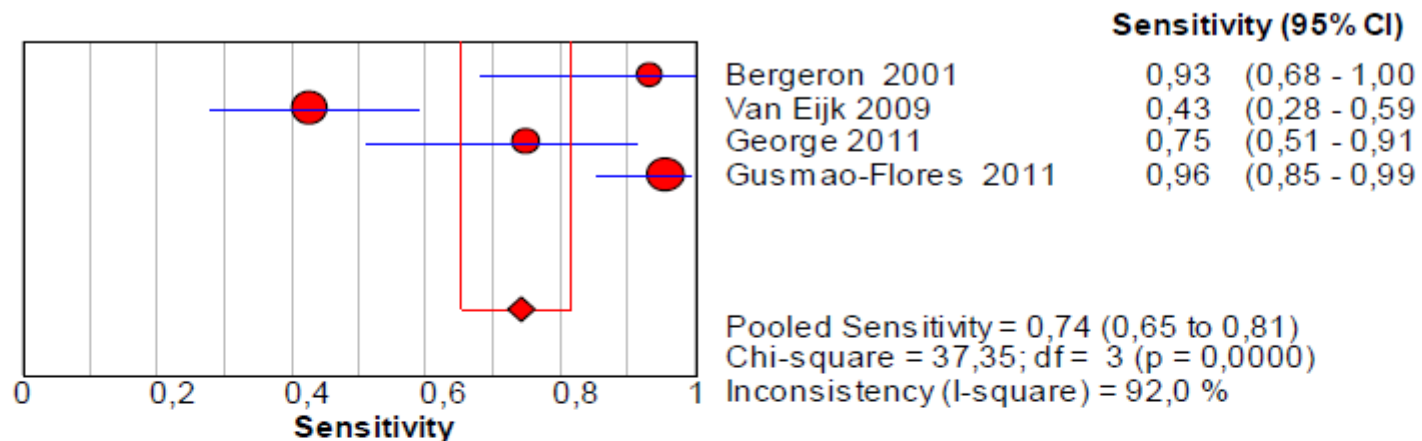


Figure 5 Forest plot of the pooled values of sensitivity and specificity of the ICDSC.

- The present meta-analysis demonstrates that the CAM ICU is an excellent tool for the detection of delirium in critically ill ICU patients regardless of the subgroup of patients evaluated



ELSEVIER

## **Comparison of CAM-ICU and ICDSC for the detection of delirium in critically ill patients focusing on relevant clinical outcomes<sup>☆</sup>**

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- the CAM-ICU has a fast application (2-5 min) and does not depend exclusively on the verbal response, thus being relevant for patients on mechanical ventilation

# Assessing Delirium

- Step 1: Level of Consciousness

## Step 1 Level of Consciousness: RASS\*

| Scale                                                                              | Label             | Description                                                                           |       |
|------------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------------------|-------|
| +4                                                                                 | COMBATIVE         | Combative, violent, immediate danger to staff                                         | VOICE |
| +3                                                                                 | VERY AGITATED     | Pulls to remove tubes or catheters; aggressive                                        |       |
| +2                                                                                 | AGITATED          | Frequent non-purposeful movement, fights ventilator                                   |       |
| +1                                                                                 | RESTLESS          | Anxious, apprehensive, movements not aggressive                                       |       |
| 0                                                                                  | ALERT & CALM      | Spontaneously pays attention to caregiver                                             |       |
| -1                                                                                 | DROWSY            | Not fully alert, but has sustained awakening to voice (eye opening & contact >10 sec) |       |
| -2                                                                                 | LIGHT SEDATION    | Briefly awakens to voice (eyes open & contact <10 sec)                                |       |
| -3                                                                                 | MODERATE SEDATION | Movement or eye opening to voice (no eye contact)                                     |       |
| If RASS is $\geq -3$ proceed to CAM-ICU (Is patient CAM-ICU positive or negative?) |                   |                                                                                       |       |
| -4                                                                                 | DEEP SEDATION     | No response to voice, but movement or eye opening to physical stimulation             | TOUCH |
| -5                                                                                 | UNAROUSABLE       | No response to voice or physical stimulation                                          |       |
| If RASS is -4 or -5 → STOP (patient unconscious), RECHECK later                    |                   |                                                                                       |       |



- Step 2: Content of consciousness

- Delirium is a syndrome characterized by acute cerebral dysfunction with a change in baseline mental status, inattention, and either disorganized thinking or altered level of consciousness.

## Step 2 Content of Consciousness: CAM-ICU

- Delirium is a syndrome characterized by acute cerebral dysfunction with a change in baseline mental status,

**Feature 1:** Acute change or fluctuating course of mental status

And

## Step 2 Content of Consciousness: CAM-ICU

- Delirium is a syndrome characterized by acute cerebral dysfunction with a change in baseline mental status, inattention

**Feature 1:** Acute change or fluctuating course of mental status

And

**Feature 2:** Inattention

And

## Step 2 Content of Consciousness: CAM-ICU

- Delirium is a syndrome characterized by acute cerebral dysfunction with a change in baseline mental status, inattention, and either disorganized thinking

**Feature 1:** Acute change or fluctuating course of mental status

And

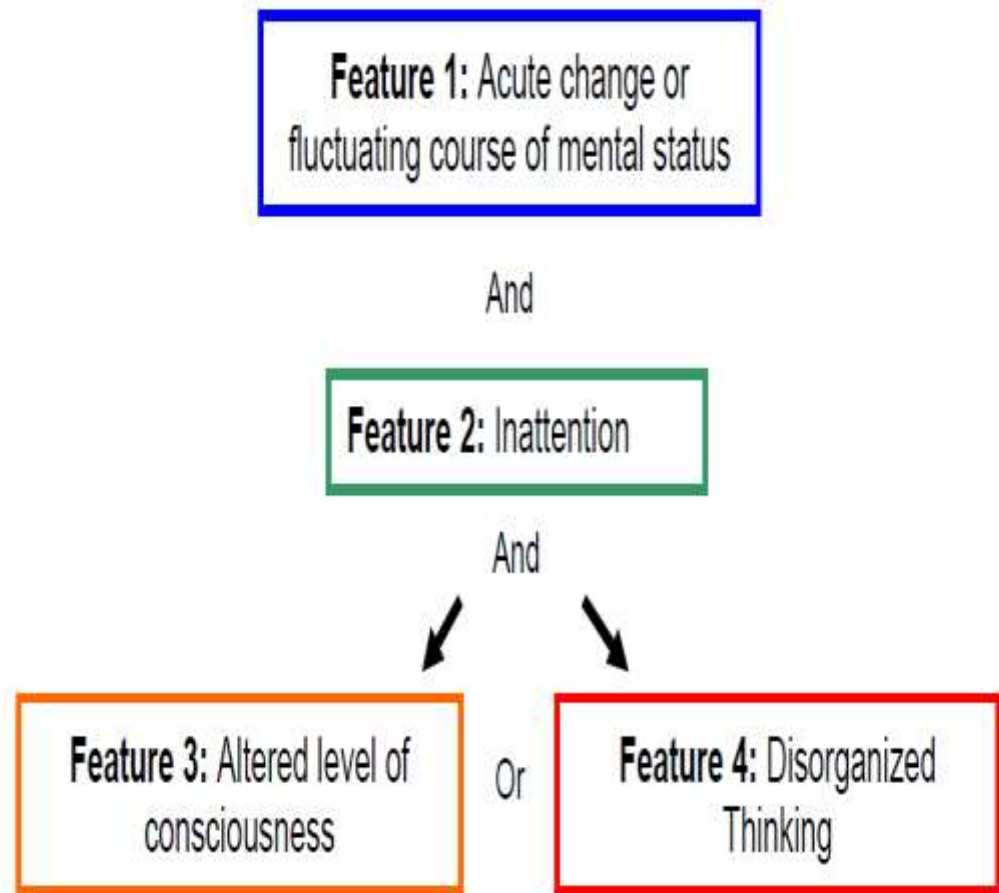
**Feature 2:** Inattention

And

**Feature 4:** Disorganized Thinking

## Step 2 Content of Consciousness: CAM-ICU

- Delirium is a syndrome characterized by acute cerebral dysfunction with a change in baseline mental status, inattention, and either disorganized thinking or altered level of consciousness.



# Confusion Assessment Method for the ICU (CAM-ICU) Flowsheet

## 1. Acute Change or Fluctuating Course of Mental Status:

- Is there an acute change from mental status baseline? OR
- Has the patient's mental status fluctuated during the past 24 hours?

NO

CAM-ICU negative  
NO DELIRIUM

YES

## 2. Inattention:

- "Squeeze my hand when I say the letter 'A'."  
Read the following sequence of letters:  
SAVEAHAART or CASABLANCA or ABADBADAAY  
ERRORS: No squeeze with 'A' & Squeeze on letter other than 'A'
- If unable to complete Letters → Pictures

0 - 2  
Errors

CAM-ICU negative  
NO DELIRIUM

## Pictures

### Step 1



### Step 2





## 2. Inattention:

- "Squeeze my hand when I say the letter 'A'."

Read the following sequence of letters:

SAVEAHAART or CASABLANCA or ABADBADAAY

ERRORS: No squeeze with 'A' & Squeeze on letter other than 'A'

- If unable to complete Letters → Pictures

0 - 2  
Errors

CAM-ICU negative  
NO DELIRIUM

> 2 Errors

## 3. Altered Level of Consciousness

Current RASS level

RASS other  
than zero

CAM-ICU positive  
DELIRIUM Present

RASS = zero

**3. Altered Level of Consciousness**  
Current RASS level

RASS other  
than zero

**CAM-ICU positive  
DELIRIUM Present**

RASS = zero

**4. Disorganized Thinking:**

1. Will a stone float on water?
2. Are there fish in the sea?
3. Does one pound weigh more than two?
4. Can you use a hammer to pound a nail?

> 1 Error

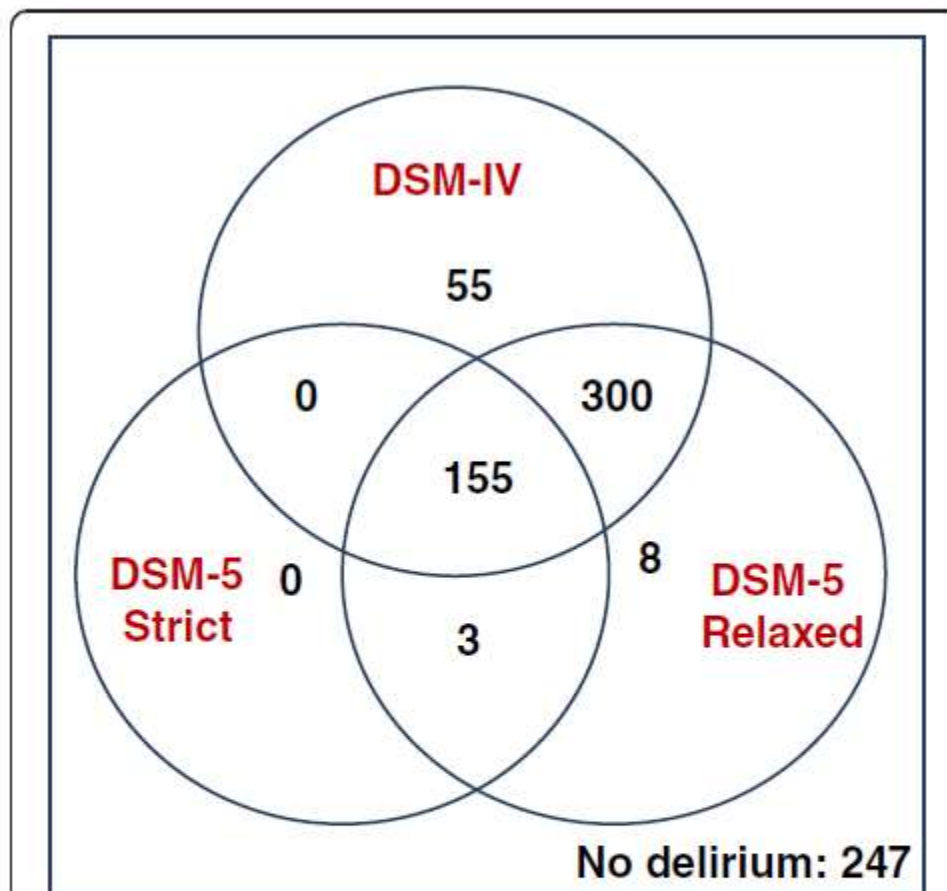
0 - 1  
Error

**CAM-ICU negative  
NO DELIRIUM**

- Versions available in Hindi and other regional languages too

# DSM V

- No major changes from DSM-IV were made to the core elements of DSM-5 criteria for delirium, there are some differences in content and wording of the criteria.



**Figure 1** Overlap between DSM-IV and strict versus relaxed interpretations of DSM-5 delirium criteria for the pooled dataset ( $n = 768$ ). Note: Relaxed interpretation of DSM-5 criteria allows for considerable overlap with DSM-IV with respect to delirium diagnosis, while strict interpretation only identified 30% of DSM-IV cases as delirium. DSM-IV, Diagnostic and Statistical Manual fourth edition; DSM-5, *Diagnostic and Statistical Manual* fifth edition.

# PREDECTING Delirium

- Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study
- 10 risk factors—age, APACHE-II score, admission group, coma, infection, metabolic acidosis, use of sedatives and morphine, urea concentration, and urgent admission

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## **Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study**

# RISK FACTORS

## ❖ Strong

- Age
- Dementia
- Hypertension
- Coma
- APACHE II
- Delirium previous day
- Emergency surgery
- Mechanical ventilation
- Polytrauma
- Metabolic acidosis

## ❖ Inconclusive

- Alcohol use
- Nicotine use
- Acute respiratory disease
- Kidney failure
- Fever
- benzodiazepines



# Delirium risk factors

- Four baseline risk factors are positively and significantly associated with the development of delirium in the ICU: **preexisting dementia**, history of **hypertension** and/or **alcoholism**, and a **high severity** of illness at admission.
- **Benzodiazepine** use may be a risk factor for the development of delirium in adult ICU patients.
- In mechanically ventilated adult ICU patients at risk of developing delirium, **dexmedetomidine** infusions administered for sedation may be associated with a lower prevalence of delirium compared to benzodiazepine infusions

**Table 1**  
Comparison of risk factors between delirious (either incidence or prevalence cases) and non delirious subjects using univariate analysis

| Risk factor                                                                                                        | Delirious subjects,<br>n= 75 (frequency) | Non-delirious subjects,<br>n= 65 (frequency) | chi-Square test/t test<br>(significance) |
|--------------------------------------------------------------------------------------------------------------------|------------------------------------------|----------------------------------------------|------------------------------------------|
| <b>Predisposing factors (host factors)</b>                                                                         |                                          |                                              |                                          |
| Age (in years)                                                                                                     | 49.53±19.27                              | 37.43±13.94                                  | 4.20 ( <i>P</i> <.001)                   |
| Elderly patients (≥65 years)*                                                                                      | 23                                       | 1                                            | 19.12 ( <i>P</i> <.001)                  |
| Gender, male                                                                                                       | 43                                       | 29                                           | 2.25 ( <i>P</i> =.13)                    |
| Smoking (have been smoking for at least 1 years regularly and currently smoking just prior to falling acutely ill) | 20                                       | 9                                            | 3.48 (0.06)                              |
| Hypertension                                                                                                       | 7                                        | 4                                            | 0.146 (0.702)                            |
| Diabetes mellitus                                                                                                  | 4                                        | 3                                            | Fisher's Exact test, <i>P</i> =1.00      |
| Chronic obstructive pulmonary disease                                                                              | 13                                       | 5                                            | 2.89 (.089)                              |
| Chronic kidney disease                                                                                             | 1                                        | 3                                            | Fisher's Exact test, <i>P</i> =.33       |
| Coronary artery disease                                                                                            | 5                                        | 0                                            | 2.76 (.096)                              |
| Anemia                                                                                                             | 40                                       | 32                                           | 0.23 (.62)                               |
| Hypothyroidism                                                                                                     | 2                                        | 2                                            | Fisher's Exact test, <i>P</i> =1.00      |
| Malignancy                                                                                                         | 4                                        | 1                                            | Fisher's Exact test, <i>P</i> =.37       |
| Past psychiatric illness                                                                                           | 6                                        | 3                                            | Fisher's Exact test, <i>P</i> =.50       |
| <b>Illness related factors</b>                                                                                     |                                          |                                              |                                          |
| Glasgow Coma Scale score                                                                                           | 6.96±2.13                                | 5.44±2.77                                    | 3.64 ( <i>P</i> <.001)                   |
| APACHE II score                                                                                                    | 19.52±5.65                               | 14.66±6.28                                   | 4.81 (.000)                              |
| CNS infarction*                                                                                                    | 6                                        | 1                                            | 1.85 (.174)                              |
| Respiratory failure                                                                                                | 48                                       | 31                                           | 3.76 (.056)                              |
| Hyponatremia (serum sodium levels <135 mEq/L)                                                                      | 30                                       | 20                                           | 1.29 (.25)                               |
| Hypernatremia (serum sodium levels >145 mEq/L)                                                                     | 15                                       | 14                                           | 0.05 (.82)                               |
| Hyperkalemia (serum potassium levels <5.0 mEq/L)                                                                   | 21                                       | 16                                           | 0.20 (.65)                               |
| Hypokalemia (serum potassium levels <3.5 mEq/L)                                                                    | 9                                        | 2                                            | 2.69 (.10)                               |
| Hyperuricemia (serum uric acid >7 mg/dl)                                                                           | 28                                       | 12                                           | 6.07 (.014)                              |
| Hypoalbuminemia (serum albumin levels <3.4 g/dl)                                                                   | 35                                       | 20                                           | 3.69 (.05)                               |
| Hyperbilirubinemia (>2 mg/dl)                                                                                      | 3                                        | 4                                            | Fisher's Exact test, <i>P</i> =.70       |
| Urea (>100 mg/dl)                                                                                                  | 5                                        | 5                                            | 0.00 (1.00)                              |
| Creatinine (>2 mg/dl)                                                                                              | 6                                        | 3                                            | 0.22 (.63)                               |
| Deranged AST (>120 IU/l)                                                                                           | 21                                       | 12                                           | 1.75 (.18)                               |
| Deranged ALT (>120 IU/l)                                                                                           | 25                                       | 12                                           | 3.96 (.047)                              |
| Acidosis (pH <7.35)                                                                                                | 45                                       | 17                                           | 16.16 (<.001)                            |
| Alkalosis (pH >7.45)                                                                                               | 22                                       | 18                                           | 0.04 (.83)                               |
| Acute renal failure                                                                                                | 3                                        | 8                                            | 2.27 (0.132)                             |
| Multiple organ failure                                                                                             | 13                                       | 8                                            | 0.69 (.40)                               |
| Respiratory infection                                                                                              | 13                                       | 16                                           | 1.12 (.28)                               |
| Sepsis                                                                                                             | 31                                       | 32                                           | 0.87 (.34)                               |
| Postoperative                                                                                                      | 5                                        | 5                                            | 0.05 (.81)                               |
| <b>Treatment-related factors</b>                                                                                   |                                          |                                              |                                          |
| Mechanical ventilation<br>(patient requiring assisted ventilation in the form of ventilator)                       | 60                                       | 34                                           | 12.10 (.001)                             |
| Steroid medication                                                                                                 | 52                                       | 34                                           | 4.733 (.030)                             |
| Sedative medication                                                                                                | 27                                       | 13                                           | 4.36 (.037)                              |
| Antibiotics                                                                                                        | 59                                       | 49                                           | 0.21 (.64)                               |
| Antipsychotics                                                                                                     | 14                                       | 7                                            | 1.70 (.19)                               |
| Antihypertensives                                                                                                  | 18                                       | 11                                           | 1.06 (.30)                               |
| Insulin                                                                                                            | 38                                       | 17                                           | 8.77 (.003)                              |
| Total number of medication received                                                                                | 5.97±1.33                                | 5.46±1.16                                    | 2.402 (.018)                             |

\* Chi-square value with Yates's correction.



## Reducing Iatrogenic Risks

### ICU-Acquired Delirium and Weakness—Crossing the Quality Chasm

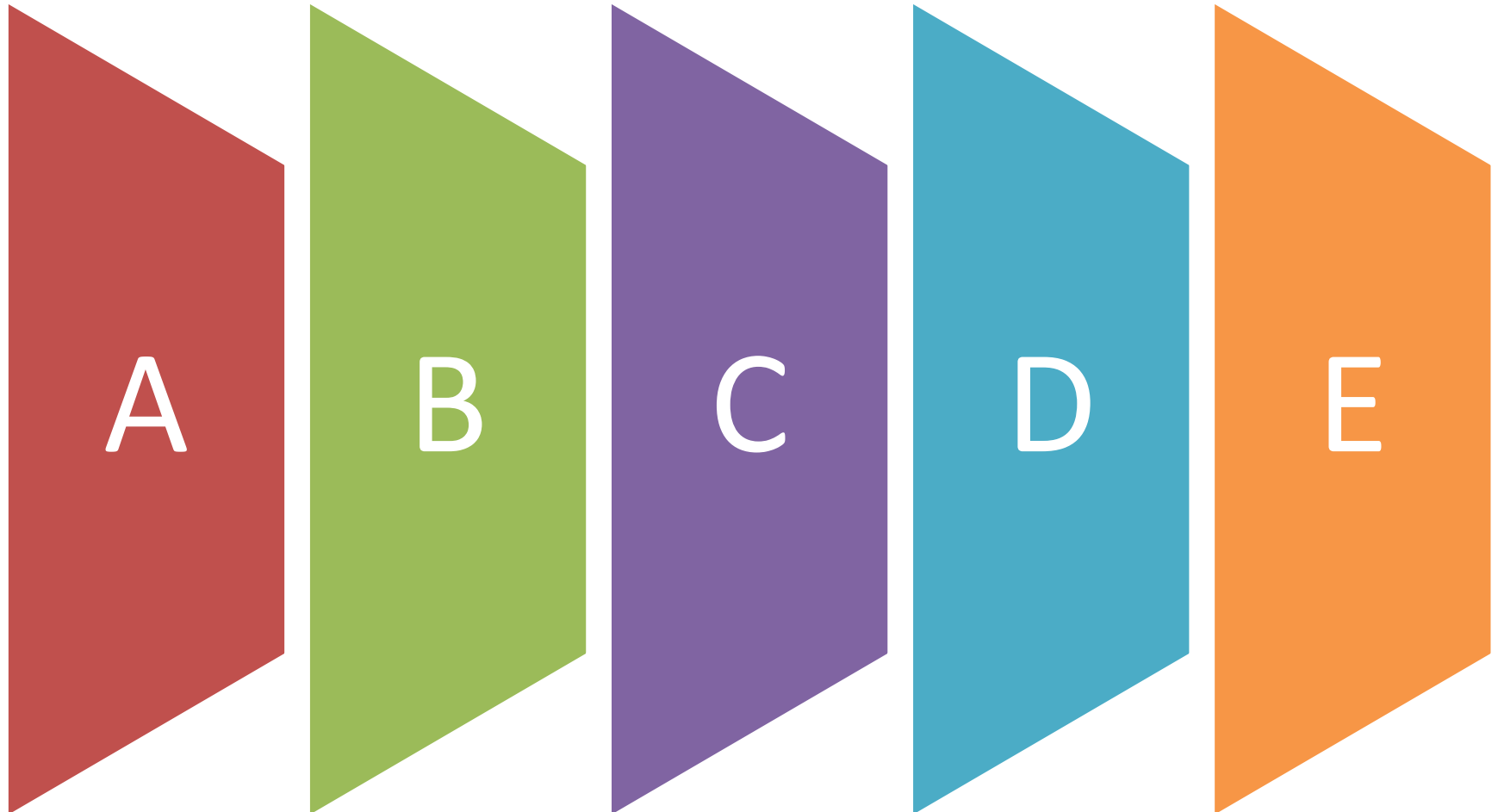
- “In this article, we advocate for the adoption and implementation of a standard bundle of ICU measures with great potential to reduce the burden of ICU-acquired delirium and weakness”

# Prevention

Individual components of this bundle are evidence based and can help standardize communication, improve interdisciplinary care, reduce mortality, and improve cognitive and functional outcomes.

- “ABCDE bundle,” for awakening and breathing coordination, delirium monitoring, and exercise/early mobility

# Building blocks of managing Pain, Agitation and Delirium



# Birth of ABCDE

A

- Kress JP, et al. N Engl J Med 2000;342:1471-7

B

- Ely EW, et al. N Engl J Med 1996;335:1864-9

C

- Riker R. et al, JAMA. 2009;301:489-499

D

- Preventing and Managing Delirium

E

- Schweickert et al, Lancet 2009;373:1874-82

# Birth of ABCDE

A

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D

- Preventing and Managing Delirium

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- Schweickert et al, Lancet 2009;373:1874-82

# Birth of ABCDE

The New England Journal of Medicine

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## EFFECT ON THE DURATION OF MECHANICAL VENTILATION OF IDENTIFYING PATIENTS CAPABLE OF BREATHING SPONTANEOUSLY

E. WESLEY ELY, M.D., M.P.H., ALBERT M. BAKER, M.D., DONNIE P. DUNAGAN, M.D., HENRY L. BURKE, M.D., ALLEN C. SMITH, M.D., PATRICK T. KELLY, M.D., MARGARET M. JOHNSON, M.D., RICK W. BROWDER, M.D., DAVID L. BOWTON, M.D., AND EDWARD F. HAPONIK, M.D.



# Spontaneous Breathing Trial

- Daily screening of the respiratory function of adults receiving mechanical ventilation, followed by trials of spontaneous breathing

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.\***

| CHARACTERISTIC                                        | INTERVENTION<br>GROUP<br>(N = 149) | CONTROL<br>GROUP<br>(N = 151) |
|-------------------------------------------------------|------------------------------------|-------------------------------|
| Male sex — no. (%)                                    | 67 (45)                            | 84 (56)                       |
| Treatment in coronary care unit — no. (%)             | 33 (22)                            | 29 (19)                       |
| Age — yr                                              | 61.7±15.8                          | 60.5±15.5                     |
| APACHE II score                                       | 19.8±6.0                           | 17.9±6.2                      |
| Acute-lung-injury score                               | 1.9±0.8                            | 1.7±0.8                       |
| Median duration of respiratory failure —<br>days†     | 3.0                                | 2.0                           |
| Mode of ventilation — no. of patients (%)             |                                    |                               |
| Intermittent mandatory ventilation                    | 42 (28)                            | 50 (33)                       |
| Pressure-support ventilation                          | 26 (17)                            | 19 (13)                       |
| Both                                                  | 64 (43)                            | 65 (43)                       |
| Pressure-control ventilation                          | 3 (2)                              | 5 (3)                         |
| Assist-control ventilation                            | 6 (4)                              | 4 (3)                         |
| Continuous positive airway pressure                   | 8 (5)                              | 8 (5)                         |
| Cause of respiratory failure — no. of<br>patients (%) |                                    |                               |
| Congestive heart failure                              | 18 (12)                            | 15 (10)                       |
| Other heart disease                                   | 17 (11)                            | 23 (15)                       |
| COPD or asthma exacerbation                           | 23 (15)                            | 22 (15)                       |
| Pneumonia                                             | 21 (14)                            | 23 (15)                       |
| ARDS or multisystem organ failure                     | 23 (15)                            | 19 (13)                       |
| Gastrointestinal and liver disease                    | 7 (5)                              | 13 (9)                        |
| Cancer or leukemia                                    | 7 (5)                              | 9 (6)                         |
| Overdose or ketoacidosis                              | 11 (7)                             | 5 (3)                         |
| Neurologic emergency                                  | 7 (5)                              | 4 (3)                         |
| Other                                                 | 15 (10)                            | 18 (12)                       |

- “Your patient has successfully completed a 2-hour trial of spontaneous breathing and has an 85 percent chance of successfully staying off mechanical ventilation for 48 hours”

**TABLE 2. COMPARISON OF OUTCOMES BETWEEN STUDY GROUPS.**

| END POINT              | INTERVENTION<br>GROUP<br>(N = 149)          |        | CONTROL<br>GROUP<br>(N = 151) |        | P<br>VALUE |
|------------------------|---------------------------------------------|--------|-------------------------------|--------|------------|
|                        | median no. of days<br>(interquartile range) |        |                               |        |            |
| Weaning time*          | 1                                           | (0–2)  | 3                             | (2–7)  | <0.001     |
| Mechanical ventilation | 4.5                                         | (2–9)  | 6                             | (3–11) | 0.003      |
| Intensive care         | 8                                           | (4–18) | 9                             | (5–16) | 0.17       |
| Hospital care          | 14                                          | (9–26) | 15.5                          | (6–30) | 0.93       |

\*Weaning time was defined as the number of days from the time the patient had a successful screening test to the discontinuation of mechanical ventilation.

A

- Kress JP, et al. N Engl J Med 2000;342:1471-7

B

- Ely EW, et al. N Engl J Med 1996;335:1864-9

C

- Riker R. et al, JAMA. 2009;301:489-499

D

- Preventing and Managing Delirium

E

- Schweickert et al, Lancet 2009;373:1874-82

# Birth of ABCDE

INTERRUPTION OF SEDATIVE INFUSIONS IN CRITICALLY ILL PATIENTS UNDERGOING MECHANICAL VENTILATION

## DAILY INTERRUPTION OF SEDATIVE INFUSIONS IN CRITICALLY ILL PATIENTS UNDERGOING MECHANICAL VENTILATION

JOHN P. KRESS, M.D., ANNE S. POHLMAN, R.N., MICHAEL F. O'CONNOR, M.D., AND JESSE B. HALL, M.D.

**TABLE 2. CHARACTERISTICS OF THE STUDY PATIENTS ON ADMISSION TO THE INTENSIVE CARE UNIT.**

| VARIABLE                                                     | INTERVENTION GROUP (N=68) | CONTROL GROUP (N=60) | P VALUE |
|--------------------------------------------------------------|---------------------------|----------------------|---------|
| Age (yr)                                                     |                           |                      | 0.57    |
| Median                                                       | 57                        | 61                   |         |
| Interquartile range                                          | 42–71                     | 40–74                |         |
| Sex (no.)                                                    |                           |                      | 0.56    |
| Male                                                         | 34                        | 26                   |         |
| Female                                                       | 34                        | 34                   |         |
| Weight (kg)                                                  |                           |                      | 0.70    |
| Median                                                       | 69.9                      | 66.0                 |         |
| Interquartile range                                          | 58.9–90.2                 | 60.4–78.8            |         |
| APACHE II score*                                             |                           |                      | 0.30    |
| Median                                                       | 20                        | 22                   |         |
| Interquartile range                                          | 15–25                     | 16–25                |         |
| Permissive hypercapnia (no.)                                 | 12                        | 15                   | 0.42    |
| Diagnosis (no.)                                              |                           |                      |         |
| Acute respiratory distress syndrome or pulmonary edema       | 20                        | 15                   | 0.72    |
| Chronic obstructive pulmonary disease or ventilatory failure | 22                        | 17                   | 0.76    |
| Asthma                                                       | 4                         | 3                    | 0.86    |
| Sepsis                                                       | 10                        | 15                   | 0.21    |
| Delirium                                                     | 8                         | 5                    | 0.73    |
| Hemorrhagic shock                                            | 1                         | 3                    | 0.52    |
| Cardiogenic shock                                            | 2                         | 2                    | 0.70    |
| Drug overdose                                                | 1                         | 0                    | 0.95    |

# Spontaneous Awakening Trial

**TABLE 3.** THE DURATION OF MECHANICAL VENTILATION, LENGTH OF STAY IN THE INTENSIVE CARE UNIT AND THE HOSPITAL, AND DOSES OF SEDATIVE DRUGS AND MORPHINE, ACCORDING TO STUDY GROUP.\*

| VARIABLE                                         | INTERVENTION GROUP<br>(N=68) | CONTROL GROUP<br>(N=60) | P<br>VALUE |
|--------------------------------------------------|------------------------------|-------------------------|------------|
|                                                  | median (interquartile range) |                         |            |
| Duration of mechanical ventilation (days)        | 4.9 (2.5–8.6)                | 7.3 (3.4–16.1)          | 0.004      |
| Length of stay (days)                            |                              |                         |            |
| Intensive care unit                              | 6.4 (3.9–12.0)               | 9.9 (4.7–17.9)          | 0.02       |
| Hospital                                         | 13.3 (7.3–20.0)              | 16.9 (8.5–26.6)         | 0.19       |
| Midazolam subgroup (no. of patients)             | 37                           | 29                      |            |
| Total dose of midazolam (mg)                     | 229.8 (59–491)               | 425.5 (208–824)         | 0.05       |
| Average rate of midazolam infusion<br>(mg/kg/hr) | 0.032 (0.02–0.05)            | 0.054 (0.03–0.07)       | 0.06       |
| Total dose of morphine (mg)                      | 205 (68–393)                 | 481 (239–748)           | 0.009      |
| Average rate of morphine infusion<br>(mg/kg/hr)  | 0.027 (0.02–0.04)            | 0.05 (0.04–0.07)        | 0.004      |
| Propofol subgroup (no. of patients)              | 31                           | 31                      |            |
| Total dose of propofol (mg)                      | 15,150 (3983–34,125)         | 17,588 (4769–35,619)    | 0.54       |
| Average rate of propofol infusion<br>(mg/kg/hr)  | 1.9 (0.9–2.6)                | 1.4 (0.9–2.4)           | 0.41       |
| Total dose of morphine (mg)                      | 352 (108–632)                | 382 (148–1053)          | 0.33       |
| Average rate of morphine infusion<br>(mg/kg/hr)  | 0.035 (0.02–0.07)            | 0.043 (0.02–0.07)       | 0.65       |

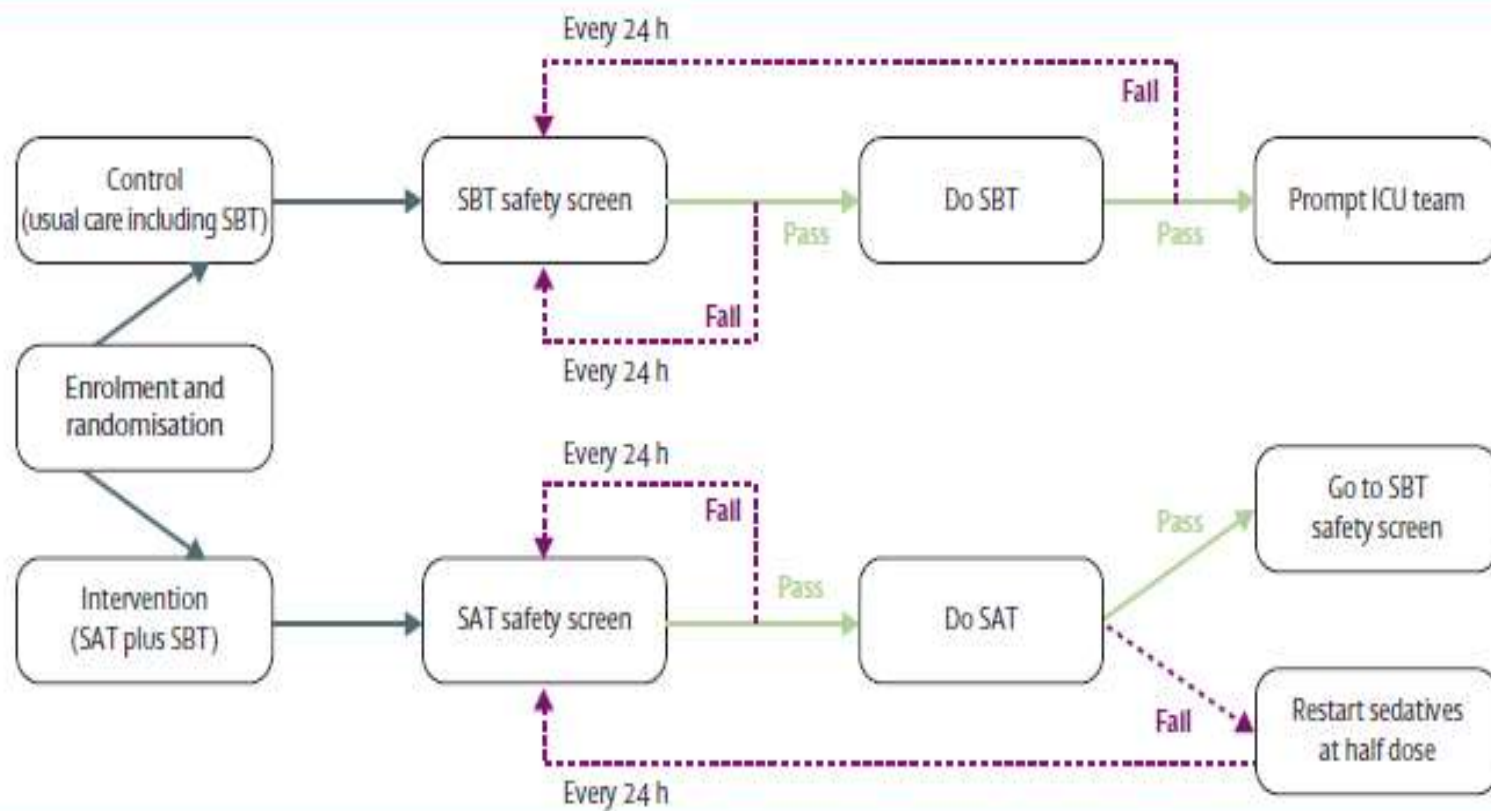


# C (A+B)

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Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial

- administration of sedatives by continuous infusion has been identified as an independent predictor of a longer duration of mechanical ventilation as well as a longer stay in the intensive care unit and in the hospital.
- Extended sedation may limit clinicians' ability to interpret physical examinations. It may be difficult to distinguish changes in mental status that are due to the action of a sedative from those that are due to neurologic injury.



|                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Intervention group (n=167) | Control group (n=168) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|-----------------------|
| Age (years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 60 (48 to 71)              | 64 (51 to 75)         |
| Sex (female)                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 77 (46%)                   | 83 (49%)              |
| APACHE II score                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 26 (21 to 33)              | 26.5 (21 to 31)       |
| SOFA score                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 9 (6 to 11)                | 8 (6 to 11.5)         |
| Diagnosis on admission to intensive care                                                                                                                                                                                                                                                                                                                                                                                                                                      |                            |                       |
| Sepsis/acute respiratory distress syndrome                                                                                                                                                                                                                                                                                                                                                                                                                                    | 79 (47%)                   | 87 (52%)              |
| Myocardial infarction/congestive heart failure                                                                                                                                                                                                                                                                                                                                                                                                                                | 22 (13%)                   | 29 (17%)              |
| Chronic obstructive pulmonary disease/asthma                                                                                                                                                                                                                                                                                                                                                                                                                                  | 17 (10%)                   | 12 (7%)               |
| Altered mental status                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 18 (11%)                   | 12 (7%)               |
| Hepatic or renal failure                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 9 (5%)                     | 5 (3%)                |
| Malignancy                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3 (2%)                     | 2 (1%)                |
| Alcohol withdrawal                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 1 (1%)                     | 1 (1%)                |
| Other*                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 18 (11%)                   | 20 (12%)              |
| RASS on first study day                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -4 (-5 to -2)              | -4 (-5 to -2)         |
| Sedation before enrolment                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                       |
| Benzodiazepines (mg)†                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 8 (4 to 34)                | 10 (2 to 41)          |
| Opiates (µg)‡                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 815 (184 to 4380)          | 850 (142 to 4685)     |
| Propofol (mg)                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 5102 (2340 to 9720)        | 3248 (1455 to 7420)   |
| Time from admission to enrolment (days)                                                                                                                                                                                                                                                                                                                                                                                                                                       | 2.2 (1.1 to 3.9)           | 2.2 (1.1 to 3.9)      |
| <p>Data are n (%) or median (IQR). APACHE II=acute physiology and chronic health evaluation II. RASS=Richmond agitation-sedation scale. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. SOFA=sequential organ failure assessment. *Including gastrointestinal bleeding, metabolic disarray, haemoptysis, pulmonary embolism, and status epilepticus. †Expressed in lorazepam equivalents.<sup>34</sup> ‡Expressed in fentanyl equivalents.<sup>34</sup></p> |                            |                       |
| <b>Table 1: Baseline characteristics</b>                                                                                                                                                                                                                                                                                                                                                                                                                                      |                            |                       |

|                                                                                                                                                                                                                                                                                                                                           | Intervention group (n=167) | Control group (n=168) | p value |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|-----------------------|---------|
| Ventilator-free days*                                                                                                                                                                                                                                                                                                                     |                            |                       |         |
| Mean                                                                                                                                                                                                                                                                                                                                      | 14.7 (0.9)                 | 11.6 (0.9)            | 0.02    |
| Median                                                                                                                                                                                                                                                                                                                                    | 20.0 (0 to 26.0)           | 8.1 (0 to 24.3)       |         |
| Time to discharge (days)                                                                                                                                                                                                                                                                                                                  |                            |                       |         |
| From intensive care                                                                                                                                                                                                                                                                                                                       | 9.1 (5.1 to 17.8)          | 12.9 (6.0 to 24.2)    | 0.01    |
| From hospital                                                                                                                                                                                                                                                                                                                             | 14.9 (8.9 to 26.8)         | 19.2 (10.3 to NA)†    | 0.04    |
| 28-day mortality                                                                                                                                                                                                                                                                                                                          | 47 (28%)                   | 58 (35%)              | 0.21    |
| 1-year mortality                                                                                                                                                                                                                                                                                                                          | 74 (44%)                   | 97 (58%)              | 0.01    |
| Duration of brain dysfunction (days)                                                                                                                                                                                                                                                                                                      |                            |                       |         |
| Coma                                                                                                                                                                                                                                                                                                                                      | 2 (0 to 4)                 | 3 (1 to 7)            | 0.002   |
| Delirium                                                                                                                                                                                                                                                                                                                                  | 2 (0 to 5)                 | 2 (0 to 6)            | 0.50    |
| RASS at first successful SBT                                                                                                                                                                                                                                                                                                              | -1 (-3 to 0)               | -2.5 (-4 to 0)        | 0.0001  |
| Complications                                                                                                                                                                                                                                                                                                                             |                            |                       |         |
| Any self-extubation                                                                                                                                                                                                                                                                                                                       | 16 (10%)                   | 6 (4%)                | 0.03    |
| Self-extubation requiring reintubation‡                                                                                                                                                                                                                                                                                                   | 5 (3%)                     | 3 (2%)                | 0.47    |
| Reintubation‡                                                                                                                                                                                                                                                                                                                             | 23 (14%)                   | 21 (13%)              | 0.73    |
| Tracheostomy                                                                                                                                                                                                                                                                                                                              | 21 (13%)                   | 34 (20%)              | 0.06    |
| Data are mean (SD), n (%), or median (IQR). RASS=Richmond agitation-sedation scale. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. *Ventilator-free days from study day 1 to 28. †Greater than 25% of patients in the SBT group remained in the hospital at study day 28. ‡Reintubation within 48 hours of extubation. |                            |                       |         |
| <b>Table 3: Main outcomes</b>                                                                                                                                                                                                                                                                                                             |                            |                       |         |

# Birth of ABCDE

A

- Kress JP, et al. N Engl J Med 2000;342:1471-7

B

- Ely EW, et al. N Engl J Med 1996;335:1864-9

C

- Riker R. et al, JAMA. 2009;301:489-499

D

- Preventing and Managing Delirium

E

- Schweickert et al, Lancet 2009;373:1874-82

# Birth of ABCDE

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

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

-

# Birth of ABCDE

- randomization to early exercise and mobilization (physical and occupational therapy) during periods of daily interruption of sedation (intervention; n=49) or to daily interruption of sedation with therapy as ordered by the primary care team



# Early Mobility and Exercise

## Primary diagnosis on admission to intensive care

|                              |          |          |
|------------------------------|----------|----------|
| Acute lung injury            | 27 (55%) | 31 (56%) |
| COPD exacerbation            | 4 (8%)   | 6 (11%)  |
| Acute exacerbation of asthma | 5 (10%)  | 4 (7%)   |
| Sepsis                       | 7 (14%)  | 9 (16%)  |
| Haemorrhage                  | 1 (2%)   | 2 (4%)   |
| Malignancy                   | 2 (4%)   | 1 (2%)   |
| Other                        | 3 (6%)   | 2 (4%)   |

Data are number of patients (%) or median (IQR). APACHE II–Acute Physiology and Chronic Health Evaluation II. COPD–chronic obstructive pulmonary disease. Barthel Index scale 0–100, APACHE II scale 0–71.

|                                                               | Intervention<br>(n=49) | Control<br>(n=55) | p value |
|---------------------------------------------------------------|------------------------|-------------------|---------|
| Return to independent functional status at hospital discharge | 29 (59%)               | 19 (35%)          | 0.02    |
| ICU delirium (days)                                           | 2.0 (0.0-6.0)          | 4.0 (2.0-7.0)     | 0.03    |
| Time in ICU with delirium (%)                                 | 33% (0-58)             | 57% (33-69)       | 0.02    |
| Hospital delirium (days)                                      | 2.0 (0.0-6.0)          | 4.0 (2.0-8.0)     | 0.02    |
| Hospital days with delirium (%)                               | 28% (26)               | 41% (27)          | 0.01    |
| Barthel Index score at hospital discharge                     | 75 (7.5-95)            | 55 (0-85)         | 0.05    |
| ICU-acquired paresis at hospital discharge                    | 15 (31%)               | 27 (49%)          | 0.09    |
| Ventilator-free days*                                         | 23.5 (7.4-25.6)        | 21.1 (0.0-23.8)   | 0.05    |
| Duration of mechanical ventilation (days)                     | 3.4 (2.3-7.3)          | 6.1 (4.0-9.6)     | 0.02    |
| Duration of mechanical ventilation, survivors (days)          | 3.7 (2.3-7.7)          | 5.6 (3.4-8.4)     | 0.19    |
| Duration of mechanical ventilation, non-survivors (days)      | 2.5 (2.4-5.5)          | 9.5 (5.9-14.1)    | 0.04    |
| Length of stay in ICU (days)                                  | 5.9 (4.5-13.2)         | 7.9 (6.1-12.9)    | 0.08    |
| Length of stay in hospital (days)                             | 13.5 (8.0-23.1)        | 12.9 (8.9-19.8)   | 0.93    |
| Hospital mortality                                            | 9 (18%)                | 14 (25%)          | 0.53    |

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

**Table 3: Main outcomes according to study group**

# Birth of ABCDE

A

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# Preventing delirium through improving sleep in the ICU

- Very little sleep in the ICU is restorative, REM sleep
- Reasons for poor sleep in the ICU include the continuous cycle of alarms, lights, beepers, care-related interruptions, pain, anxiety and ventilator dyssynchrony.
- medications that disrupt REM sleep including sedatives (particularly benzodiazepines), analgesics, vasopressors, beta-agonists, and corticosteroids

Crit Care Clin. 2013 January ; 29(1): 51–65

# Preventing delirium through improving sleep in the ICU

- Peak noise is not the main determinant disturbing the patient in the ICU. Phones ringing and people talking are reported as more annoying
- Patients sleeping with earplugs showed 15% mild confusion, whereas the control patients scored 40% in this category. Taking both categories, delirium and mild confusion, into account, 60% of the control group showed cognitive disturbances against only 35% in the study group.

# **Preventing delirium through pharmacologic interventions**

- no medication is FDA approved for the prevention or treatment of delirium

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

- Results of prophylactic treatment were compared with a historical control group and a contemporary group (n = 299 + 177)
- The predicted chance of developing delirium in the intervention and control group was  $75 \pm 19\%$  and  $73 \pm 22\%$ , respectively (P = 0.50)
- intravenous haloperidol 1 mg/8 h

- The actual delirium incidence was 65% in the intervention group, compared with 75% in the control group ( $P = 0.01$ )
- Prophylactic treatment with haloperidol resulted in a relative 28-day mortality reduction of 20% (hazard rate 0.80; 95% CI 0.66 to 0.98).
- Haloperidol was stopped in 12 patients because of QTc-time prolongation ( $n = 9$ ), renal failure ( $n = 1$ ) or suspected neurological side-effects ( $n = 2$ ).



- Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial
- to receive haloperidol 2 ▪ 5 mg or 0 ▪ 9% saline placebo intravenously every 8 h

- Patients in the haloperidol group spent about the same number of days alive, without delirium, and without coma as did patients in the placebo group
- These results do not support the hypothesis that haloperidol modifies duration of delirium in critically ill patients

# The HARPOON study

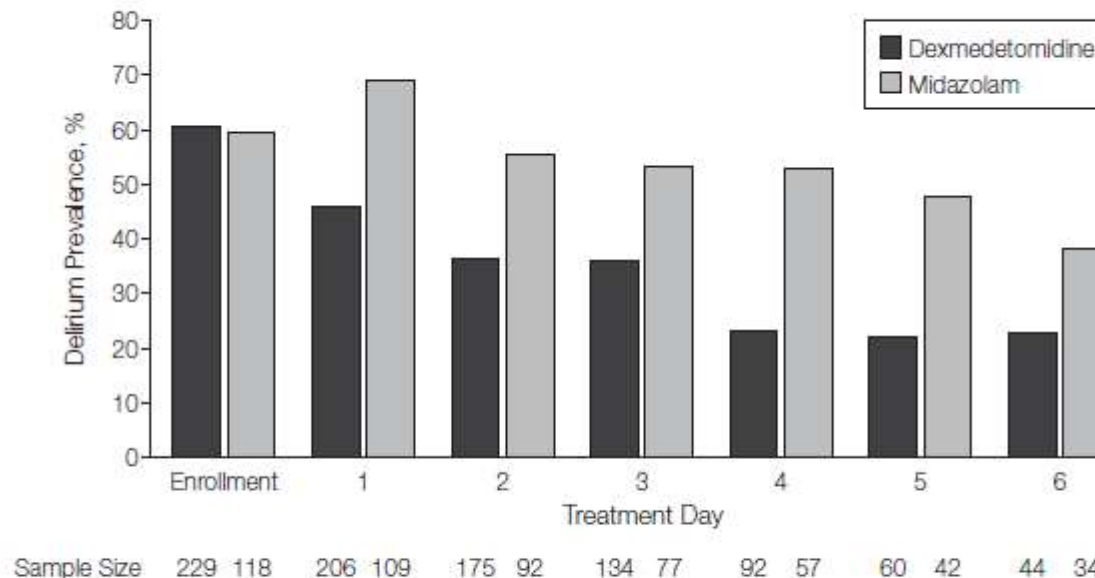
- Efficacy and safety of haloperidol prophylaxis for delirium prevention in older medical and surgical at-risk patients acutely admitted to hospital through the emergency department

# Preventing delirium through management of sedatives

## Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients A Randomized Trial

# Choice of Sedation

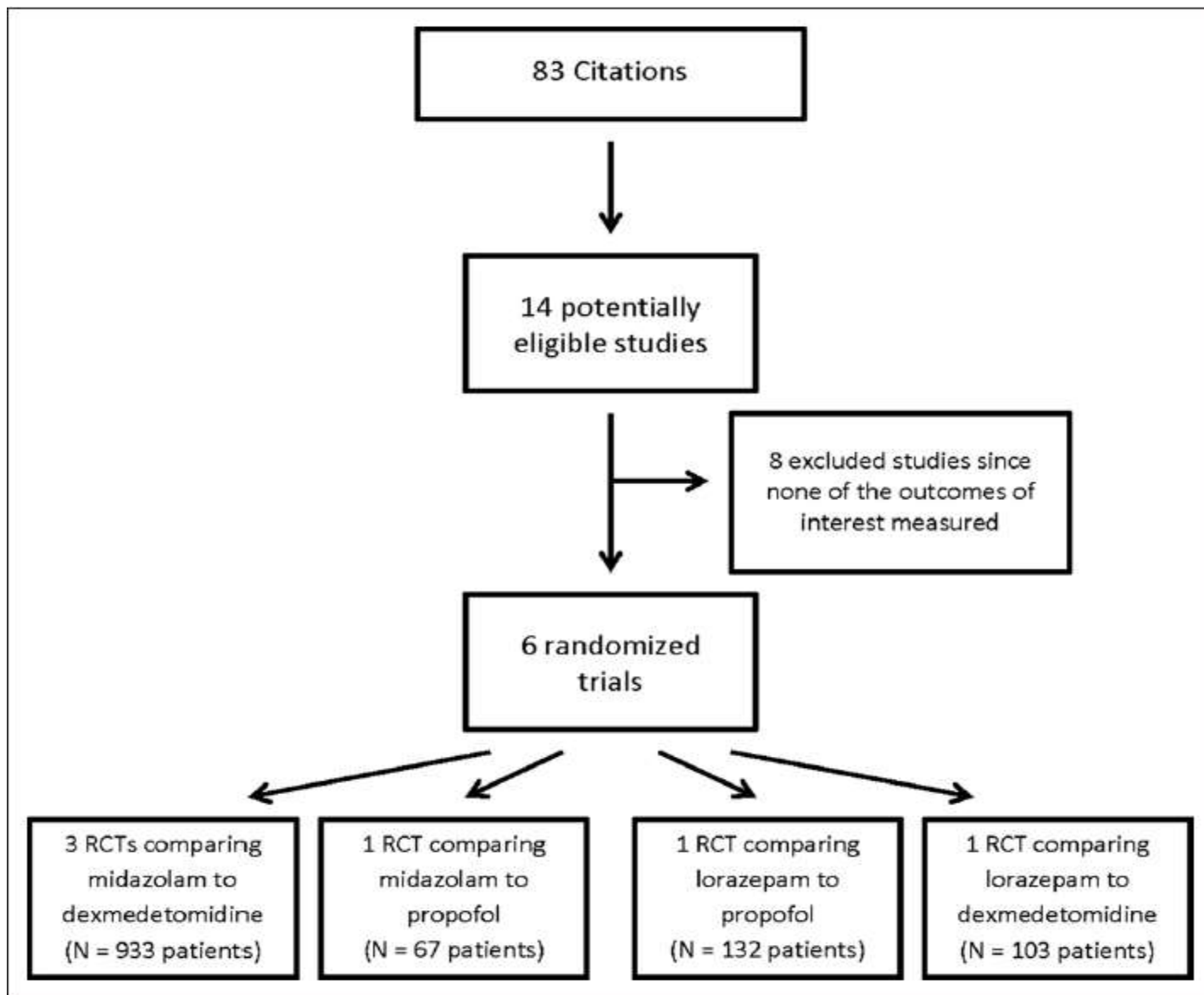
**Figure 2.** Daily Prevalence of Delirium Among Intubated Intensive Care Unit Patients Treated With Dexmedetomidine vs Midazolam



Delirium was diagnosed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).<sup>24</sup> At baseline, 60.3% of dexmedetomidine-treated patients and 59.3% of midazolam-treated patients were CAM-ICU-positive ( $P = .82$ ). The effect of dexmedetomidine treatment was significant in the generalized estimating equation<sup>27</sup> analysis, with a 24.9% decrease (95% confidence interval, 16%-34%;  $P < .001$ ) relative to midazolam treatment. Numbers differ from those for primary analysis because patients were extubated, discharged from the intensive care unit, or had missing delirium assessments.

# **Preventing delirium through management of sedatives**

- Benzodiazepine Versus Nonbenzodiazepine-Based Sedation for Mechanically Ventilated, Critically Ill Adults: A Systematic Review and Meta-Analysis of Randomized Trials



# Benzodiazepine Versus Nonbenzodiazepine-Based Sedation

Compared to a benzodiazepine sedative strategy, a nonbenzodiazepine sedative strategy was associated with

- a shorter ICU length of stay (n = 6 studies; difference = 1.62 d; 95% CI, 0.68–2.55; p = 0.0007)
- duration of mechanical ventilation (n = 4 studies; difference = 1.9 d; 95% CI, 1.70–2.09; p < 0.00001)

But

- a similar prevalence of delirium (n = 2; risk ratio = 0.83; 95% CI, 0.61–1.11; p = 0.19)



# **Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients**

- Seven studies, covering 1624 participants, compared dexmedetomidine with traditional sedatives
- reduced the mean duration of mechanical ventilation by 22% (95% CI 10% to 33%; four studies, 1120 participants, low quality evidence)
- the length of stay in the intensive care unit (ICU) by 14% (95% CI 1% to 24%; five studies, 1223 participants, very low quality evidence).
- no evidence that dexmedetomidine decreased the risk of delirium (RR 0.85; 95% CI 0.63 to 1.14; seven studies, 1624 participants, very low quality evidence)

# Preventing delirium through pain management

- ICU patients who were assessed for pain were less likely to receive sedatives, particularly deliriogenic benzodiazepines, and more likely to receive analgesic medications (non-opioids or opioids) than those who never had a pain assessment

# Delirium prevention

- Early mobilization of adult ICU patients whenever feasible to reduce the incidence and duration of delirium.
- no recommendation for using a pharmacologic delirium prevention protocol in adult ICU patients, as no compelling data demonstrate that this reduces the incidence or duration of delirium in these patients.
- Haloperidol or atypical antipsychotics administration is not recommended to prevent delirium in adult ICU patients.
- We provide no recommendation for the use of dexmedetomidine to prevent delirium in adult ICU patients, as there is no compelling evidence regarding its effectiveness in these patients.

# Treatment

- Nonpharmacological and pharmacological therapy.
- the therapy of potential underlying cause, that is, medical conditions that promote delirium should be evaluated and treated.
- The nonpharmacological treatment strategy is in large part similar to the prevention strategies.

- The question how to treat delirium correctly is not easily answered, because there has been no conclusive evidence from a multitude of surveys

- In the previous version of these guidelines, the recommended use of haloperidol for the treatment of delirium was a Level C recommendation based only on a case series. These data did not meet the evidence standard for this version of the guidelines.
- No recent prospective trials have verified the safety and efficacy of haloperidol for the treatment of delirium in adult ICU patients. Data on the use of other antipsychotics in this patient population are similarly sparse.
- Robust data on haloperidol in non-ICU patients that could potentially be applied to the ICU patient population are lacking

- Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: A comparison of efficacy, safety, and side effects
- were equally effective in the management of delirium; however, they differed in terms of their side-effect

- The atypical antipsychotics are attractive alternatives to haloperidol with improved safety profiles but are flawed by limited data to support dosing and efficacy
- Future studies that provide large, prospective, double-blinded, placebo-controlled data to support the implementation of these agents as standard therapy over haloperidol are needed



- Rapidity of onset – Haloperidol has an onset of action 15 to 20 minutes after intravenous infusion.
- Duration of effect – it's duration of effect varies and depends upon the cumulative dose.
- Dosage regimens — The administration of haloperidol intravenously is common, but it has not been approved by the United States' Food and Drug Administration (FDA).
- 2 to 10 mg intravenous bolus doses administered every 20 to 30 minutes until calm is achieved

# Take home message

- Identifying patients with high risk factors
- Frequent formal assessment for delirium
- Assess for pain at frequent intervals
- Sticking to a bundled approach for delirium prevention
- Haloperidol prophylaxis in patients with high risk
- Non pharmacological treatment of delirium