Critical Care PRN and Society of Critical Care Medicine Focus Session—Sedation and Delirium in the ICU: Update on the Status of the 2011 SCCM Guidelines
Activity No. 0217-0000-11-079-L01-P (Application-Based Activity)

Monday, October 17
3:45 p.m.–5:45 p.m.
Convention Center: Spirit of Pittsburgh Ballroom A

Moderator: Jeremy D. Flynn, Pharm.D., BCPS
Assistant Professor, Department of Pharmacy Practice and Science, University of Kentucky, Lexington, Kentucky

Agenda

3:45 p.m.	Pharmacologic Options for Analgesia and Sedation in the Critically Ill *Joseph F. Dasta, M.S., FCCP* Professor Emeritus, The Ohio State University College of Pharmacy, Adjunct Professor, The University of Texas College of Pharmacy, Austin, Texas
4:15 p.m.	Interruption and Mobilization *John Kress, M.D.* Associate Professor of Medicine, University of Chicago Department of Medicine, Section of Pulmonary and Critical Care Director, MICU, Chicago, Illinois
4:45 p.m.	Recognizing, Preventing, and Treating Delirium in the Critically Ill *John W. Devlin, Pharm.D., FCCP, BCPS* Associate Professor of Pharmacy, Northeastern University, Boston, Massachusetts
5:15 p.m.	Practical Application of the Guidelines to Daily Practice *Gilles L. Fraser, Pharm.D., FCCM* Professor of Medicine, Tufts University School of Medicine; Clinical Specialist, Critical Care, Maine Medical Center, Portland, Maine

Faculty Conflict of Interest Disclosures

Joseph F. Dasta: consultant/member of advisory board for Cadence Pharmaceuticals, Hospira, Pacira Pharmaceuticals, Otsuka America Pharmaceuticals, Edge Therapeutics; speaker's bureau for Cadence Pharmaceuticals.
John W. Devlin: speaker's bureau for Hospira Pharma; received grant funding/research support from Hospira Pharma.
Gilles L. Fraser: no conflicts to disclose.
John Kress: speaker's bureau for Hospira; received grant funding/research support from Hospira.

Learning Objectives

1. Summarize the pharmacologic options for analgesia and sedation in ICU patient populations.
2. Review and implement the guideline recommendations, specifically those that represent significant changes in practice.
3. Discuss the current literature that supports the recommendations.
4. Discuss the barriers and challenges to daily sedation interruption in a heterogenous group of ICU patients (medical, surgical, neuro, etc.) .
5. Review the literature and benefit of early mobilization in ICU patients and it's association with clinical outcomes .
6. Determine the potential influence of sedation pharmacotherapy on mobilization, neuromuscular weakness, and clinical outcomes.
7. Describe the association between sedation interruption, mobilization, and functional outcomes of ICU patients.
8. Describe the clinical significance of delirium in patients in the ICU.
9. Describe how to incorporate the use of delirium screening tools into daily practice.
10. Identify reversible risk factors for delirium in critically-ill patients and then develop practice strategies to minimize the exposure of patients to these risk.
11. Develop an evidence-based treatment plan for delirium in a critically-ill patient.
12. Discuss the potential difficulties with incorporating the major changes suggested in the guidelines to daily practice.
13. Review potentials strategies to successfully implement daily interruption of sedation and early mobilization into daily practice.
14. Develop a comprehensive sedation plan to minimize adverse events, avoid delirium and hasten separation from mechanical ventilation.

Self-Assessment Questions

Self-assessment questions are available online at *www.accp.com/am*

Pharmacologic options for analgesia and sedation in the critically ill

Joseph F. Dasta, M.Sc., FCCM, FCCP
Professor Emeritus
The Ohio State University
Adjunct Professor
University of Texas

Disclosures

- Consultant
  - Cadence, Hospira, Pacira
- Member, speakers bureau
  - Cadence
  - France Foundation (funded by Hospira)

Update on the SCCM Guideline *Pain, Agitation, Delirum (PAD)*

- First official meeting January 2006
- 20 expert panel members -3 Pharmacists
  - pain, sedation, delirium, outcomes teams
- Database >19,000 articles
- GRADE system used
  - Quality of the evidence
  - Strength of the recommendations
- Each team developed relevant questions

Update of the SCCM Guideline *Pain, Agitation, Delirum (PAD)*

- Each question
  - Evidence (high, moderate, low/very low)
  - Strength of recommendation
    - Strong, i.e., We recommend….
    - Weak, i.e., We suggest….
    - No recommendation (expert opinion not permitted)
- No industry funding or involvement
- Conflict of interest statement reported by all members

Update of the SCCM Guideline *Pain, Agitation, Delirum (PAD)*

- Published in full Critical Care Medicine
- Executive summary AJHP
  - ASHP is a sponsoring organization
- Due to rigorous process there should be
  - No surprises
- Task force members embargoed until guideline appears in public forum (in press)

ICU Analgesic Pharmacopeia

- IV opioids
- IV NSAIDS
- IV acetaminophen
- Elastomeric pumps with local anesthetics delivered to the wound site
- IV ketamine
- Epidural, neuraxial administration
- Potential future drugs
  - IV diclofenac
  - Depo-bupivacaine injected at wound site
  - Sublingual sufentanil delivery device
  - Morphine 6-glucuronide

Clinical and Economics of Inappropriate Acute Pain Management

- Continued pain can result in increased complications, delirium, and longer LOS
- Oversedation prolongs ventilator time & LOS
- Difficult to implement early mobilization efforts when ICU patients experience pain
- Multimodal approach is often successful
- Analgesic ADEs are expensive
- Most analgesics have a low acquisition cost
- No cost-effectiveness studies exist

Pain in the ICU

- >50% of ICU patients experience pain
  - Procedural and non-procedural pain
- Too many patients relate the terrors of experiencing pain acutely, which can lead to chronic pain
- We just aren't doing a very good job
- Pain should be assessed repeatedly
- Validated pain assessment tools should be used – examples include BPS, CPOT

Treating Agitation

- Trend towards titrating to a lighter degree of sedation
- Increasing use of early mobilization
- Trend to minimizing wide-spread use of benzodiazepines
- Increased appreciation of pharmacoeconomic implications of Inadequate or excessive sedation
  - Effects on LOS and time on the ventilator
  - Increase in health care costs

Life in the real world

- Greater than 40% patients are more deeply sedated than desired
- Drug-induced coma present during 32% of patient evaluations
  - Yet only 2.6% rated as "oversedated"
- How could this be?
- Not in my ICU

Crit Care Med 2007;35:393 *Anesthesiology* 2007;106:687

ICU Sedation Pharmacopeia

- Benzodiazepines – GABA agonists
  - Long history of use acutely and long-term
  - Differ by pharmacokinetic properties
  - Recent appreciation of deliriogenic effects
  - Respiratory and cardiovascular depression
- Propofol – GABA agonist
  - Long history of use in OR and ICU
  - Respiratory and cardiovascular depression
  - Recent appreciation of PRIS

ICU Sedation Pharmacopeia

- Fospropofol (Aqueous solution)
  - Prodrug converted to propofol in blood
  - One pilot study in ICU patients
    - Sedation target achieved
    - Triglyceride concentrations fell by 6 mg/dL with fospropofol; increase by 31 mg/dL with propofol
- Ketamine
  - Resurgence of interest
  - Use in non-dissociative dosages
  - Opioid sparing and sedative sparing

Anesth Analg 2011;113:550

Dexmedetomidine

- Alpha-2-adrenergic agonist
  - Sedating, anxiolytic, and opioid-sparing properties
  - Permits patient awareness and responsiveness upon stimulation ("cooperative" sedation)
- Clinical perspective
  - No loading dose needed
  - Does not cause respiratory depression
  - May play a role in ventilator weaning
  - Sympatholytic (hypotension and bradycardia)
  - Don't adjust dosage any sooner than q 20-30 min
  - Increasing experience in alcohol withdrawal

Ann Pharmacother 2009;43:2064

SEDCOM: Dexmedetomidine vs Midazolam

- Double-blind, randomized, multicenter trial comparing long-term (> 24 hr) dexmedetomidine (dex, n = 244) with midazolam (mz, n = 122)
- Sedatives (dex 0.2-1.4 µg/kg/hr or mz 0.02-0.1 mg/kg/hr) titrated to light sedation (RASS -2 to +1), administered up to 30 days
- All patients underwent daily arousal assessments and drug titration Q 4 hours

Outcome	Midazolam (n = 122)	Dexmedetomidine (n = 244)	*P*-Value
Time in target sedation range, %	75.1	77.3	0.18
Duration of sedation, days	4.1	3.5	0.01
Time to extubation, days	5.6	3.7	0.01
ICU LOS, days	7.6	5.9	0.24
Delirium prevalence	93 (77%)	132 (54%)	0.001
Delirium-free days	1.7	2.5	0.002

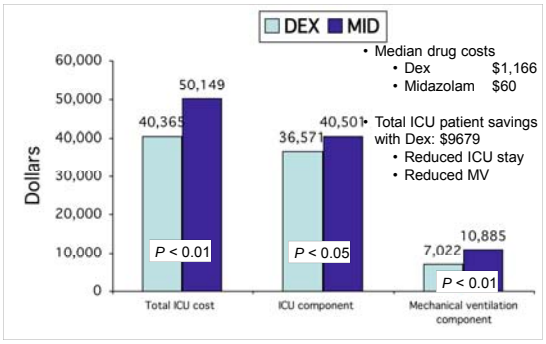
JAMA. 2009;301(5):489

SEDCOM Trial: Safety Outcomes

Outcome	Midazolam (n = 122)	Dexmedetomidine (n = 244)	*P*-Value
Bradycardia	23 (18.9%)	103 (42.2%)	0.001
Bradycardia needing treatment	1 (0.8%)	12 (4.9%)	0.07
Tachycardia	54 (44.3%)	62 (25.4%)	0.001
Hypertension requiring intervention	36 (29.5%)	46 (18.9%)	0.02
Hyperglycemia	52 (42.6%)	138 (56.6%)	0.02
Infections	24 (19.7%)	25 (10.2%)	0.02

JAMA. 2009;301(5):489

SEDCOM Cost of Care



Crit Care Med. 2010;38:497-503.

Effects of Early Mobilization in Mechanically-ventilated ICU patients

- Shift in care from deep to light sedation
- Early mobilization of patients may improve functional outcomes and delirium
- 104 ICU patients ventilated <72 hours
- Randomized trial
  - Daily sedation interruption with early exercise and mobilization (PT and OT)
  - Daily sedation interruption and standard care

Lancet 2009;373:1874.

Results

Variable	Control	Intervention	*P*-value
Days ICU delirium	4 (2-7)	2 (0-6)	0.03
% time with delirium	57 (33-69)	33 (0-58)	0.02
Days of ventilation	6.1 (4-9)	3.4 (2-7)	0.02
Days of ICU stay	7.9 (6-13)	5.9 (4-13)	0.08

Lancet 2009;373:1874.

Analgosedation

- Provide analgesics First, then supplement with sedative-hypnotic, if needed
- Also known as analgesia-first (A-1) sedation
- Acknowledges that pain is a cause of agitation
- Nine trials in Europe, one trial in Thailand
- Continuous infusion of remifentanil or fentanyl vs. sedative-hypnotic based regimen and prn opioids
- 30–74% required benzodiazepine/propofol rescue
- Encouraging results of shorter ICU time with analgosedation regimen but the final word isn't in yet

Anesthesiology. 2004;101:640
Br J Anaesth. 2007;98:76
Intensive Care Med. 2009;35:291
Lancet. 2010;375(9713):475

Summary

- Renewed focus on pain, then agitation
- Better understanding of benefits and risks of the pharmacopeia of available agents
- Protocolized care is preferred
- Evaluate total cost of care
- Promising new analgesics that may reduce the incidence of opioid-associated ADEs
- No new sedatives in the horizon

Recognizing, Preventing and Treating Delirium in the Critically Ill

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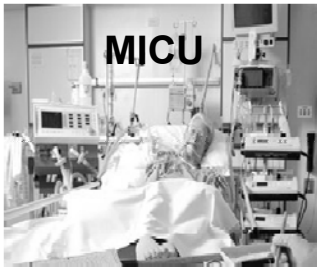
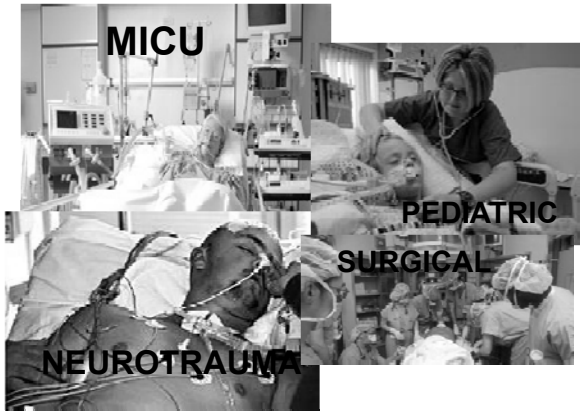
Northeastern UNIVERSITY

Tufts Medical Center





D

DELIRIUM: EPIDEMIOLOGY AND RISK FACTORS

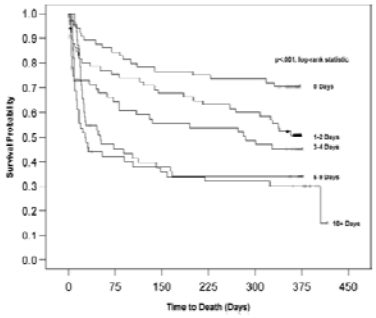
Prevalence of ICU Delirium

- Adults: 60-80% of MICU/SICU/TICU mechanically ventilated patients develop delirium
- Children: 13.2%
- 20-50% of lower severity ICU patients develop delirium
- Hypoactive more common than hyperactive
- Most delirium goes undiagnosed in ICU if a validated delirium screening tool is not implemented

Ouimet S, et al. *Intensive Care Med*. 2007;33:66-73
Dubois MJ, et al. *Intensive Care Med* 2001;27:1297-1304
Ely EW, et al. *Intensive Care Med*. 2001;27:1892-1900.
Ely EW, et al. *JAMA*. 2001;286,2703-2710.
Pandharipande PP, et al. *J Trauma*. 2008;65:34-41.
Lat I, et al. Crit Care Med 2009; 37:1898
Smith HAB, et al. Crit Care Med 2011; 39:150-7.

Duration of Delirium Affects Mortality

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



Pisani M. et al. Am J Respir Crit Care Med. 2009 Dec 1;180(11):1092-7.
Shehabi Y. et al. Crit Care Med 2010 (ahead of press)

Sequelae of Delirium

During the ICU/Hospital Stay

- Increased mortality
- 3x greater re-intubation rate
- Average 10 additional days in hospital
- Higher costs of care

After Hospital Discharge

- Increased mortality
- Development of dementia
- Long-term cognitive impairment
- Requirement for care in chronic care facility
- Decreased functional status at 6 months

Girard TD et al. Crit Care Med 2010; 38:1513-1520
Milbrant EB, et al. *Crit Care Med* 2004;32:955-962.
Jackson JC, et al. *Neuropsychol Rev.* 2004;14(2):87-98.
Nelson JE, et al. *Arch Intern Med.* 2006; 166:1993-1999.
Ely EW, et al. *JAMA.* 2004;291:1753-1762.

Paradigm Shift in the Outcomes Being Evaluated in Clinical Research

Outcomes During ICU Stay

- Time spent within sedation goal
- Episodes of agitation
- Episodes of agitated-related events
- Delirium
  - Prevalence of delirium
  - Days spent with delirium
- Duration of mechanical ventilation
- Duration of ICU stay
- ICU mortality

Outcomes After ICU Stay

- Disposition and functionality
- Cognition/Dementia
- Sleep quality
- ICU memories/PTSD
- Quality of life
- Depression
- Executive function

Skrobik Y. Lancet. 2010 Nov 27;376(9755):1805-7
Desai SV et al. Crit Care Med. 2011 Feb;39(2):371-9.

Patient Factors
***Alcoholism**
Increased age
Male gender
Living alone
Smoking

Environment
***Use of physical restraints**
Isolation
No clock
No daylight
No visitors
Noise

Less Modifiable

More Modifiable

Prexisting Disease
***Dementia**
***Hypertension**
Pulmonary disease
Renal disease

Acute Illness
***Severity of Illness**
***Development of coma**
Length of stay
Fever
Medicine service
Lack of nutrition
Sepsis/Hypotension
Metabolic disorders
Tubes/catheters

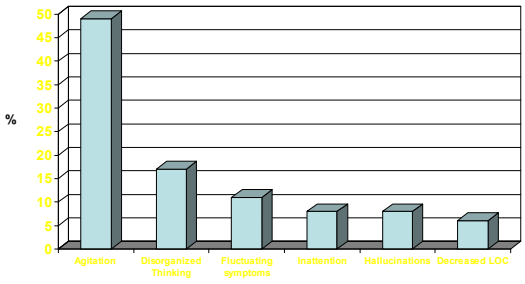
Medications:
***Benzodiazepines**
Opioids
Anticholinergics
Corticosteroids

Inouye SK et al. *JAMA.* 1996; 275: 852.
Dubois MJ, et al. *ICM.* 2001;27:1297-1304.
Ouimert S et al. *ICM.* 2007; 33:66-73.
Van Rompaey B et al. *Crit Care.* 2009; 13:R77.
Pandharipande P, et al. *Anesthesiol.* 2006:104:21-26.

D

DELIRIUM MONITORING

Survey: Symptoms Most Associated with Delirium



Devlin JW et al. Ann Pharmacother 2011 (in press)

Confusion Assessment Method (CAM-ICU)

1. Acute onset of mental status changes or a fluctuating course

and

2. Inattention

and

3. Altered level of consciousness

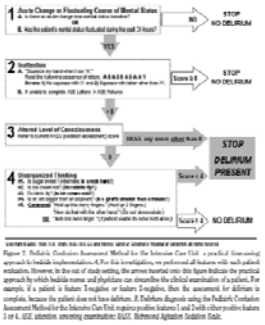
or

4. Disorganized thinking

= Delirium

Ely EW, et al. *Crit Care Med.* 2001;29:1370-1379.
Ely EW, et al. *JAMA.* 2001;286:2703-2710.

Pediatric CAM-ICU



146 paired assessments

Age = 12.2 years old

2 critical care clinicians vs. pediatric psychiatrist

Sensitivity = 83% (95% CI, 66-93%)

Specificity = 99% (95% CI, 95-100%)

Inter-rater reliability = K=0.96

Smith HAB, et al. Crit Care Med 2011; 39:1

Intensive Care Delirium Screening Checklist

1. Altered level of consciousness
2. Inattention
3. Disorientation
4. Hallucinations
5. Psychomotor agitation or retardation
6. Inappropriate speech
7. Sleep/wake cycle disturbances
8. Symptom fluctuation

Score 1 point for each component present during shift.
- Score of 1-3 = Subsyndromal Delirium
- Score of ≥ 4 = Delirium

Bergeron N, et al. *Intensive Care Med.* 2001;27:859-864.

Ouimet S, et al. *Intensive Care Med.* 2007; 33:1007-1013.

Current Delirium Screening Practices of Critical Care Pharmacists

- Delirium status frequently or always discussed: 50%
- Delirium status screened ≥ 50% of the time: 18%
- Pharmacist screened for delirium ≥ 1 patient: 32%
  - 64% screen for delirium in ≤ 10% of patients
- Barriers to delirium screening per pharmacists:
  - Lack of time = 34%
  - Is a nursing role = 24%
  - Do not feel comfortable using screening tool = 13%

Devlin JW et al. Ann Pharmacotherapy 2011 (in press)

Trauma-Surgical Nurses in a STICU where delirium screening tool not yet implemented

Bedside RN	Phase 1	Phase 2	Phase 3
Method delirium detection	No screening tool	ICDSC	ICDSC
Education	None	ICDSC validation On;y	Didactic lecture in classroom by ICU PharmD, web-based module with self ass't questions and bedside teaching in at least 2 pts by ICU RN educator
Detection of delirium vs. validated judge (kappa)	0.403	0.624	0.735
Delirium knowledge (out of 10)	6.1± 1.4`	6.5 ± 1.4	8.2 ± 1.4; p=0.001 (phase 2 vs. phase 3)

Gesin, G….Devlin JW. Am J Crit Care (in press)

Strategies to Boost Delirium Screening

- Ensure sedation assessment is occurring regularly and reliably
- Obtain strong buy-in from both RN and MD ICU managers
- Education:
  - Didactic (e.g. web) and at bedside
  - Delivered to both day and night nurses
  - Ensure that education is repeated on a continuous basis
  - Should include all physicians
- Ability to recognize delirium may be compromised in routine practice (e.g. sensitivity of CAM-ICU = 47% in 10 Dutch ICUs)
- Clinicians should be very comfortable with "not being able to evaluate" all symptoms of delirium in some patients.
- Nurses have been evaluating many delirium symptoms for years…..they just do not realize it!
- Incorporate in any DA-SBT protocol and daily rounds checklist

Devlin JW et al. Crit Care 2008 12; R19
Devlin JW et al. Intens Care Med 2007;33:929-40
Devlin JW et al. *Crit Care Med.* 2007: 35:2721-2724.
Van Eijk MM et al. AJRCCM 2011;184(3):340-4.

D

DELIRIUM PREVENTION

Early Mobilization

	Mobilization (N = 49)	Control (N = 55)	*P* - Value
ICU/hospital days with delirium (days)	2	4	0.03
% time in ICU with delirium	33%	57%	0.02
% time in Hospital with Delirium	28%	41%	0.01

Schweickert WD, et al. *Lancet.* 2009;373:1874-1882.

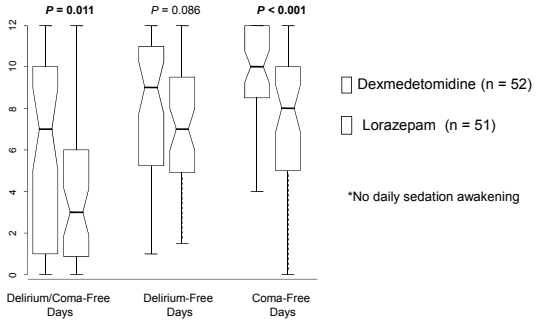
Daily Awakening –Spontaneous Breathing Trial

	DA-SBT (N = 49)	SBT only (N = 55)	*P* - Value
Coma (days)	2	3	0.03
Delirium (days)	2	2	0.55

*Median days

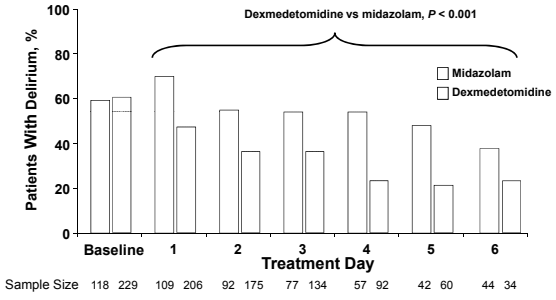
Girard TD, et al. *Lancet.* 2008;371:126-134.

MENDS: Dexmedetomidine vs Lorazepam



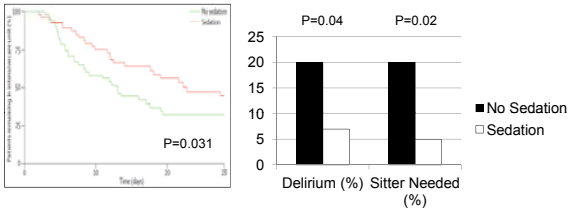
Pandharipande PP, et al. *JAMA* 2007; 298(22) 2644-2653.

SEDCOM: Reduced Delirium with Dexmedetomidine vs Midazolam



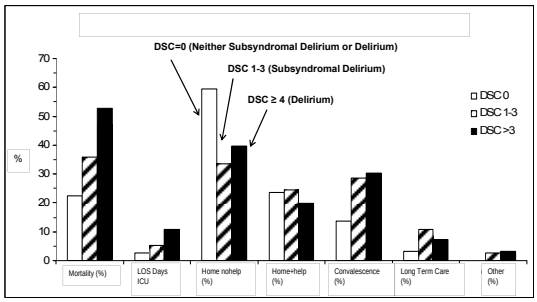
Riker RR, et al. *JAMA.* 2009;301(5):489-499.

Impact of an Analgesia-First Strategy



Strøm T, et al. *Lancet.* 2010;375(9713):475-480.

ICDSC Score Predicts Patient Outcome: The Importance of Subsyndromal Delirium



Ouimet S et al. *Intensive Care Med* 2007; 33:66-73.

Canadian ICU Sedation Protocol Decreased Subsyndromal Delirium but Not Delirium Incidence When Coma and Benzodiazepine Use Was Avoided

Protocol Emphasized:

- Pain assessment and treatment first
- Maintenance 24/7 of patients in an awake/slightly sleepy state
- Minimize use of continuous sedation infusions
- Minimize use of benzodiazepines

Parameter	Before-Protocol N=604	After-Protocol N=610	P value
No exposure to benzodiazepines (%)	39	45	<0.03
Delirium (ICDSC ≥4) (%)	34	35	0.002
Subsyndromal delirium (ICDSC=1-3) (%)	33	25	0.009
Discharged to home (%)	45	52	0.024

Skrobik Y, et al. *Anesth Analgesia* 2010 2010;111:451-63.

Mechanically Ventilated Patients with Sub-syndromal Delirium [ICDSC 1-3]

Haloperidol 1mg IVP q6h | **Placebo**

- No antipsychotic rescue medication or dexmedetomidine allowed
- Sedation titrated to maintain SAS ≥ 3

Outcomes:
Primary: % of patients progressing to full delirium
(confirmed by Staff Psychiatrist using DSM-IV criteria)
Secondary:
1. Hours spent agitated
2. Hours spent mechanically ventilated
3) Safety
4) 1 week sleep, pyschologic and cognitive evaluation
5) 6 month sleep, psychologic, cognitive and functional evalution

Supported by 1R15AG034915-01A1 NIA

D

DELIRIUM TREATMENT

Mechanisms for Delirium in the Critically Ill are Numerous and Still Not Clearly Understood

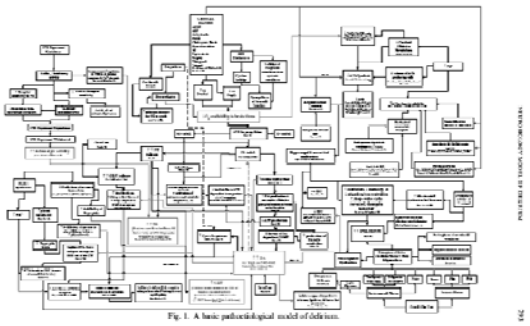


Fig. 1. A basic pathoetiological model of delirium.

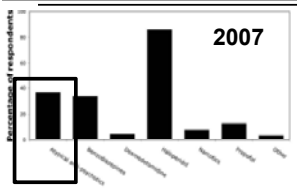
Maldonado. Crit Care Clin 2008; 24:789

Use of Atypical Antipsychotic Therapy is Increasing

Table 4. Medication used by healthcare professionals to treat delirium in the intensive care unit

Drug	2001 No.	%
Antipsychotics	634	70
Haloperidol	603	66
Atypical antipsychotics	34	4
Sedatives	150	16
Benzodiazepines	145	16
Propofol	15	2

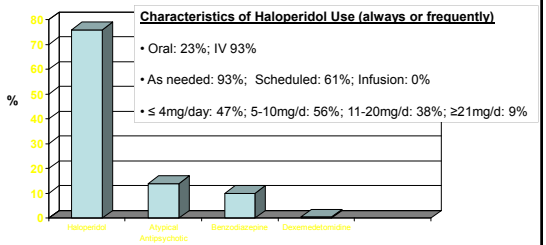
Data were derived from answers to question 10 of the Appendix.



Ely EW et al. Crit Care Med 2004;32:106-12
Patel RP et al. Crit Care Med 2009; 37:825-832

Survey: First-Choice Delirium Treatment Options

- **Delirium should always be managed with a medication: 85%**
- **Use ≥ 2 medications to treat delirium: 68%**



Characteristics of Haloperidol Use (always or frequently)

- Oral: 23%; IV 93%
- As needed: 93%; Scheduled: 61%; Infusion: 0%
- ≤ 4mg/day: 47%; 5-10mg/d: 56%; 11-20mg/d: 38%; ≥21mg/d: 9%

Devlin JW et al. Ann Pharmacother 2011 (in press)

Modifying the Incidence of Delirium (MIND) Trial

- Design: Double-blind, placebo-controlled, randomized trial
- Setting: 6 tertiary medical centers
- Patients: Mechanically ventilated adults with an abnormal level of consciousness or who were receiving continuous sedatives/analgesics
  Note: Patients had brain dysfunction but only 49% had delirium at baseline
- Intervention:
  - Haloperidol (5mg) vs ziprasidone (40mg) vs placebo
  - Max 14 days
  - Dose interval increased if CAM-ICU negative
  - Could give IM if NPO up to max 8 doses
  - Oversedation: ↓dose frequency when RASS ≥2 levels above target (after holding sedation therapy)
  - If delirium reoccurred after d/c of study drug then restarted at last effective dose (and weaned again as per above)
- Primary outcome:
  - Number of days patient alive without delirium or coma during the 21-day study period
    - Delirium = + CAM-ICU
    - Coma = RASS (-4) [ie. responsive to physical but not verbal stimulation] or RASS (-5) [ie. not responsive to either]

Girard TD, et al. *Crit Care Med.* 2010;38(2):428-437.

MIND Trial Results

Outcome	Haloperidol, n = 35	Ziprasidone, n = 30	Placebo, n = 36	*P*-value
Delirium/coma-free days	14.0	15.0	12.5	0.66
Delirium days	4	4	4	0.93
Resolution of delirium on study drug, n (%)	24 (69)	23 (77)	21 (58)	0.28
Coma days	2	2	2	0.90
% of days accurately sedated	70	64	71	0.91
Ventilator-free days	7.8	12.0	12.5	0.25
Length of stay, days				
ICU	11.7	9.6	7.3	0.70
Hospital	13.8	13.5	15.4	0.68
21-day mortality, n (%)	4 (11)	4 (13)	6 (17)	0.81
Average extrapyramidal symptoms score	0	0	0	0.56

Girard TD, et al. *Crit Care Med.* 2010;38(2):428-437.

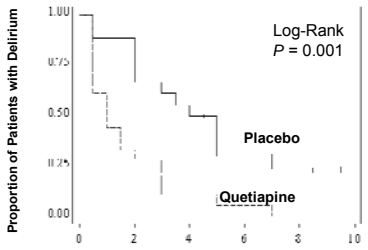
Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study*

John W. Devlin, PharmD; Russel J. Roberts, PharmD; Jeffrey J. Fong, PharmD; Yoanna Skrobik, MD; Richard R. Riker, MD; Nicholas S. Hill, MD; Tracey Robbins, RN; Erik Garpestad, MD

- Design: Double-blind, placebo-controlled, randomized trial
- Setting: 3 academic medical centers
- Intervention:
  - Quetiapine 50mg PO/NGT twice daily titrated to a maximum of 200mg twice daily) vs Placebo
  - PRN IV haloperidol protocolized and encouraged in each group
  - Oversedation: hold study drug when SAS ≤ 2 (after holding sedation therapy)
- Primary outcome:
  - Time to first resolution of delirium (ie. first 12 hour period when ICDSC ≤ 3)

Devlin JW, et al. *Crit Care Med*. 2010;38(2):419-427.

Patients with First Resolution of Delirium



Devlin JW, et al. *Crit Care Med*. 2010;38(2):419-427.

Clinical Outcomes

	Quetiapine (n=18)	Placebo (n=18)	P value
Time of study drug administration (hours)	102 (84-168)	186 (108-228)	0.04
Time in delirium (hours)	36 (12-87)	120 (60-195)	0.006
Time spent agitated (SAS ≥ 5) (hours)	6 (0-38)	36 (11-66)	0.02
Percent of time spent in delirium after ICU discharge	0 (0-0)	14 (0-47)	0.05
Subject placement after hospital discharge (%)			
Home / rehabilitation center	89	56	0.06
Chronic care facility / another acute care hospital / death	11	44	

- Five episodes of somnolence and one episode of hypotension were observed that were felt to be possibly related to the administration of quetiapine.
- No episodes of EPS were experienced during the study drug period.
- The number of subjects with QTc prolongation as determined by a > 60 msec increase from baseline (39 vs. 44%, p=0.74), QTc > 500 msec (22 vs. 28%, p=1.0), or other CPMP definitions (50 vs. 72%, p=0.31) was similar between the quetiapine and placebo groups.

Devlin JW, et al. *Crit Care Med*. 2010;38(2):419-427.

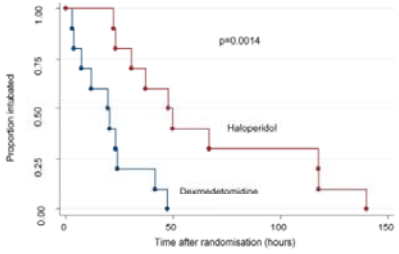
Impact of Quetiapine on the Resolution of Individual Delirium Symptoms

Median ICDSC and individual delirium symptoms similar at study baseline

	Quetiapine	Placebo	P value
Median time to symptom resolution			Log rank
Inattention	3 hrs	8 hrs	0.10
Disorientation	2 hrs	10 hrs	0.10
Symptom fluctuation	4 hrs	14 hrs	0.004
Agitation	5 hrs	1 hrs	0.04
Time with each symptom [median (IQR)]			Comparison of Proportions
Inattention	47 (0-67) %	78 (43-100) %	0.02
Hallucinations	0 (0-17) %	28 (0-43) %	0.10
Symptom fluctuation	47 (19-67) %	89 (33-100) %	0.04

Devlin JW, et al. Crit Care 2011 (in press)

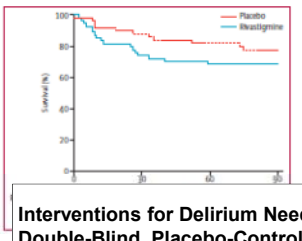
Dexmedetomidine vs Haloperidol for the Treatment of Delirium



Haloperidol: 0.5-2mg/hr infusion to maintain RASS=0
Dexmedetomidine: 0.2 – 0.7 mcg/kg/hr to maintain RASS=0

Reade RC et al. Crit Care 2009; 13:R75

Rivastigmine: Greater mortality and less efficacy in resolving delirium than placebo



Interventions for Delirium Need to be Based on Double-Blind, Placebo-Controlled, RCT Evidence

Mortal

Primary outcome			
Delirium duration (days)	5·0 (2·7–14·7)	3·0 (1·0–9·3)	0·06
Endpoint of end of delirium (n=35 vs n=34)	4·0 (2·0–16·0)	2·5 (1·0–5·8)	0·06
Endpoint of hospital discharge (n=7 vs n=12)	6·0 (3·5–11·5)	6·0 (3·0–21·5)	0·95
Endpoint of death (n=12 vs n=4)	9·5 (4·8–11·8)	8·0 (1·0–9·0)	0·29

Van Eijk, MMJ et al Lancet 2010; 376: 1829

Methodologic Considerations for Fruture Studies Investigating Antipsychotic Therapy For ICU Delirium Prevention or Treatment

- Interventions shown to reduce delirium in the ICU are maximized.
- Patients with conditions know to mimic delirium are excluded.
- Use of a placebo arm that does not involve antipsychotic administration.
- Evaluate the response of individual delirium symptoms.
- Antipsychotic dose strategy in study based on formalized dose-response testing.
- Avoidance of excessive levels of sedation
- Adequate sample to standard ICU patient outcomes.
- Evaluation of post-ICU psychologic, sleep and functional outcomes.

Devlin JW et al Harvard Rev Psychiatry 2011;19(2):59-67.

DELIRIUM? Stop and THINK

Do any meds need to be stopped, decreaed or changed?

- Is patient on the minimal amount of sedation needed?
- Daily sedation awakening
- Do sedatives need to be changed?
  - E.g. benzodiazepine to dexmedetomidine?

Toxic Situations
- CHF, shock, dehydration
- New organ failure (liver/kidney)

Hypoxemia

Infection/sepsis nosocomial),
Immobilization

Nonpharm interventions
- Hearing aids, glasses, reorient, sleep protocols, music, noise control, ambulation

K+ or electrolyte problems

Slide Courtesy of Brenda Pun, RN

American Psychiatric Association Guidelines (1999)
- "Antipsychotic medications are often the treatment of choice"

(Grade I = recommended with substantial clinical confidence)

SCCM Guidelines (2002)
- "Haloperidol is the preferred agent for the treatment of delirium in critically ill patients." (Grade C recommendation)

UK Delirium Guidelines (2010)

"Low dose and short-term haloperidol or olanzapine therapy if patient remains distressed or agitated that is severe enough to cause arm AFTER identify and manage all possible underlying causes and provide effective communication, reorientation and reassurance" (Grade 2B)

German Guidelines (2010)
- May be role for antipsychotic therapy for treatment
- Consider treatment with alpha-2 agonist (not graded)

SCCM Guidelines (2012)

Trzepacz P et al. *APA .1999* (accessed April 4 2010)
Jacobi J et al. *Crit Care Med*. 2002; 30:119-141.
Nice Quick Reference Guide http//ww.nice.org
Martin J et al. Ger Med Sci 2010
Barr, J et al. Crit Care Med 2012 (under review)

Pharmacological Considerations When Treating Delirium

- Pharmacological therapy should be considered ONLY after underlying causes for delirium are reversed/treated
- Pharmacological therapy should be reserved for patients with severe agitation that will affect patient/caregiver safety
- Wean down any antipsychotic regimen to off if patient no longer agitated
- Make sure there is a plan to discontinue any antipsychotic regiment at ICU/hospital discharge

Inouye SK. *N Engl J Med.* 2006; 354:1157-1165.
Trzepacz PT, et al. *Semin Clin Neuropsych* .2000; 5:132-148.
Dubois MJ, et al. *Intensive Care Med.* 2001; 27:1297-1304.
Skrobik Y, et al. *Crit Care Clinics.* 2009 25:585-587.

Scheduled Antipsychotic Use in the LTACH Setting

80 consecutive mechanically ventilated patients admitted from an acute care ICU to a 240-bed academic LTACH who had neither a major psychiactric disorder or dementia at admission

Scheduled AP use ≥ 24h	**39% (31/80)**
- % started on AP at outside ICU	- 45%
- % of LTAC days scheduled AP administered	- 52%
- Name of AP administered	quetiapine (77%); olanzapine (10%)
% of scheduled AP days the following were administered:	
- 'As needed' AP	14%
- Anxiolytic (100% benzodiazepine)	35%
- Restraints	24%
% of scheduled AP days that key delirium words documented	
- Delirium	1.0%
- Inattention	0.3%
- Confusion	6.8%
- Agitation	4.2%
% of scheduled AP patients ever evaluated by a psychiatrist	35%
- ECG conducted (as a % of the AP days)	0.7% (no values ≥ 500 msec)
- Pts experiencing ≥ 1 extrapyramidal symptom	3.2%
- Pts experiencing ≥ 1 episode of a SBP≤90 mmHg	52%
- Pts experiencing ≥ 1 fall	3.2%
- Pts initiated on scheduled insulin (i.e. not receiving at AP start)	0%

Alqadheeb N….Devlin JW. Submitted to SCCM Congress 2012

Conclusions

- Delirium is common in both critically ill adults and children.
- Pharmacists can play a key role in screening for delirium with either the CAM-ICU or ICDSC.
- Education that is substantial, occurs at the bedside and is repeated on a regular basis should accompany any new delirium screening effort.
- Treat pain and screen for delirium before administering sedation.
- Optimize non-pharmacologic delirium prevention efforts that decrease coma and improve functionality (e.g. DA-SBT, early mobilization).
- Dexmedetomidine may lead to less coma and delirium than benzodiazepine therapy.
- No rigorous evidence to support prophylactic antipsychotic therapy.
- No rigorous evidence that haloperidol improves outcome in any ICU population.
- Antipsychotics should only be used (on a short term basis) for patients having delirium that is accompanied by agitation.
- Pharmacists can play a key role in decreasing the number of ICU and post-ICU patients exposed to antipsychotic therapy.

Rationale and Bedside Application of the *"proposed"* SCCM Guidelines for the Management of Pain, Agitation, Delirium

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Maine Medical Center

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Conflicts of Interest

Your Job for Today

- Understand new data that redefine risks and benefits of drug management options
- Identify barriers to the bedside incorporation of the major changes of the revised PAD guidelines
- Evaluate various strategies for beside implementation of best practice
- Develop a comprehensive plan to provide patient comfort in the ICU

My Job for Today

- Indirectly discuss details of the upcoming SCCM guidelines (currently proprietary)
  - Data supporting these guidelines IS a matter of public record

Step 1….Incorporate Valid and Reliable Assessment Tools

(and know their limitations!)

- Pain
  - Patient self report = NRS
    - Otherwise, BPS and CPOT
      - In patients with motor function
  - Hemodynamic changes are not specific
- Agitation and Sedation
  - RASS, SAS, etc
    - Not useful for deep sedation or with therapeutic paralysis
- Intentionally deep sedation or with pharmacologic paralysis
  - Auditory evoked potential, bispectral index, patient state index, state entropy
    - Only if clinical evaluation is unavailable or when EMG artifact is limited
- Delirium
  - CAM-ICU, ICDSC, etc
    - Scoring may be dependent on status of sedation

Assessing ICU Pain and Discomfort

- Why is this so difficult for caregivers?
  - What is routine to us is hardly routine to the patient
    - Mere presence of an ETT, repositioning, catheters in every orifice, machines, noise, sleep deprivation, inability to communicate, loss of autonomy, drug-induced stupor, confusion, delirium, fear, loss of health, constipation, being tethered and tied down, etc, etc
  - Underappreciation for how poorly we assess pain
    - 82% remember pain and discomfort as traumatic. Schelling CCM 2003
  - Underuse of validated behavioral pain scales
    - CPOT (Critical Care Pain Observation Tool) and BPS (Behavioral Pain Score)
    - Based on facial expression, body movement, and compliance with the vent
  - Underuse of analgesia including pre-emptive use with painful procedures Puntillo. Am J Crit Care 2001

Clinical practice pearl: Patient self-report remains the gold standard and if not possible—*and* motor function is intact--- behavioral pain scales should be utilized. Hemodynamic derangement is not an adequate indicator of pain, but can be used to prompt further evaluation.

Monitoring Agitation and Sedation

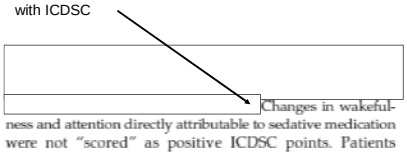
- Several validated scales available
  - RASS, SAS, etc
  - Associated with improved outcomes by identifying aberrant behaviors early
    - **60%** reduction in severe agitation Chanques. CCM 2006
  - Only for patients who are able to respond…once coma or paralyzed, these scales do not provide useful information
    - Computerized processed EEG may be helpful for these patients as long as EMG artifact is appreciated.
      - Auditory evoked potential, bispectral index, patient state index, state entropy

Why Systematically Assess Delirium?

- Any data suggesting that this reduces delirium prevalence?
  - No!
- Any data suggesting that this reduces its severity?
  - No!
- So why bother?
  - Prompts timely identification of clinically relevant reversible causes …infections, etc
  - Prompts scrutiny of drug therapy

Validated Delirium Screening Tools

- CAM-ICU
  - Twice daily evaluations involving patient-nurse interactions
- ICDSC
  - Twice daily evaluations based on nursing observations
- Both based on DSM IV criteria, but sedation influence is less with ICDSC



Assessment of Delirium Relative to Daily Sedative Interruption

JT Poston MD, MW Sjoding MD, AS Pohlman RN MSN, BK Gehlbach MD, JB Hall MD, JP Kress MD
Section of Pulmonary and Critical Care Medicine
University of Chicago

ATSCCM 2010 A6701

55 blinded delirium assessments in 21 MICU patients

CAM results are highly influenced by degree of sedation at the time of delirium assessment

Before sedative interruption: Delirium-Coma free: 1, **Delirious: 40**, Coma: 14
After sedative interruption: Delirium-Coma free: 23, **Delirious: 27**, Coma: 5

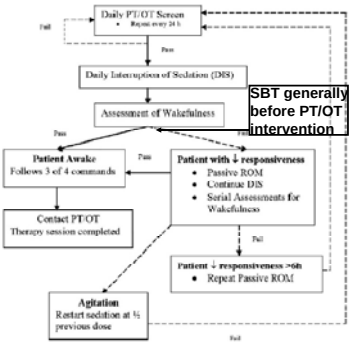
Are all deliria the same?

Is ICU delirium similar to geriatric medical delirium?
Is drug induced delirium similar to delirium from a metabolic or infectious cause?

Practical Points About Assessing PAD

- Optimal time for assessment = when patient is awakened to the point of responding to commands
  - Allows self-report for pain
  - Facilitates patient readiness for extubation and helps to avoid iatrogenic coma
  - Identifies sedative medications as a potential source for delirium
  - Facilitates early mobility efforts

Early Mobility; A Matter of Coordination



Pohlman. CCM 2010

More Practical Aspects of Early Mobilization

- Coordination of efforts
  - Frequent communication between RN, RT, PT/OT re: SAT, SBT, and EM efforts
- Timing may be critical
  - NO SENSE to do this when patients are busy with exams, imaging, and travel
    - If standardized, done in the late morning or afternoon?
- Short acting drugs (fentanyl, propofol, dexmedetomidine) facilitate effort Tanios J Crit Care 2009
- May require expansion of ICU PT/OT resources

Typical Sedation Titration Goal = "Light" Sedation

- But what is light sedation?
- No consensus on this definition
- Overarching goal is to consistently focus on patient safety and comfort
  - If sedation is required, titrate to responsiveness and awareness
  - Wakefulness = ability to respond to commands: open eyes, maintain eye contact, squeeze hand, stick out tongue, wiggle toes

Providing Pharmacologically Based Interventions: Importance of Protocolization

- Helps bring "best practice" to the bedside
- Limits practice variation
- Reduces delays in management
  - Encourages regular assessment of pain, agitation, delirium
  - Facilitates pharmacologic interventions: drug choice, dosing, titration

Surveys of ICU Sedation Practices

Mehta Crit Care Clin 2009

16-88% **20-80%** **1-78%**

Table 3
Reported use of sedation strategies in published surveys

Author	Assessment Tools	Protocol-Directed Sedation	Daily Sedative/Analgesic Interruption
Christensen & Thunedorg, 1999[35]	16% (all Ramsay)	33%	NR
Murdoch & Cohen, 2000[36]	67% (28% Ramsay)	NR	NR
Soliman et al, 2001[37]	43% (74% Ramsay)	NR	NR
Samuelson et al, 2003[38]	16% (Ramsay, Addenbrooke, Newcastle, SAS)	27%	1%
Rhoney & Murry, 2003[39]	78% (43% GCS, 42% Ramsay)	33%	NR
Guldbrand et al, 2004[40]	53% (24% MAAS, 9% Ramsay)	41%	15%
Martin et al, 2005[23]	31% (8% Ramsay)	21%	NR
Arroliga et al, 2005[8]	NR	NR	NR
Kamel et al, 2005[22]	14% (all Ramsay)	20%	NR
Tanios et al, 2005[21]	NR	64%	49%
Mehta et al, 2006[24]	49% (67% Ramsay, 10% SAS, 9% GCS, 8% MAAS)	29%	40%
Egerod et al, 2006[25]	44% (mostly Ramsay)	23%	31%
Martin et al, 2006[26]	46% (mostly Ramsay)	52%	34%
Martin et al, 2007[27]	35% (mostly Ramsay)	38%	16%
Ahmad et al, 2007[28]	28% (48% Ramsay, 16% RASS, 15% SAS)	36%	0%
Payen et al, 2007[29]	88% (66% Ramsay)	80%	78%
Reschreiter et al, 2008[30]	75% (GCS 56%, SAS 25%, 8% RASS)	54% sedation 51% analgesia	62%
O'Connor & Bucknall, 2009[31]	8%	43%	Sedative 20% of days Analgesic 9% of days
Patel et al, 2009[32]	88% (38% Ramsay, 25% RASS)	71%	22% practice drug interruption on 75%-100% of days

Adherence to protocols ~50%

Tamos. J Crit Care 2009

Why Are Protocols Not Used?

- Potential barriers
  - Nursing acceptance, potential for medical device removal, airway compromise, and patient discomfort. Roberts. J Crit Care 2010, Tanios Crit Care Med 2005: A793
  - Lack of a physician order along with difficulties in managing patient issues in real time Tanios. J Crit Care 2009
  - *ICU patients and protocols are too complex*

Facilitating Rapid Knowledge Transfer to the Bedside

- Options
  - Use clinical practice guideline as a model
  - Develop protocols for managing pain/agitation/delirium
  - Develop preprinted or electronic "order sets" based on institution specific protocols
  - Offer real time clinical decision support
  - Create "bundles" for implementing essential components of practice guidelines
    - Consider daily rounding pharmacist or quality checklist with these elements Marshall. Crit Care Med 2008, Dubose J Trauma 2008

Hint: ADAPT then ADOPT previously developed tools

ICU Care Bundles

- Many examples: VAP, sepsis, central line placement, etc
- Elements should
  - Be easy to implement and measure
  - Have proven benefit
  - Be supported by sound scientific and clinical reasoning
  - Be relevant across a wide range of patient populations and health-care systems
- Bundle metrics can be used for caregiver feedback and as part of a rapid-cycle change process improvement effort

Pain, Agitation, Delirium (PAD) Bundle Major Components = *Identify, Manage, Monitor* with Metrics

Make your own "bundle" with elements and metrics

1. Systematically assess and document PAD
   - At least 4x/shift for pain and agitation and 1x/shift for delirium
2. Ensure that measures to prevent and treat PAD are a part of routine ICU care
   - Adhere to institution-specific protocols
   - Provision of analgesia prior to painful procedures
   - Provide management < 0.5 h of discomfort or agitation
   - Achieve sedation goal without coma or dangerous agitation
   - Document strategies to prevent delirium each day
3. Monitor the effectiveness of these strategies
   - % time spent in drug induced coma (SAS 1-2)
   - % patients reporting moderate to severe pain
   - % SBT failed due to excessive sedation or agitation
   - ICU ventilator time (or ventilator-free time)
   - % patients developing delirium during the ICU stay

Translation Into Practice

Assumes that
1) primary causes for pain, agitation, and delirium are addressed
2) non-pharm management options are in place including adjustment of vent settings
3) patient behaviors are troublesome and/or pose a risk

Step 1 → Assess and treat pain

- Routinely assess pain in all ICU patients using self-report if possible (NRS)
- For patients with intact motor function, but unable to self-report, assess pain with BPS or CPOT
- Preemptively treat procedural pain
- Opiates may be preferred especially if an analgesia-first approach is used.

Translation Into Practice

Assumes that
1) primary causes for pain, agitation, and delirium are addressed
2) non-pharm management options are in place including adjustment of vent settings
3) patient behaviors are troublesome and/or pose a risk

Step 2 → Assess delirium and the need for sedation

- Assessment for delirium and agitation/sedation should be routine for all ICU patients
  - Use CAM-ICU or ICDSC assessment tools for delirium
  - Use RASS or SAS assessment tools for sedation
  - Use protocols and checklists to facilitate sedation management

Translation Into Practice

Assumes that
1) primary causes for pain, agitation, and delirium are addressed
2) non-pharm management options are in place including adjustment of vent settings
3) patient behaviors are troublesome and/or pose a risk

Step 3 → Treat delirium and manage sedation

- Early mobilization
- Employ analgesia-first sedation in intubated patients
- Avoid benzodiazepines when delirium is not related to alcohol or benzodiazepine withdrawal
- Target lightest level of sedation possible or use daily sedation interruption

To improve is to change; to be perfect is to change often. **Winston Churchill**

For questions/comments/copy of slides
email: fraseg@mmc.org