Overview of the New Pain, Agitation, and Delirium Guidelines

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

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Supporting Organizations:
American College of Critical Care Medicine (ACCM) under the oversight of the Society of Critical Care Medicine (SCCM) with review of the guidelines by the American Society of Health-System Pharmacists (ASHP)

Barr J et al. *Crit Care Med.* In press.

What's Different about this Version of the PAD Guidelines? *Methods*

- Grade methodology
  - www.gradeworkinggroup.org
- More rigorous, transparent process for developing statements and recommendations
- Strength of recommendation based on BOTH strength of evidence and the relative risks & benefits of interventions
- Expert opinion NOT used as a substitute for making recommendations in the absence of evidence

Barr J et al. *Crit Care Med.* In press.

Level of Evidence	Quality of Evidence	Type of Evidence	Definition
A	High	High Quality Randomized Controlled Trial (RCT)	Further research is unlikely to change our confidence in the estimate of effect.
B	Moderate	RCT with significant limitations (downgraded), or high quality Observational Study (OS) (upgraded).	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C	Low	Observational study	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Adapted from Guyatt GH et al. *BMJ.* 2008; 336:924-6.

Barr J et al. *Crit Care Med.* In press.

Considerations	Effect on Strength of Recommendation
Quality of evidence	Lower quality of evidence reduces the likelihood of a strong recommendation, and vice versa.
Uncertainty about the balance between desirable and undesirable effects	Higher degree of uncertainty about the balance between risks and benefits reduces the likelihood of a strong recommendation, and vice versa.
Uncertainty or variability in values and preferences	Wide variability in values and preferences across groups reduces the likelihood of a strong recommendation, and vice versa.
Uncertainty about whether the intervention represents a wise use of resources	A higher overall cost of treatment reduces the likelihood of a strong recommendation, and vice versa.

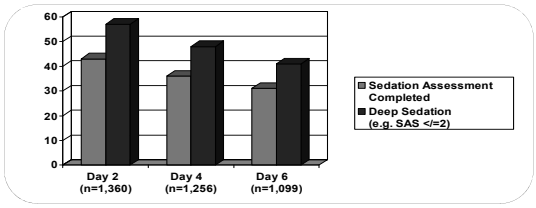
Barr J et al. *Crit Care Med.* In press.

What's Different about this Version of the PAD Guidelines? *Methods*

- Anonymous online voting (E-survey) by all Task Force Members
- Standardized voting thresholds used
  - A recommendation in *favor* of an intervention (or the comparator) required at least 50% voting in *favor*, with ≤20% voting *against*; failure to meet these voting thresholds resulted in *no recommendation* being made.
  - For a recommendation to be graded as *strong* rather than *weak*, at least 70% of those voting had to vote for a *strong* recommendation, otherwise it received a *weak* recommendation.

Barr J et al. *Crit Care Med.* In press.

Oversedation in the ICU is Common

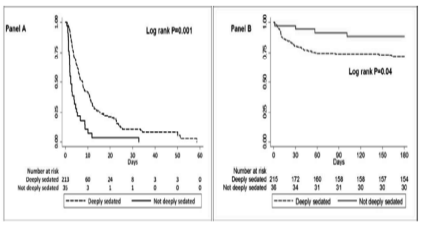


- N=274 MICU patients
- 32% unarousable
- 21% no spontaneous motor activity
- Little variation over 24 hours in LOC, motor activity, or drug dose given
- **Only 2.6% of RNs thought "oversedated"**

Payen JF et al. *Anesthesiology.* 2007; 106:687-95.
Weinert CR et al. *Crit Care Med.* 2007; 35:393-401.

Early Deep Sedation is Associated with Both a Longer Duration of Mechanical Ventilation and Reduced 6-month Survival

Time to Extubation

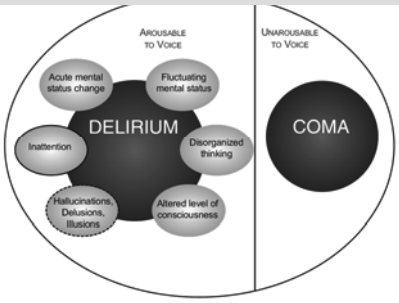


6 month Mortality

Figure 4: Kaplan Meier curves for time to extubation and mortality at 180 day

Shehabi Y et al. *Am J Respir Crit Care Med*. 2012; 186:724-31.

Acute Brain Dysfunction



Morandi A et al. *Intensive Care Med*. 2008; 34:1907-15.

Which of the following has been shown in studies to be an outcome of maintaining mechanically ventilated adult patients at a light (rather than deep) level of sedation?

- A greater incidence of post-traumatic stress disorder.
- A greater incidence of patient-initiated device removal (e.g., self-extubation).
- A shorter duration of mechanical ventilation.

Question: **Should adult ICU patients be maintained at a light level of sedation? (actionable)**

Answer: Maintaining light levels of sedation in adult ICU patients is associated with improved clinical outcomes (e.g., shorter duration of mechanical ventilation and a shorter ICU length of stay) (B). We recommend that sedative medications should be titrated to maintain a light rather than deep level of sedation in adult ICU patients, unless clinically contraindicated (+1B).

Barr J et al. *Crit Care Med.* In press.

Impact of a Combined SAT-SBT Strategy on Patient Outcomes

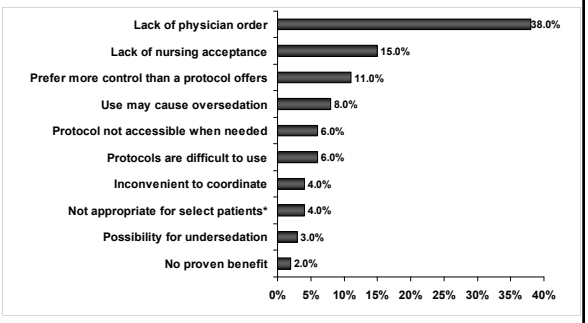
Outcome	SBT	SAT+SBT	P-value
Ventilator-free days	12	15	0.02
Coma, days	3	2	0.002
Time-to-event, days			
Successful extubation	7	5	0.05
ICU discharge	13	9	0.01
Hospital discharge	19	15	0.04

Compliance with SAT and SBT components of protocol in this controlled study was ≥ 90%

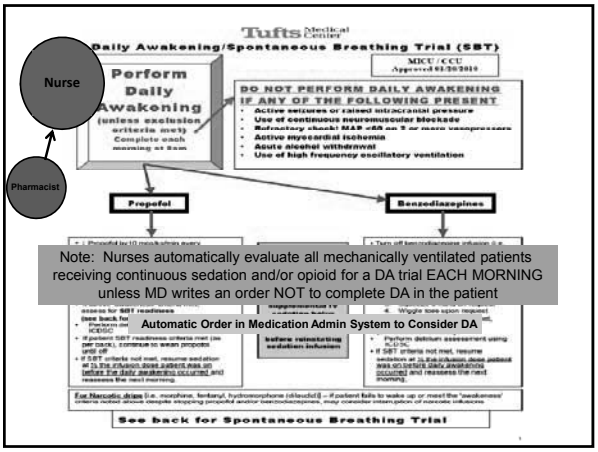
SAT = Spontaneous Awakening Trial
SBT = Spontaneous Breathing Trial

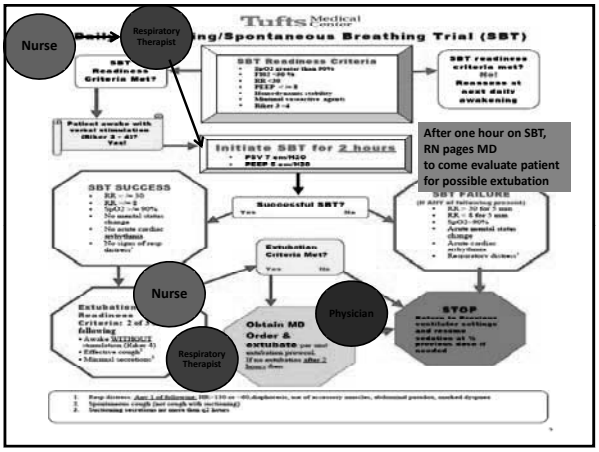
Girard TD et al. *Lancet.* 2008; 371:126-134.

Perceived Barriers to Use of Daily Sedation Interruption: Engaging the Bedside RN is the Key!

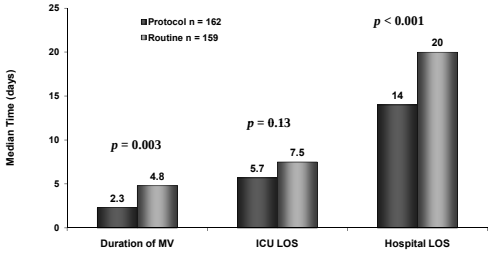


Tanios MA et al. *J Crit Care*. 2009; 24:66-73.





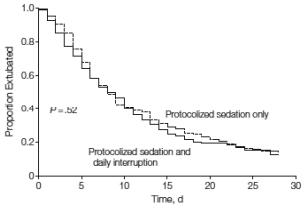
Nursing-Implemented Sedation Protocol: Barnes Jewish Pilot United States



Brook AD et al. *Crit Care Med*. 1999; 27:2609–15.

Hourly Protocol + SAT (DIS)/SBT versus Hourly Protocol + SBT alone

Figure 2. Kaplan-Meier Curves for Time to Successful Extubation



No. at risk						
Protocolized sedation only	209	146	72	49	34	23
Protocolized sedation and daily interruption	214	140	81	42	28	16

P value calculated from log-rank statistic.

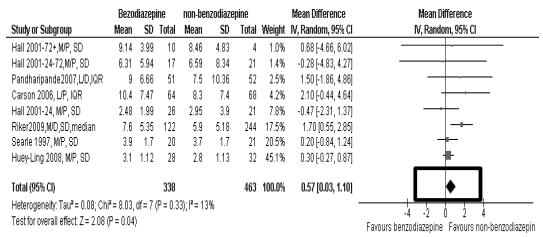
Mehta S et al. *JAMA*. 2012; 308:1985-92.

***Question*: Should a protocol that includes either daily sedative interruption or a light target level of sedation be used in mechanically ventilated adult ICU patients? (actionable)**

***Answer*:** We recommend either daily sedation interruption or a light target level of sedation be routinely used in mechanically ventilated adult ICU patients (+1B).

Barr J et al. *Crit Care Med.* In press.

Duration of Mechanical Ventilation



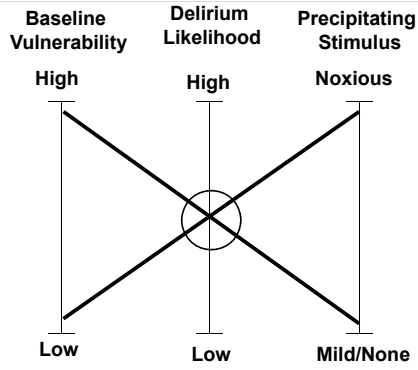
Barr J et al. *Crit Care Med.* In press.

***Question*: Should non-benzodiazepine-based sedation, instead of sedation with benzodiazepines, be used in mechanically ventilated adult ICU patients? (actionable)**

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

Barr J et al. *Crit Care Med.* In press.

Framework for Risk



***Question*: Which instruments available for delirium monitoring have the strongest evidence for validity and reliability in ventilated and non-ventilated medical and surgical ICU patients? (descriptive)**

***Answer*:** The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium monitoring tools in adult ICU patients (A).

Barr J et al. *Crit Care Med.* In press.

Strategies to Boost Delirium Recognition in the ICU

- Sedation assessment (i.e., SAS or RASS) should be occurring regularly and reliably
- Need buy-in from both nurse and physician managers
- Education
  - Both didactic (e.g., classroom/web) and at bedside
    - Both nurses and pharmacists can deliver this education
  - Deliver education to all nurses (i.e., both day and night shift), physicians, and pharmacists
- Ensure that clinicians are comfortable with "not being able to evaluate" components of delirium at certain times
- Documentation of delirium evaluation
- Mandatory discussion of delirium evaluation during daily rounds

SAS=Sedation-Agitation Scale
RASS=Richmond Agitation-Sedation Scale

Devlin JW et al. *Best Pract Res Clin Anaesthesiol*. 2012; 26:385-93.

Early Mobilization

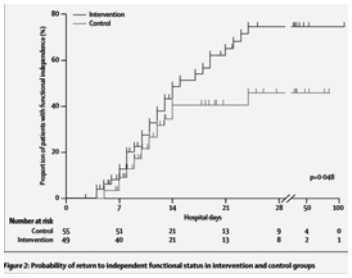


Figure 2: Probability of return to independent functional status in intervention and control groups

Return to independent functional status at d/c
- 59% in intervention group
- 35% in control group (p=0.02)

Schweickert WD et al. *Lancet.* 2009; 373:1874-82.

Early Mobility Study Results

Outcome	Intervention (n=49)	Control (n=50)	P
Functionally independent at 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 discharge	75 (7.5-95)	55 (0-85)	0.05
ICU-acquired paresis at discharge	15 (31%)	27 (49%)	0.09
Ventilator-free days	23.5 (7.4-25.6)	21.1 (0.0-23.8)	0.05
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

Schweickert WD et al. *Lancet.* 2009; 373:1874-82.

***Question*: Should a non-pharmacological delirium protocol in the ICU be used to reduce the incidence or duration of delirium? (actionable)**

***Answer*:** We recommend that early mobilization of adult ICU patients be performed whenever feasible to reduce the incidence and duration of delirium **(+1B).**

Which of the following is MOST true about the role of antipsychotic therapy for either the prevention or treatment of delirium in the ICU?

- Haloperidol is approved by the FDA for the treatment of delirium in the ICU.
- Quetiapine has been shown in one randomized, controlled trial to prevent delirium in the ICU.
- Neither of the above.

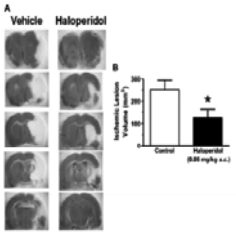
***Question*: Should haloperidol or atypical antipsychotics be used prophylactically to prevent delirium in ICU patients? (actionable)**

***Answer*:** We do not suggest that either haloperidol or atypical antipsychotics be administered to prevent delirium in adult ICU patients (-2C).

Barr J et al. *Crit Care Med.* In press.

Haloperidol: A Sigma-1 Receptor Antagonist

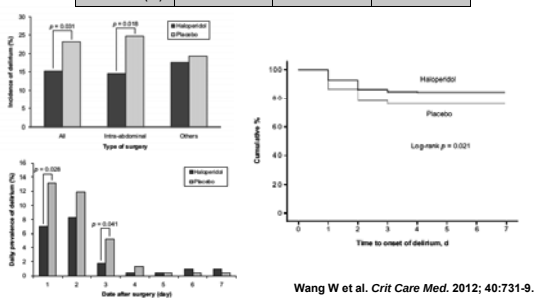
- The Sigma-1 ligand PPBP protects the brain from ischemia
- Haloperidol is a Sigma-1 receptor antagonist
- Low dose haloperidol (0.05 mg/kg) when administered after an induced transient cerebral artery occlusion in rats decreased ischemic lesion volume by 50%



- Assuming that delirium is mediated by a diffuse, low-level ischemia, associated with critical illness, this Sigma-1 receptor antagonism may be an important mechanism by which haloperidol may prevent delirium in the critically ill.

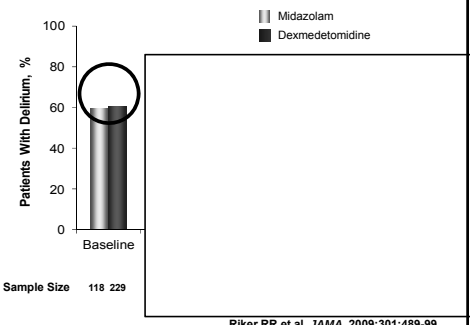
Schetz JA et al. *Brain Res.* 2007; 1181:1-9.

	Haloperidol (n=229)	Placebo (n=228)	P value
Age	74.0 ± 5.8	74.4 ± 7.0	0.50
APACHE-2	8.7± 3.0	8.6 ± 2.8	0.58
Intubated (%)	78.6	77.6	0.80



Wang W et al. *Crit Care Med.* 2012; 40:731-9.

SEDCOM Trial: Delirium Resolution



Riker RR et al. *JAMA.* 2009;301:489-99..

Dexmedetomidine vs. Morphine: DEXCOM

Outcome Variables	Dexmedetomidine (*n* = 152)	Morphine (*n* = 147)	*P* Value
Delirium outcomes			
Patients with delirium, n(%)	13 (8.6)	22 (15.0)	0.088
Delirium days, median (IQR)	2 [1-7]	5 [2-12]	0.031
Patients with IABP and delirium, n (%)	3/20 (15)	9/25 (36)	0.001

IABP = intraaortic balloon pump

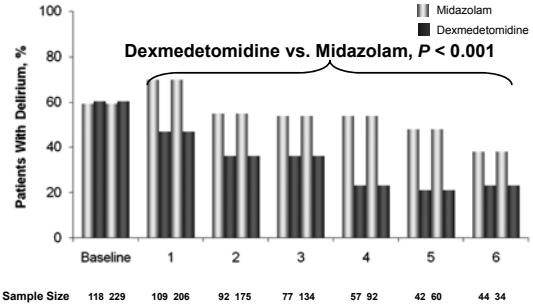
Shehabi Y et al. *Anesthesiology.* 2009:111:1075-84.

***Question*: Should dexmedetomidine be used prophylactically to prevent delirium in ICU patients? (actionable)**

***Answer*:** 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 (0,C).

Barr J et al. *Crit Care Med.* In press.

SEDCOM Trial: Prevalence of Delirium



Riker RR et al. *JAMA.* 2009;301:489-99.

***Question*: For mechanically ventilated, adult ICU patients with delirium who require continuous IV infusions of sedative medications, is dexmedetomidine preferred over benzodiazepines to reduce the duration of delirium? (actionable)**

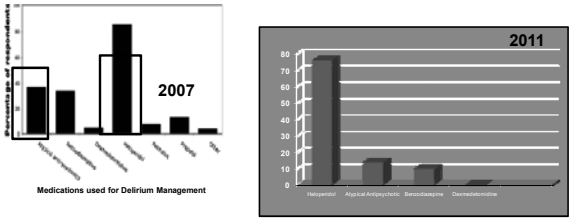
***Answer*:** We suggest that in adult ICU patients with delirium which is not related to either alcohol or benzodiazepine withdrawal, continuous intravenous infusions of dexmedetomidine rather than benzodiazepine infusions be administered for sedation in order to reduce the duration of delirium in these patients (+2B).

Barr J et al. *Crit Care Med.* In press.

Use of Antipsychotic Therapy to Treat Delirium Remains High in American ICUs

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

2002 Drug	No.	%
Antipsychotics	634	70
Haloperidol	603	66
Atypical antipsychotics	34	4



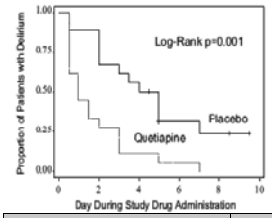
Ely EW et al. *Crit Care Med.* 2004;32:106-12.
Patel RP et al. *Crit Care Med.* 2009; 37:825-32.
Devlin JW et al. *Ann Pharmacother.* 2011;45:1217-29.

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

- n=36 (18 quetiapine, 18 placebo) with delirium based on ICDSC assessment
- QUETIAPINE 50mg PO/tube bid (max 200mg bid) vs. PLACEBO
  - PRN IV haloperidol could be used to treat agitation in either group
- Baseline characteristics between groups were similar
- Primary Outcome
  - Time to first resolution of delirium was significantly less with quetiapine 1 day vs 4.5 days (p=0.001)

Devlin JW et al. *Crit Care Med.* 2010; 38:419-27.



Safety

- **Somnolence (n= 5 episodes)**
- **Hypotension (n=1 episode)**
- **No episodes of EPS**
- **The number of subjects with QTc prolongation was similar between the quetiapine and placebo groups.**

	Quetiapine (n=18)	Placebo (n=18)	P-value
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	

Devlin JW et al. *Crit Care Med.* 2010;38:419-27.

***Question*: Does treatment with haloperidol reduce the duration of delirium in adult ICU patients? (descriptive)**

***Answer*:** There is no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients (No Evidence).

***Question*: Does treatment with atypical antipsychotics reduce the duration of delirium in adult ICU patients? (descriptive)**

***Answer*:** Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C).

Barr J et al. *Crit Care Med.* In press.

Role of the Pharmacist in Implementing the New Pain, Agitation, and Delirium Guidelines

Gilles L. Fraser, Pharm.D., FCCM
Professor, School of Medicine, Tufts University
Director, PGY2 Critical Care Residency, Maine Medical Center
Outcomes Team Leader, SCCM PAD Guidelines

Learning Objectives
The Pharmacist Will

- Accept a leadership role to create an ICU that is a more humane environment to heal and to die
- Evaluate AND understand the rationale for PAD management recommendations
- Successfully adapt the guidelines to local clinical resources and goals
- Organize a multifaceted interdisciplinary approach to implement adaptation of these guidelines

What We've Learned: Goals for Our ICU Patients

- THEN: Survival and discharge
- NOW: Don't fix patients and break them at the same time
  - Complications extend beyond hospital discharge
    - Delirium
    - Long-term cognitive impairment
    - PTSD

Gestational Period

- Mouse = 20 days
- Human = 9 months
- Elephant = 22 months
- PAD guidelines = 80 months

2006-13 SCCM Guidelines for the Management of Pain, Agitation, and Delirium

Sedation	Analgesia	Delirium	Outcomes
J Barr, Chair	K Puntillo, Lead	W Ely, Lead	G Fraser, Lead
D Fontaine	D Coursin	B Pun	J Dasta
M Ramsay	C Gelinas	C Sessler	J Davidson
R Riker	D Herr	Y Skrobik	J Devlin
B Robinson	A Joffe		JP Kress
A Tung			

2013 PAD Guidelines

- Focus is on the patient, these are NOT sedation guidelines
- 12 pharmacologic recommendations
- Surprises
  - No recommendation on haloperidol
  - Either daily sedation interruption OR careful titration
  - Benzo's as potential risk for delirium
  - Dexmedetomidine

Yes/No Poll

- Our ICU uses
  - A sedation protocol
  - A behavioral pain scale
  - A delirium screening tool

Yes No

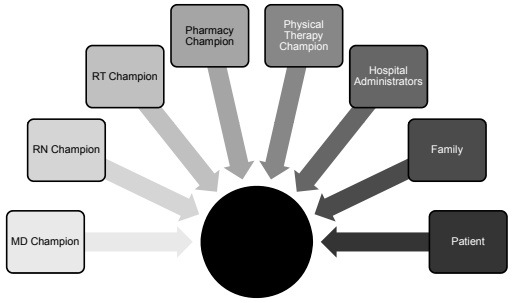
Perceived vs. Actual Practice

- Survey 85 ICUs = 24-h practice snapshot
- Sedation protocols used in 50% ICUs
- Sedation interruption reported in 66% ICUs
  - *Performed in 36% patients*
- Delirium monitoring reported in 25% ICUs
  - *Performed in 10% of patients*

Gill KV et al. *Ann Pharmacother.* 2012; 46:1331-9.

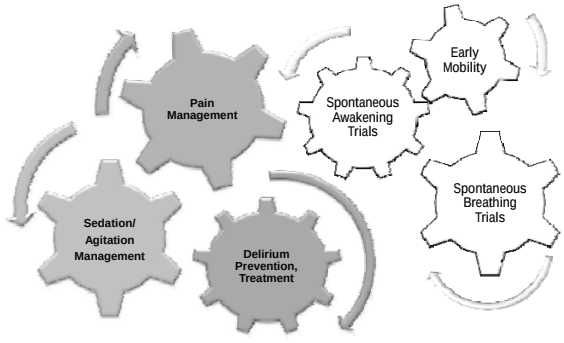
Ever Feel Like You Are Going in Circles?

PAD Interdisciplinary Team



Courtesy J Barr, MD

Integrated PAD Management



Courtesy J Barr, MD

Changing Practice Behaviors

- Multifaceted approach IS necessary
  - Champions
    - All disciplines should be represented
  - Education
    - A first step to inform and demonstrate relevance
  - Protocols
    - Efficient way to make it easy to do the right thing
  - Point of use reminders
    - For those who need a little help remembering nuances
  - Feedback loops
    - For those needing "encouragement" to do the right thing

Why is This So Important?

- Benefits of implementing guidelines
  - –Reduced time on the ventilator and in the ICU
  - –Lower rates of ICU complications
  - –Improved quality of life after discharge
  - –Less delirium and cognitive impairment

Facilitating Knowledge Transfer to the Bedside

- –Use clinical practice guideline as a model
- –Develop protocols for managing PAD
- –Develop "order sets" based on institution specific protocols
- –Create "bundles" for implementing essential components of practice guidelines
  - Consider daily rounding pharmacist or quality checklist with these elements

Marshall J et al. *Crit Care Med.* 2008; 36:427-33.
DuBose JJ et al. *J Trauma*. 2008; 64:22-7.

- –Offer real time clinical decision support

NOT to WORRY! We've got a plan!

Importance of Protocolization

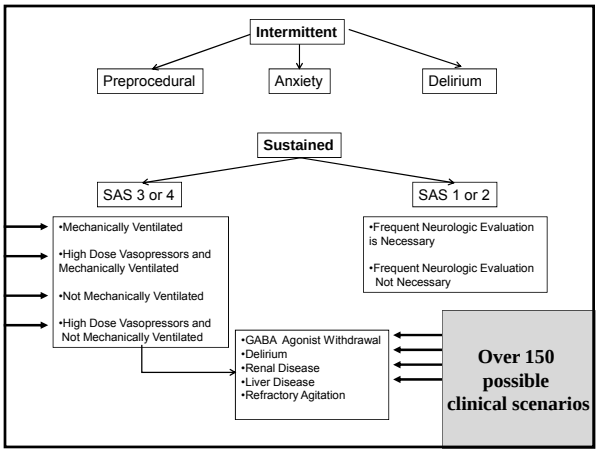
- Brings "best practice" to the bedside
- Limits practice variation
- Reduces delays in management
  - –Encourages regular assessment of pain, agitation, delirium
  - –Facilitates pharmacologic interventions: drug choice, dosing, titration

Why are Protocols Not Used?

- Potential barriers
  - –Nursing acceptance
  - –Potential for medical device removal, airway compromise, and patient discomfort

Roberts RJ et al. *J Crit Care*. 2010; 25:660.e1-7.
Tanios MA. *Crit Care Med.* 2005: A793.

- –Lack of physician buy in Tanios MA et al. *J Crit Care.* 2009; 24:66-73.
- –*ICU patients and protocols are too complex*



Complex to Simple: ICU Care Bundles

- Examples: sepsis, central line placement, and now PAD!
- 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
- Metrics allow caregiver feedback and serve as part of a rapid-cycle change process improvement effort

ICU PAD Bundle Web-based Toolkit

- Educational Tools
  - PowerPoint presentations
    - PAD guideline staff education
    - PAD implementation strategies
  - Instructional videos
    - Use of pain, sedation, delirium assessment tools
    - Early mobility techniques
- Implementation Tools
  - Pocket cards
    - ICU PAD Care bundle
    - PAD guideline recommendations
  - Apps for smart phone, tablets
    - Monitoring tools
    - Drug dosing guidelines
  - Templates
    - Check lists
    - Goals sheets
  - Sample protocols
- Performance Improvement Metrics

Courtesy J Barr, MD

EXAMPLE

SCCM PAD Guidelines

Two-sided "pocket"card

Available when guidelines are published

SCCM PAD Bundle

Identify, Manage, Monitor

Available when guidelines are published

EXAMPLE: Pain Bundle

Stepwise process

Incorporate valid pain monitoring tools
Address analgesia adequacy daily

Implement protocols to prevent and manage pain

Monitor adherence and effectiveness of these protocols

Track performance to understand barriers and identify strategies for improvement

Some Things Are Easy

- Job #1 = Patient comfort, patient and caregiver safety, maintenance of oxygenation and perfusion
- Don't complicate things
  - Avoid deliriogenic drugs
  - Avoid propofol in pancreatitis
  - Avoid morphine in renal disease, etc.
  - Avoid propofol and dexmedetomidine with high dose vasoactive therapy
- Initiate home medications IF and when appropriate

Cure sometimes

Comfort always

Armstrong & Crisp (Turkel)
New Horizons 1994:2:85