

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

AGITATION AND DELIRIUM MANAGEMENT IN THE ICU

SUMMARY

Sedation is an essential component of care for critically ill patients necessitating appropriate selection and monitoring of drug therapy. Each sedative agent possesses specific risks, benefits, and economic cost which must be all considered in choosing an appropriate therapy. Midazolam and propofol are appropriate where short-term sedation is necessary while lorazepam and diazepam are appropriate for long-term sedation. Due to its cost and risk profile, propofol should be reserved for patients in whom conventional sedation has failed, rapid assessment of neurologic function is necessary, or intracranial hypertension is present.

Delirium is an important form of organ dysfunction. Clinical practice guidelines for critically ill adults recommend routine assessment for the presence of delirium. Although the Confusion Assessment Method (CAM) has been advocated, its use is not practical in all critically ill populations. Several pharmacologic agents have been described and/or evaluated for the management of delirium. The most extensive experience has been with haloperidol which is an effective agent in this patient population.

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **Sedatives should be titrated to a Riker Sedation-Agitation Scale (SAS) score of 3 to 4.**
 - **Lorazepam is the drug of choice for non-ventilated patients.**
 - **Midazolam is the drug of choice for short-term anxiolysis in ventilated patients (anticipated time on ventilator <24 hours). Intermittent administration is preferred. Continuous infusion should only be used after intermittent dosing and/or addition of haloperidol fails.**
 - **Lorazepam is the anxiolytic of choice for patients anticipated to be ventilated for 24 hours to 5 days. Continuous infusion is generally not necessary.**
 - **Propofol should be reserved for the following populations:**
 - **Failure of conventional sedation**
 - **Need for rapid neurologic assessment**
 - **Presence of intracranial hypertension**
- **Level 3**
 - **Diazepam is the drug of choice for long-term anxiolysis (anticipated time on ventilator greater than 5 days). Lorazepam may be used for breakthrough agitation.**
 - **Critical care practitioners should be aware of and assess for the clinical manifestations of delirium.**
 - **Currently available delirium assessment tools are not practical for use in the surgical critical care population.**

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

Sedation is an essential component of care for the critically ill patient. An ideal regimen should control pain, anxiety, agitation, and delirium while minimizing adverse effects. Practices of ICU sedation vary widely. Monitoring tools frequently include subjective assessments by caregivers or sedation scales that are not validated. Inappropriate therapy may result in adverse drug reactions, prolonged mechanical ventilation, extended ICU stays, and increased costs.

Selection of drug therapy is based on identification and differentiation of pain, anxiety, agitation, and delirium. Anxiety is a psychophysiologic response to real or imagined danger, while agitation refers to excitement accompanied by motor restlessness. Benzodiazepines and propofol have been extensively studied in critically ill patients. Benzodiazepines are considered first-line agents for the management of anxiety and agitation. Midazolam has a short half-life (2-3 hours) and undergoes hepatic metabolism to an active metabolite. Substantial accumulation may occur with high doses or prolonged infusions. Lorazepam has an intermediate half-life (10-20 hours) and is glucuronidated in the liver. Significant accumulation does not occur. Diazepam has a long half-life (20-80 hours) and is further hepatically metabolized to several active metabolites. Propofol is classified as a short acting sedative-hypnotic agent and is useful in the management of refractory intracranial hypertension. Its use has been associated with hypotension, metabolic acidosis, rhabdomyolysis, methemoglobinemia, and potentially life-threatening bradyarrhythmias (see propofol guidelines).

Delirium is considered to be a global manifestation of brain dysfunction. It is characterized by an acute change or fluctuation in mental status, inattention, disorganized thinking and an altered level of consciousness that may or may not be accompanied by agitation. Hyperactive delirium is easily recognized by agitation, combative behavior, lack of orientation and progressive confusion after sedative therapy. Hypoactive delirium, on the other hand, is characterized by a calm appearance, inattention and decreased mobility. A flat affect or apathy may be present in otherwise calm and alert patients. Hypoactive delirium has a worse prognosis than hyperactive delirium and is the most commonly missed subtype.

Delirium is exacerbated in critically ill patients when they are exposed to a stressful environment for prolonged periods of time. Risk factors include preexisting cognitive impairment, advanced age, use of psychoactive drugs, mechanical ventilation, untreated pain and sleep deprivation. Clinical practice guidelines for critically ill adults recommend routine assessment for the presence of delirium as well as pharmacologic management strategies with neuroleptic agents (1). Neuroleptic agents are thought to stabilize cerebral function by antagonizing dopamine-mediated neurotransmission at the cerebral synapses and basal ganglia. Although no neuroleptic agent is FDA-approved for the treatment of delirium, haloperidol is considered to be the preferred agent in critically ill patients. Newer atypical antipsychotic agents have also been suggested due to the potential for decreased adverse effects.

LITERATURE REVIEW

Agitation

Despite the widespread use of sedatives, there are few well-designed trials addressing optimal drug therapy. Most existing studies did not use a validated sedation scale. Many were not blinded and confounding variables (analgesic use and neuromuscular blockade) were not controlled. Endpoints were variable and the "ideal" level of sedation was not consistent among studies.

Riker and colleagues performed a study to test the Riker Sedation-Agitation Scale (SAS) for reliability and validity in adult ICU patients (2). The SAS includes seven levels of agitation, ranging from dangerous agitation to unarousable. Paired evaluators (experienced ICU nurses) simultaneously and independently scored patients using the SAS, Ramsey, and Harris scales. Reliability was confirmed for all scales by the high interrater proportion of agreement (0.95). Validity was established based on a high correlation with the Ramsey and Harris scales.

Ostermann and colleagues conducted a systematic review in ventilated ICU patients to determine which sedatives were associated with optimal sedation, shortest time to extubation, and shortest length of ICU stay (3). Studies assessing short term sedation were analyzed separately from those assessing long term sedation. Nine trials evaluating short-term sedation (less than 24 hours) in surgical or mixed ICU patients were identified. Six compared midazolam with propofol. Propofol provided a better quality of sedation in three trials, while the remainder reported no difference. Only three trials evaluated time to extubation and reported propofol to be superior. Length of ICU stay was not addressed. Of the studies assessing long-term sedation (greater than 24 hours), seven compared midazolam with propofol and one compared midazolam with lorazepam. Quality of sedation for both midazolam and propofol was comparable. Time to extubation was shorter with propofol, although this was not statistically significant in all trials. A single study reported no difference in length of stay between midazolam and propofol. No difference in quality of sedation was found in the trial comparing midazolam with lorazepam.

Further references regarding the use of sedative agents in the ICU can be found in the American College of Critical Care Medicine / Society of Critical Care Medicine practice parameters for ICU sedation (1).

Delirium

A survey was conducted to assess the opinions of healthcare professionals regarding the incidence, prevalence, clinical relevance, proper screening for, and treatment of delirium (4). Respondents included physicians (n=753), nurses (n=113), pharmacists (n=13), physician assistants (n=12), respiratory care practitioners (n=8) and others (n=13). Sixty percent of healthcare professionals thought that >25% of their patients experienced delirium. The top three risk factors were believed to be baseline dementia, the administration of sedative and/or analgesic drugs and age. Delirium was recognized as an under diagnosed syndrome by 78% of respondents, yet only 32% thought that routine monitoring was supported by the current literature and only 40% performed routine screening. Delirium was considered a significant problem in the ICU by 92% of health care professionals. Haloperidol was used by 66% of respondents. Use of benzodiazepines, clozapine, olanzapine, quetiapine, and risperidone was also reported. More than half of the respondents reported giving ≤ 10 mg/day of haloperidol. The highest dose reported in a 24-hour period was 1200 mg (median, 30 mg/24 hours). The most common adverse reactions believed to be associated with haloperidol use were oversedation, neuroleptic malignant syndrome, extrapyramidal symptoms and QT interval prolongation. (Class III)

Ely and colleagues evaluated the effects of delirium in mechanically ventilated ICU patients (medical or coronary) on 6-month mortality and length of stay (5). Delirium was assessed using the CAM-ICU tool. Neurologic status was determined daily and categorized as normal, delirious, or comatose. Level of arousal was determined using the Richmond Agitation-Sedation Scale (RASS). Two hundred twenty four patients were included in the analysis. The cohort was divided into two groups depending on whether or not they developed delirium in the ICU. Eighty-two percent of patients developed delirium in the ICU for a median of 2 days. Overall, 22% of ICU days were spent as normal, 43% as delirious and 35% as comatose. Lorazepam administration was significantly higher in the delirium group. Thirty-four percent of patients in the delirium group died versus 15% of patients in the no delirium group ($p=0.03$). Each additional day in the ICU was associated with a 10% increased risk of death. Compared with the no delirium group, those who developed delirium spent a median of 10 days longer in the hospital overall. There were significantly fewer days free of mechanical ventilation among patients in the delirium group. The use of neuroleptic agents was not addressed. (Class II)

Skrobik and colleagues evaluated the safety and efficacy of olanzapine for the management of delirium in a prospective, randomized, controlled trial (6). Medical-surgical ICU patients (n=73) were randomized to receive either enteral haloperidol (2.5-5 mg every 8 hours) or olanzapine (5 mg daily). Intravenous haloperidol was permitted as rescue therapy. Patients in the haloperidol group received a mean enteral daily dose of 6.5 mg (range 1-28 mg). The percentage of patients receiving rescue haloperidol, as well as the amount of rescue medication, did not differ significantly between groups. The delirium index scores decreased in both groups over time and did not differ significantly between groups. Most patients received continuous infusions of fentanyl and there was no difference in benzodiazepine administration between groups. No adverse effects attributable to olanzapine were noted. (Class I)

Confusion Assessment Method for the Diagnosis of Delirium in the ICU (CAM-ICU) (1)

FEATURE	ASSESSMENT VARIABLES
1. Acute onset of mental status changes or fluctuating course	<ul style="list-style-type: none"> • Is there evidence of an acute change in mental status from baseline? • Did the (abnormal) behavior fluctuate during the past 24 hours, i.e., tend to come and go or increase and decrease in severity? • Did the SAS or GCS fluctuate in the past 24 hours?
2. Inattention	<ul style="list-style-type: none"> • Did the patient have difficulty focusing attention? • Is there a reduced ability to maintain and shift attention? • How does the patient score on the Attention Screening Examination?
3. Disorganized thinking	<ul style="list-style-type: none"> • <i>Extubated Patients</i> <ul style="list-style-type: none"> ○ Is thinking disorganized or incoherent (rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject)? • <i>Mechanically Ventilated Patients</i> <ul style="list-style-type: none"> ○ Can the patient answer the following 4 questions correctly? <ul style="list-style-type: none"> ▪ Will a stone float on water? ▪ Are there fish in the sea? ▪ Does 1 pound weigh more than 2 pounds? ▪ Can you use a hammer to pound a nail? ○ Can the patient follow commands? <ul style="list-style-type: none"> ▪ "Are you having any unclear thinking?" ▪ "Hold up this many fingers." ▪ "Now do the same thing with the other hand."
4. Altered level of consciousness [any level of consciousness other than alert (i.e., vigilant, lethargic, stupor, or coma)]	<ul style="list-style-type: none"> • <i>Alert</i> <ul style="list-style-type: none"> ○ Normal, fully aware of environment, interacts appropriately • <i>Vigilant</i> <ul style="list-style-type: none"> ○ Hyperalert • <i>Lethargic</i> <ul style="list-style-type: none"> ○ Drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally • <i>Stupor</i> <ul style="list-style-type: none"> ○ Difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as stimuli ceases lapses back into the unresponsive state • <i>Coma</i> <ul style="list-style-type: none"> ○ Unarousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the interviewer

Patients are diagnosed with delirium if they have both features 1 and 2 and either feature 3 or 4.

REFERENCES

1. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30:119-141.
2. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the sedation-agitation scale for adult critically ill patients. *Crit Care Med* 1999;27:1325-9.
3. Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. *JAMA* 2000;283:1451-9.
4. Ely EW, Stephens RK, Jackson JC, et al. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: A survey of 912 healthcare professionals. *Crit Care Med* 2004; 32:106-112.
5. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *Crit Care Med* 2004; 29:1753-1762.
6. Skrobik YK, Bergeron N, Dumont M, et al. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med* 2004; 30:444-449.