

EVALUATION AND MANAGEMENT OF THE ANXIETY-AGITATION-DELIRIUM CONTINUUM

ANXIETY

In the absence of adequate control of anxiety and agitation, achievement of other objectives and therapeutic endpoints is greatly impaired. Anxious or agitated patients are more likely to remove feeding tubes, bladder catheters, and endotracheal tubes, resulting in loss of nutritional support, trauma, and potential airway complications. However, unresponsive, comatose patients are often the end result of “overshooting” sedation and this is equally detrimental. As such, the delicate balance of sedation and agitation is often difficult to achieve (even among the most experienced physicians) and even more difficult to teach to those in training.

Assessment Scales for Monitoring the Sedation-Agitation Continuum

In the absence of rational and agreed upon target levels, different members of the patient’s healthcare team will demonstrate quite disparate treatment goals, increasing the risk of complications and decreasing recovery potential. Scales such as the Riker Sedation-Agitation Scale (SAS) and Ramsay Scale have been developed to address this problem and are in wide use in many ICUs and hospitals. However, the Richmond Agitation-Sedation Scale (RASS) is the only scale demonstrated to be a valid and reliable tool for measuring the sedation-agitation levels over the patient’s hospital course. The RASS utilizes the duration of eye contact following verbal stimulation as the primary method of assessment and means of titrating sedation. Similar to the Glasgow Coma

Scale, the RASS separates verbal and physical stimulation to allow for better grading of arousal levels. It is for these reasons that our institution universally utilizes the RASS in all trauma and surgical patients.

Richmond Agitation-Sedation Scale (RASS)

+4	Combative	Combative, violent, immediate danger to staff
+3	Very Agitated	Pulls or removes tube (s) or catheter (s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive, but movements are not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening and contact >10 seconds)
-2	Light Sedation	Briefly awakens to voice (eye opening and contact <10 seconds)
-3	Moderate Sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep Sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Daily Awakening and Interruption of Sedation

Continuous sedative infusions result in delayed awakening that appears to increase ICU stays through prolonging time on mechanical ventilation. Several studies have noted a reduction in ICU length of stay and mechanical ventilator days with daily interruption of sedation. Daily awakening trials involve the interruption of sedating medications until the patient is awake and responsive to commands or until the patient becomes agitated. Not surprisingly, such trials have been met with resistance as some physicians question the

feasibility of performing daily “awakening trials” in their ICUs and because of concerns of long-term psychological effects. However, such these trials have actually been associated with a lower risk for post-traumatic stress disorder.

Achieving Sedation and Treating Anxiety

Benzodiazepines

Benzodiazepines may be used to provide brief procedural sedation, anxiolysis, or a continuous sedated state. Though they lack any actual analgesic effect, their impact on reducing opioid requirements by attenuating anticipatory pain is well documented. In addition, some drugs in this class (most notably midazolam) carry potent antegrade amnestic effects. Elderly and those with hepatic or renal insufficiency are most likely to experience adverse events from these agents. Respiratory depression, slurred speech, nystagmus, and obtundation are but a few side effects of this class. Additionally, these agents may contribute to delirium, particularly in the elderly population and consideration of their use must be balanced by the potential to lead to prolonged delirium in this populations.

The most common agents used for sedation are midazolam and lorazepam. Lorazepam has a longer half life and can be given by both intermittent and continuous administration to achieve continuous sedation while midazolam’s short half life usually mandates continuous infusion to achieve continuous sedation. Midazolam has a significant propensity for tachyphylaxis requiring escalating dosages.

Intermittent administration: In patients with baseline anxiety or persistent benzodiazepine requirements, use of intermittent (but scheduled) enteral diazepam or lorazepam is preferred. An as needed approach is preferable in the hospitalized patient requiring occasional dosing for illness related stress and anxiety.

Continuous infusions: In patients requiring frequent repeat dosing, utilization of a continuous infusion may be preferred and offer smoother titration and maintenance of RASS targets. Midazolam should be used for continuous infusion as it has a fairly rapid onset and much shorter half-life than other benzodiazepines. However, its active metabolites may result in prolonged sedation in those with renal insufficiency.

Propofol

Propofol is an intravenous general anesthetic agent whose sedation properties can be achieved at lower doses. The rapid onset and short duration of action make this drug a preferred agent in many clinical settings, including those requiring frequent neurological assessments. It may be used as a continuous infusion, with initial achievement obtained through bolus administration. Propofol provides similar depth and quality of sedation to midazolam but demonstrates quicker extubation and recovery times. Adverse events are primarily related to duration of therapy (pancreatitis, hypertriglyceridemia, lactic acidosis); therefore, propofol use should be limited to 48 hours or less. Additionally, propofol has no analgesic properties and should be administered in conjunction with opiates.

Alpha-2 agonists

Selective alpha-2 adrenergic receptor agonists exhibit sedative, analgesic, and anxiolytic effects. These agents maintain adequate sedation with less risk for producing hemodynamic instability or respiratory depression. Dexmedetomidine has the added benefit of analgesia (with less opiate requirements) and lacks the respiratory depression seen with propofol. When employed in settings where other agents have been unsuccessful (but the patient is successfully controlled with dexmedetomidine), we transition these patients to clonidine. In our experience, enteral (0.1-0.3mg TID) and/or transdermal clonidine (0.1-0.3 mg patch) helps maintain light sedation and agitation control in those responsive to dexmedetomidine. Adverse events associated with its use include hypotension, hypertension, severe bradycardia, and other arrhythmias.

Sedative agents for intermittent and continuous administration

	<i>Initial dosing</i>	<i>Half-life</i>	<i>Renal dosing</i>	<i>Hepatic dosing</i>	<i>Adverse events/comments</i>
Diazepam	2-5 mg I.V. q 4-6 hr	20-80 hr	No adjustment	Use with caution with hepatic impairment	Active metabolites that may produce quite prolonged sedation.
Lorazepam	0.5 mg-1.0 mg I.V. q 4-8 hr	6-8 hr	Avoid with renal failure	Avoid with hepatic failure	No active metabolites
Midazolam	1.0 mg/hr I.V., titrate for desired RASS	2-3 hr	Decrease dose by 50% with CrCL <10	Use with caution in hepatic failure	Hypotension, significant respiratory depression
Dexmedetomidine	0.2 mcg/kg/hr I.V., titrate for desired RASS	1.5-2 hr	Decrease dose with CrCL <50	Decrease dose with any Child-Pugh class	May load with 1.0 mcg/kg I.V., but beware hypotension, bradycardia; do not exceed 24 hour infusion
Propofol	5 mcg/kg/min, titrate by 5-10 mcg/kg/min for desired RASS	3-12 hr	None	None	"Infusion syndrome" seen with doses > 80 mcg/kg/min; hypotension, apnea; fatty tissue distribution may prolong effect

AGITATION

Agitation, a heightened state of arousal and non-purposeful motor activity, represents the extreme of the arousal continuum. Its onset is usually quite abrupt, almost universally disruptive to patient care, and frightening to the patient and their family members.

Immediate Evaluation of Agitation

A rapid assessment should begin with ruling out any life-threatening situations. Many of these conditions (tension pneumothorax, occluded endotracheal tubes) can present with severe agitation and mental status changes and should be excluded first. Simultaneously, the patient should be protected from harming themselves through falls, self-extubation, and tube removal. Identifying and correcting less life-threatening issues should follow; ruling out ventilator dyssynchrony, bladder catheter occlusion, un-addressed pain, or pending bowel incontinence (especially in patients unable to communicate). Once such diagnoses have been excluded, appropriate management of agitation can proceed.

Pharmacological Management of Agitation

Haloperidol

Haloperidol is often utilized for the rapid control of the acutely and severely agitated patient. Initial dosing of 5 mg intravenously should be used and may be repeated every 10-15 minutes (usually with increasing dosages) until adequate control is achieved. If intravenous access is lost or unobtainable, intramuscular use is also successful but likely to take longer to achieve results. Its side effect profile, however, has historically limited

the enthusiasm for its use. Concomitant use of benzodiazepines or benztropine decreases extra-pyramidal symptoms (EPS) in the acutely agitated patient.

Atypical anti-psychotics

Atypical anti-psychotics have gained increased attention for use as alternative agents for management of acute agitation. In lower doses than that required for acute psychoses management, risperidone, ziprasidone, and olanzapine have been shown to be appropriate alternatives for treatment of acute agitation. Their safety profiles include lower incidence of EPS and better patient tolerance. As well, once agitation is under control, these agents can be changed to the enteral route for continued use until agitation has resolved.

However, these agents carry equal, if not higher, risk of arrhythmias. As such, they have failed to demonstrate a superior safety profile to haloperidol in managing the acutely agitated patient.

DELIRIUM

Prevalence and Impact on Outcomes

Delirium is a global disturbance of consciousness characterized by fluctuating mental status, inattention, and disorganized thinking. Delirium has been historically dismissed as an expected complication of the hospitalized elderly patient, and its impact on outcomes thought to be negligible. However, recent studies have shown that delirium is significantly under-diagnosed, not limited to the elderly patient, and is associated with a 3-fold higher mortality. Additionally, patients with delirium have higher hospital costs and experience significant cognitive impairment long after discharge. We have recently

demonstrated that delirium occurs in 80% of mechanically ventilated medical ICU patients and over 75% of mechanically ventilated patients in surgical ICUs. Surprisingly, we noted that the trauma ICU population, which is much younger than that of either medical or surgical ICU patients and less likely to have co-morbidities, has an almost 70% prevalence of delirium.

Assessment of Delirium

The Confusion Assessment Method for the ICU (CAM-ICU) tool is a valid and extremely reliable tool, taking an average of 60 seconds to perform. The CAM-ICU is comprised of four features: acute change or fluctuation in mental status (Feature 1), inattention (Feature 2), disorganized thinking (Feature 3) or an altered level of consciousness (Feature 4) (Figure 3). In patients who are medically, traumatically, or pharmacologically comatose (RASS of -4 or -5), CAM-ICU is not assessed due to lack of any response to verbal stimulation. In patients with RASS scores of -3 or higher, CAM-ICU should be utilized. To be diagnosed as delirious, the patient should have a RASS score of -3 or higher, with an acute change or fluctuation in mental status (feature 1), accompanied by inattention (feature 2) and either disorganized thinking (feature 3) or an altered level of consciousness (feature 4).

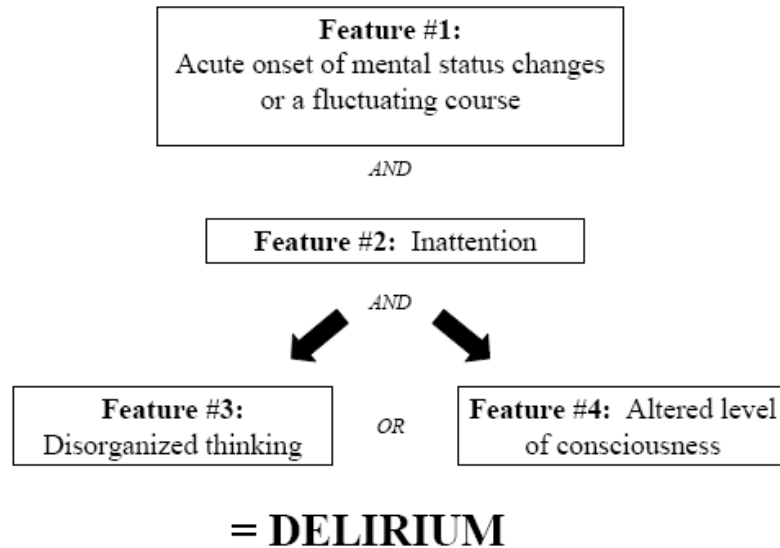
Confusion Assessment Method for the ICU (CAM-ICU) for evaluating delirium

Step #1: Sedation Assessment (RASS)

If RASS is -4 or -5, then **STOP** and **REASSESS** patient at a later time.

If RASS is above -4 (-3 through -4), **PROCEED TO STEP 2.**

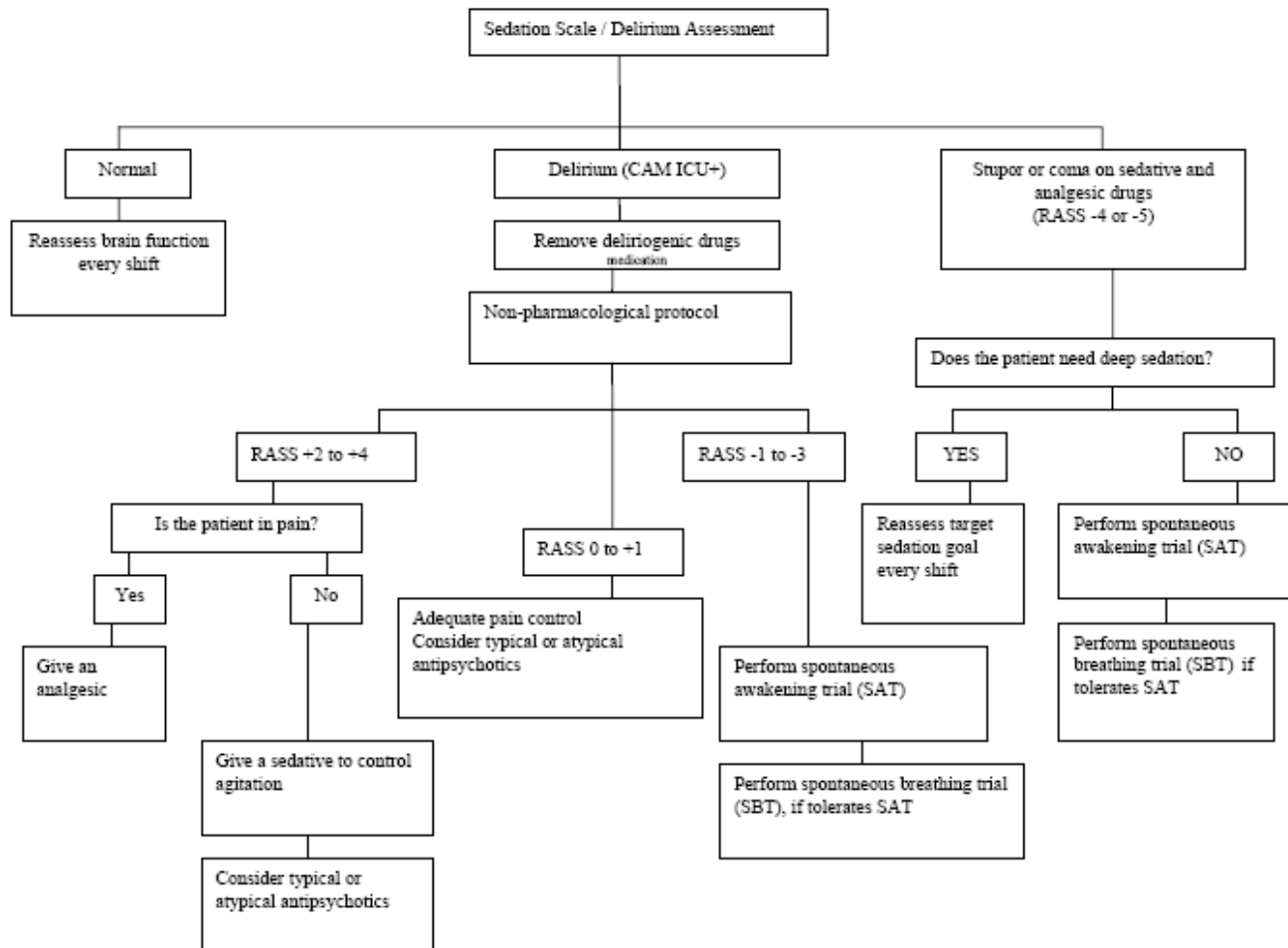
Step #2: Delirium Assessment (CAM-ICU)



Risk Factors for the Development of Delirium

Sleep deprivation, hypoxia, sensory impairment, as well as exposure to numerous medications (sedatives, analgesics, anti-cholinergics, anti-histamines, anti-arrhythmics, and steroids) have all been implicated as risk factors for delirium. In a recent study of surgical and trauma patient, we identified only two risk factors for developing delirium. Midazolam was associated with a 3 fold higher risk of developing delirium. This is consistent with data from our MICU study in which lorazepam was an independent risk factor. In addition, fentanyl demonstrated an increased risk for development of delirium, while morphine appeared to have a protective effect. This “protective effect,” however,

needs to be considered in the context that fentanyl is often (inappropriately?) used as a sedative, while morphine is exclusive used as an analgesic.



Prevention of Delirium

Avoiding high risk medications, preserving sleep hygiene, and treating symptoms with appropriately targeted medications (i.e.-opiates for pain, benzodiazepines for anxiety, anti-histamines for pruritus, not for sleep) are the foundations upon which one can hope to prevent delirium. Preserving or re-establishing the patient’s senses (eye glasses and hearing aids) and providing sufficient daytime cognitive stimulation (through staff and

family interactions) may help to prevent development of delirium or at least shorten its duration and reduce symptom severity.

FIRST STEP TO APPROACHING CAM-ICU (+) PATIENT (i.e.- (+) delirium)

1. Remove deliriogenic medications – Substitute meds such as benzodiazepines, anticholinergic medications (metochlorpromide, H2 blockers, promethazine, diphenhydramine), steroids etc
2. Non pharmacological interventions (see below)
3. Analgesia – Adequate pain control may decrease delirium. Consider intermittent morphine if feasible.
4. Atypical or typical antipsychotics – may consider 1-2 mg haloperidol as starting doses in elderly. Usual maximum dose is 20 mg/day of haloperidol. Monitor EKG.
5. Spontaneous Awakening Trial (SAT) – Stop sedation or decrease infusion by ½, especially benzodiazepines, till RASS 0 to –2, as tolerated.
6. Spontaneous Breathing Trial (SBT) – CPAP/PS trial if on <50% and ≤ 8 PEEP
7. Remove sedative and analgesics drugs – commonly benzodiazepines, propofol, fentanyl, or morphine

Treatment of Delirium

Initial management

Initial treatment is aimed at reversing and or treating any underlying medical conditions suspected of contributing to its development. After evaluating potential metabolic or infectious sources, all efforts should be made to remove “deliriogenic” medications. These include benzodiazepines, anti-histamines, anti-cholinergics (specifically diphenhydramine), and corticosteroids. Instituting daily interruption of sedatives and analgesics, and using these agents within a strict protocol, has both been shown to improve patients’ outcomes. Next, interventions focusing on environmental control,

cognitive re-orientation, and “normalization” of clinical parameters should be implemented. Environmental control entails re-establishing sleep hygiene, through control of excessive noise and staff disturbances at night and ensuring lights are on in the daytime and off at night. Sleep agents may be added to assist with sleep onset, depth, and duration. Increasing daytime communication with family and friends, increasing physical activity, and ensuring replacement of eye glasses and hearing aids is vital to achieving re-orientation of the delirious patient.

NON-PHARMACOLOGICAL APPROACH TO DELIRIUM

Orientation

- Provide visual and hearing aids
- Encourage communication and orientation to day/time/location by nurses and family
- Have familiar objects from patient’s home in the room
- Attempt consistency in nursing staff
- Allow television during the daytime with daily news
- Non-verbal music

Environment

- Sleep hygiene: LIGHTS OFF AT NIGHT, LIGHTS ON DURING THE DAY.
- Consider sleep aids (zolpidem, mirtazapine)
- Control excess noise (staff, equipment, visitors) at night
- Ambulate or mobilize patients

Clinical parameters

- Maintain systolic blood pressure > 90 mm Hg
- Maintain saturations >90%
- Treat underlying metabolic derangements and infections
- Discontinue any unnecessary and potentially deliriogenic medications

Pharmacological intervention

Haloperidol: Haloperidol is the agent most often used at our institution as it has few anti-cholinergic effects, few active metabolites, and mild sedating side effects. It is available in oral and intramuscular forms, but we typically use it intravenously (although not FDA approved) because of its rapid onset and control of agitation.

Atypical anti-psychotics: In patients with enteral access, risperidone, olanzapine, quetiapine, and ziprasidone are available and have been used at our institution. These medications, however, often require titration to higher doses and increased frequency, but are associated (as with haloperidol) with arrhythmias, including QTc prolongation and Torsades de pointes. Use of these medications has, in our experience, been associated with better tolerance of treatment and fairly quick return to the patient's baseline mental status. Improved sensorium and resolution of delirium symptoms appear to coincide with the re-establishment of the sleep-wake cycle. Unless delirium is felt to be the result of sedative or alcohol withdrawal, benzodiazepine monotherapy should be avoided.

Agents utilized for agitation and delirium

	<i>Initial dosing</i>	<i>Half-life</i>	<i>Renal Dosing</i>	<i>Hepatic Dosing</i>	<i>Adverse events/comments</i>
Haloperidol	2-5 mg IM/IV* ; double dose until effect achieved; use effective dose (?PO) scheduled q 6 h	21-24 hr	No adjustment	Caution with severe hepatic impairment	Neuroleptic malignant syndrome (NMS), akathisia, tardive dyskinesia, arrhythmias
Olanzapine	2.5-5 mg IM (or 5-10 mg PO/PT) q 2 hr prn; if effective, start 2.5-5 mg PO/PT qhs	21-50 hr	No adjustment	Caution with severe hepatic impairment	NMS, akathisia, tardive dyskinesia, severe hyperglycemia
Risperidone	0.5 mg-1 mg PO/PTq 6 hr prn, then use effective dose q 12 hr	20-36 hr	Half dose with CrCL<50; half dose and use qd with CrCL <10	Half dose and use qd with severe impairment	Available as dissolving tablet; NMS, akathisia, tardive dyskinesia
Quetiapine	25-50 mg PO/PT q 4-6 hr prn, then use effective dose q 12 hr	6-8 hr	No adjustment	Half dose and use qd with severe impairment	NMS, tardive dyskinesia, QTc prolongation, headache, severe hyperglycemia, hyperlipidemia
Ziprasidone	10-20 mg IM q2-4 prn or 20 mg PO/PT q 4-6 hr prn, then use effective dose q 12 hr	6-8 hr	Avoid IM use	No adjustment	NMS, tardive dyskinesia, QTc prolongation, headache, akathisia

*Not FDA approved for intravenous administration

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