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Assessment of analgesia, sedation, delirium and sleep disturbance in the intensive therapy unit and description of non-pharmacological interventions

Ocenjevanje analgezije, sedacije, delirija in motenj spanja v enoti intenzivne terapije ter opis nefarmakoloških ukrepov

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Abstract

Treatment in the intensive therapy unit is very stressful for most patients. It has an important impact on their quality of life and can have long-term consequences. Among others, there are serious complaints such as pain, fear, sleeplessness, thirst, helplessness, fatigue, confusion and agitation. These all can exert adverse impact on the therapy process and clinical outcome. Patients often develop delirium, which is not only a great burden for the patient but also for the personnel caring for the patient. Delirium also has a long-term negative impact on the patient's cognitive functions. Medical staff has a great responsibility for detecting and dealing with these problems, especially in patients with limited cognitive functions or impaired communication ability. There are different tools for the assessment of pain, sedation, delirium and sleep quality. In this article, we describe the most frequently used validated scoring systems for the assessment of pain, sedation, delirium and sleep disturbance. Furthermore, the non-pharmacological approach is described.

Izvleček

Za bolnike je zdravljenje v enoti intenzivne terapije v veliki večini primerov zelo stresno obdobje, ki pomembno poseže v kakovost njihovega življenja in lahko pusti dolgotrajne posledice. Bolečine, strah, nespečnost, žeja, nemoč, utrujenost, zmedenost, vznemirjenost so resne težave, ki lahko pomembno vplivajo na potek in izid zdravljenja. Pogosto se pri takih bolnikih razvije še delirij, ki pomeni veliko obremenitev tako za bolnika kot za osebje, ki zanj skrbi. Delirij lahko dolgoročno negativno vpliva na bolnikove spoznavne funkcije. Medicinsko osebje nosi veliko odgovornost pri prepoznavanju in reševanju bolnikovih težav, še posebej pri bolnikih z omejenimi spoznavnimi funkcijami oziroma z omejeno sposobnostjo sporazumevanja. Poznamo različna orodja za ocenjevanje bolečine, sedacije, delirija in kakovosti spanja. V prispevku so natančneje opisani najpogosteje uporabljani validirani točkovniki za oceno bolečine, sedacije, delirija in motenj spanja. Na koncu so opisane tudi možnosti nefarmakološkega ukrepanja.

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1 Introduction

In addition to the underlying disease, critically ill patients in the intensive therapy unit (ITU) also have problems that are more difficult to evaluate and therefore easier to overlook. During treatment in the ITU, patients suffer from insomnia, fatigue, thirst, pain, stress, fear, helplessness, noise, confusion (1).

Three months after being treated in the ITU, 40% of patients report confusion and disorientation, as well as impaired cognitive functions. This condition persists in 24–34% of patients for longer than a year (2). 25–33% also have post-traumatic stress disorder (PTSD) after one year (3). According to data from the literature, the incidence of PTSD is higher in those who were sedated for a longer period of time (3,4). Risk factors for the development of PTSD include the use of benzodiazepines, fear, isolation for hygienic reasons, dependence on replacement therapy due to failure of one or more organs (e.g. haemodialysis, mechanical ventilation, and extracorporeal membrane oxygenation) (5).

To reduce or prevent all side effects in critically ill patients, it is extremely important to identify and assess pain, sedation, fear, delirium, stress and other phenomena.

In 2015, extensive updated guidelines were published by the German Association for Anaesthesiology and Intensive Care (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin, DGAI) and the German Interdisciplinary Association for Intensive and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin, DIVI), and in 2018, the Society of Critical Care Medicine (SCCM) published the updated American guidelines (6,7). According to the cited literature, the German guidelines are the most comprehensive of their kind, and are currently in the process of being updated.

Both guidelines provide recommendations for identifying, preventing and treating pain, agitation/sedation, delirium, sleep disturbances, stress, and fear.

This article describes the most common tools for assessing pain, sedation, delirium and sleep disorders, and possible non-pharmacological measures.

2 Assessment of sedation, analgesia, stress, sleep disorders and delirium

Therapeutic concepts in intensive care medicine must be patient-oriented and must include goals that are tailored to each individual (6). Achieving the goals first requires an appropriate assessment of the patient's problems (e.g. pain) and then an assessment of the effects of the treatment. Nurses and physicians carry a great responsibility of properly assessing the patient's condition, comfort, well-being, and the appropriate action. One and the other are a dynamic process, as action needs to be constantly adapted to the results of the assessment. Regular assessment of delirium, pain, fear and other problems should be as self-evident as, for example, the long-established control of haemodynamics. Assessment of sedation, analgesia and occurrence of delirium with the help of validated scoring systems should provide guidance for the adjustment of therapy to the individual patient, and assessments should be regularly recorded in medical records (6,7). The goal is to optimize the patient's health condition and well-being, while avoiding too low or too high a dose of medication as well as reducing the accompanying side effects of these medications. A multidisciplinary approach to

analgesia and sedation has been shown to reduce the duration of mechanical ventilation, nosocomial infections, ITU treatment, mortality and treatment costs (8,9).

There are various validated scoring systems for monitoring and assessing the depth or adequacy of sedation and analgesia and the assessment of delirium. The German guidelines recommend assessing and recording the adequacy of analgesia, sedation and signs of delirium at least once per shift (every 8 hours). The drafters of these guidelines are of the opinion, however, that it is not so important which validated scoring system is used. It is more important that the evaluation is carried out on a regular basis (6). In a 1995 study, 75% of patients reported inadequate analgesia during treatment at the ITU, while 80% of their physicians were mistaken in believing that their patients had satisfactory analgesia (10).

3 Assessment of pain and adequacy of analgesia

Pain is the symptom that patients and their relatives fear the most. Pain is a very individual symptom. Patients may have acute and/or chronic pain, but chronic pain may worsen. Depending on the origin, the pain can be visceral, somatic, neuropathic, or a mixture of all of the above. Individual patients experience and tolerate pain very differently. By definition, it is an unpleasant sensory and emotional experience that may be associated with existing or potential tissue damage, and the presence of the latter is not necessary for the sensation of pain (11). Critically ill patients suffer from pain both while resting and during procedures (1,7). The experience of pain while resting is negatively affected by psychological factors (e.g. fear and depression) and demographic factors such as youth, associated illnesses, previous surgeries, and chronic use of analgesics, especially opioids. Pain during the procedure depends on the type of procedure, previous pain, recent surgery, or injury. Severe pain is usually experienced by younger people, women and non-white people (6,7,12).

According to patients, the most painful procedures performed during treatment in the ITU include: *insertion of an arterial cannula, removal of a chest drain, removal of a wound drain, turning and placement in bed, and suction of secretions (aspiration) from the trachea* (7). Severe pain during the procedure can also cause serious side effects: a marked decrease or increase in heart rate and/or blood pressure, and a dangerous decrease in arterial blood oxygen saturation (13). Due to the great influence of the subjective experience of pain and its multidimensionality, there is no universal scale for assessing pain. *The first rule is that the patient must be trusted!* In the literature, the most recommended scale to assess pain and adequacy of analgesia in patients who are able to express themselves independently is the visually enlarged laminated Numeric Rating Scale (NRS-V). With the help of the NRS-V, the patient rates the pain from 0–10 (14). The NRS-V has the highest negative predictive value of all pain self-assessment scales; it is a one-dimensional scale (14). Twinning et al. have embarked on a multidimensional approach to pain assessment that is slowly penetrating clinical practice abroad. It is a Clinically Aligned Pain Assessment tool (CAPA tool), the components of which are shown in Table 1 (15). This tool should facilitate communication between the patient experiencing pain and his or her caregivers. Using the pain assessment from different angles should thus reduce dissatisfaction on both sides: the patient can manage pain better and the staff are more satisfied with the efficiency and quality of their work (16).

Table 1: Clinically Aligned Pain Assessment tool, CAPA tool. Adapted from Twinning et al., 2019 (15).

Area	Responses
Comfort	intolerable
	tolerable with great discomfort
	relative comfort that can be improved
	negligible pain
Change in Pain	the pain gets worse
	the pain does not change
	the pain decreases
Pain Relief	insufficient
	in part
	enough
Functioning	can't do anything because of pain
	pain keeps me from doing most of what I need to do
	can do most things, but pain gets in the way of some
	can do everything I need to do
Sleep	awake with pain most of the night
	awake with occasional pain
	normal sleep

It is significantly more difficult to assess the pain and adequacy of analgesia in sedentary patients and in patients with limited cognitive functions or limited ability to communicate. In such patients, a third-party assessment is required. The staff must be properly trained to assess pain, because the reliability of pain assessment is essential (17). On the one hand, pain is often underestimated, and on the other hand, analgesics have clinically important side effects (nausea, vomiting, constipation). All this needs to be recognized, recorded and acted upon. It is even better to prevent side effects if at all possible (18). The most commonly used assessments in these cases are: The Behavioural Pain Scale (BPS) with the version for intubated and non-intubated patients, the components of which are shown in Table 2, and the Critical Care Pain Observational Tool (CPOT) shown in Table 3 (6,7,19,20). Both scales are expected to be equivalent in terms of predictive value (21-23). At this point, I would like to specifically mention the problem of patients with head injuries, as research on pain assessment using these scales has been done in a small number of such patients. And what is more, often no grimacing and muscle rigidity are observed in such patients (7). However, the American guidelines nonetheless recommend the use of BPS or CPOT even in severe head injury (7,24).

Changes in physiological variables (e.g. heart rate, blood pressure…) should not be the sole criterion for assessing pain because they coincide very poorly with the degree and experience of pain. However, they are an important warning sign for staff that something is going on with the patient; it can also be a consequence of pain (7). It is practically impossible, however, to reliably assess pain in deeply sedated patients. Despite some promising results, currently reliable objective measurement methods for assessing analgesia (e.g. measurement of skin resistance, pupillometry, heart rate variability…) are not yet available due to a number of interfering factors. Further research is needed to clarify their reliability (7,25). The American guidelines also mention the possibility of assessing a relative's pain. However, there is currently no good evidence in the literature for the reliability of pain assessment using this method (7).

4 Assessment of sedation

In order to reduce the feeling of fear, anxiety, stress, discomfort during mechanical ventilation, agitation or even aggression in patients, various drugs with sedative effects (sedatives) are often used in the ITU. Sedatives have a number of side

Table 2: Behavioural Pain Scale (BPS) for patients with or without intubation (non-intubated). Adapted from Aissaoui et al., 2005 (27).

Indicator	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g. brow lowering)	2
	Fully tightened (e.g. eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with the ventilator (intubated) or	Tolerating movement	1
	Coughing while moving	2
	Cannot bear ("fights") the ventilator	3
	Ventilation is impossible	4
Vocalization (extubated)	Does not vocalize due to pain	1
	Moaning ≤ 3 times/min and ≤ 3s	2
	Moaning > 3 times/min and > 3s	3
	Crying or verbally expressing him-/herself, including "ow" or holds breath > 3s.	4

Note: The goal of satisfactory analgesia is for the patient to score less than 6 points. In patients with a ventilator (intubated), compliance with the ventilator is assessed, and in those without it (extubated) vocalization is assessed.

effects associated with many complications and increased morbidity and thus patient mortality (7,28). In addition to complications in the cardiovascular system, prolonged need for mechanical ventilation, and undesirable drug interactions, patients often have short-term and long-term consequences in terms of mental problems, reduced cognitive functions and poorer locomotor rehabilitation (7,29). The decision to sedate should always be based on appropriate indications. The target depth of sedation and its duration must be clearly defined. It is necessary to check the need for sedation at least once a day and determine the target depth of sedation for an individual patient at a specific time. It is recommended to check the depth of sedation and achieve the target sedation at least once in each shift, which should also be recorded in the patient's documentation (6). The American and German guidelines recommend mild sedation in critically ill patients who require mechanical ventilation (6,7). In practice, we are faced with the problem of the concept of mild, moderate and deep sedation not being clearly defined (7). Mild sedation is generally considered when a patient scores –2 to +1 points on the most commonly used Richmond Agitation-Sedation Scale (RASS) (Table 4) (7). There is also no clear connection between the type of sedative, the depth of sedation and the physiological or genetic characteristics of the individual patient. It is not clear what the relationship is between the depth of sedation and the ability to assess pain, delirium and sleep quality (7). Data from recent meta-analyses do not confirm the advantage of a daily sedation cessation protocol (reduction of sedative dosing during the day to achieve the RASS score of -1 to +1 in a patient) over protocol-based sedation depth adjustment (sedatives are dosed to reach a pre-agreed target sedation depth, according to the RASS, for example) (7,30). The authors of the American guidelines believe that both of the above-mentioned options for achieving mild sedation are comparatively safe. At the same time, they note that most studies comparing the two options have been conducted with benzodiazepines, which are no longer recommended as the first choice among sedatives. They also note that the protocol of daily cessation of sedation is associated with a greater workload of staff, and at the same time, such a protocol should not be an excuse for the sedation being too deep in the afternoon and at night (7,31).

Table 3: Critical-Care Pain Observational Tool (CPOT) in ITU. Adapted from Gellinas C et al., 2006 (26).

Indicator	Score		Description
Facial expression	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Frowning, brow lowering, orbit tightening, facial tension, opening eyes or tearing during painful procedures
	Grimacing	2	All signs above plus eyelid tightly closed (mouth may be open or biting the tube)
Body movement	Absence of movements, normal position	0	Does not move at all (does NOT necessarily mean absence of pain) or normal position (movements not aimed toward the pain site, not made for the purpose of protection)
	Protective posture – careful movements	1	Slow, cautious movements, touching, rubbing the pain site, seeking attention through movements
	Restlessness, agitation	2	Pulling tube, attempting to sit up, trying to climb out of bed, moving limbs, not following commands, striking at staff
Compliance with the ventilator (intubated) or	Tolerating ventilator and movement	0	Alarms not activated, easy ventilation
	Coughing, but tolerating ventilation and movement	1	Coughing, alarms may be activated but stop spontaneously
	Fighting the ventilator	2	Asynchrony: blocking ventilation, alarms frequently activated
Vocalization (extubated)	Talking in normal tone	0	Talking in normal tone or no sound
	Sighing, moaning	1	Sighing, moaning
	Screaming, crying, sobbing	2	Screaming, crying, sobbing
Muscle tension	Relaxed	0	No resistance to passive movements
	Tense, rigid	1	Resistance to passive movements
	Very tense or rigid	2	Strong resistance to passive movements or incapacity to complete them
Total:	_____ / 8		

Note: The goal of satisfactory analgesia is for the patient to collect ≤ 2 points. In patients with a breathing tube (intubated), compliance with the ventilator is assessed, and in those without it (extubated) vocalization is assessed.

There are various scoring systems for controlling the depth of sedation. The most reliable and validated is the Richmond Agitation-Sedation Scale (RASS), which is recommended by both the German and the American guidelines (6,7,32). Other scales may also be used, e.g. the RAMSAY Sedation Scale (RSS) and others, like the Sedation-Agitation Scale (SAS) and Motor Activity Assessment Scale (MAAS) (6).

To control deep sedation, there are objective measurement methods that have certain shortcomings. Deep sedation is rarely required in clinical practice (increased intracranial pressure, tetanus) (6).

Different monitors are available that capture the EEG and convert it to different indexes (e.g. a BIS monitor) (6). The American guidelines express the opinion that, according to data from the literature, a BIS monitor is probably currently the best option for monitoring deep sedation. In addition to the limitations of the BIS monitor itself, the problem is the

Table 4: Richmond-Agitation-Sedation-Scale (RASS). Adapted from Sessler et al., 2001 (33).

Score	Term	Description
+ 4	Combative	Presents immediate danger to him-/herself and staff
+ 4	Very agitated	Pulls or removes the breathing tube or catheter, is aggressive towards staff
+ 2	Agitated	Frequent non-purposeful movement or non-synchronized mechanical ventilation ("fights ventilator") or non-synchronized breathing during mechanical ventilation
+ 1	Restless	Anxious, but movements not aggressive or vigorous
0	Alert and calm	
– 1	Sleepy, drowsy	Not fully alert, but has sustained awakening (>10 s), eye contact to voice
– 2	Light sedation	Briefly awakens (<10 s), eye contact to voice
– 3	Moderate sedation	Movement without eye contact to voice
– 4	Deep sedation	No response to voice, movement to physical stimulation
– 5	Unarousable	No response to voice or physical stimulation

non-standardized methodology of various studies comparing the BIS monitor with rating scales. The problem of EEG signal processing is in many factors that interfere with the capturing of the relevant signal and are difficult to avoid in the ITU (e.g. patient care, other devices that interfere with the EEG signal, noise) (34). It is also possible to measure the raw EEG. The problem is reading the EEG, as only a few can master it. The raw EEG measurement is recommended in cases where the cause of impaired consciousness is unknown (6). In particular, it can be used to confirm or rule out non-convulsive status epilepticus, which, according to data from the literature, occurs in approximately 20% of cases of impaired consciousness of critically ill patients (35). It makes sense to use the sedation depth control in the ITU as a complementary method of subjective assessment to avoid the sedation being too deep. When using monitors to measure the depth of sedation, we must always keep in mind the possible influence of external interfering factors (6,7).

5 Assessing the presence of delirium

It often happens that an ITU patient develops delirium (36). This is an acute disorder of attention with a disorder of consciousness, perception and thinking as a consequence of disease activity in any organ system (37). It can be accompanied by a number of other nonspecific symptoms (38). The diagnosis is made on the basis of the clinical picture. It is basically a reversible state of brain dysfunction. Delirium is the result of the concomitant action of various factors that may have been present even before admission to the ITU. Factors are divided into basic factors related to various interventions within the treatment, and psychological, social and environmental factors (38,39). The basic factors include previous illnesses, previous cognitive deficits, dementia, increasing age, alcoholism and dependence on other psychoactive substances, pre-existing depression, severity of acute illness, chronic pain, current limitations in mobility or immobility (38,40,41). Factors associated with various interventions include blood transfusion, recent emergency surgical and other invasive procedures, recent injuries, depth and duration of sedation, use of anticholinergics, benzodiazepines, antipsychotics, and anticonvulsants (7,28,42,43). When delirium occurs, it is important to look for and treat possible causes such as infection, hypoxia, hypoperfusion, post-withdrawal condition, metabolic and endocrine disorders (43,44). According to recent literature, gender, the use of opioid

analgesics, and mechanical ventilation have not been associated with an increased risk of delirium (7).

In the literature, there is a large range in the occurrence of delirium (30–80%), which differs according to the examined groups of patients (45,46). The occurrence of delirium negatively affects the outcome of treatment (38,47). It prolongs the need for mechanical ventilation, treatment time in the ITU and hospital, and has a long-term negative effect on the patient's cognitive functions (2,48-52). Risk factors for delirium can also be divided into predisposing and precipitating factors (53). Predisposing factors are the basic factors listed earlier, which in most cases cannot be changed, while the precipitating factors are factors the patient is exposed to during treatment. The precipitating factors include all invasive procedures (operations, procedures for replacing organ function, establishing vascular access...), use of anticholinergics, benzodiazepines, depth and duration of sedation, mechanical ventilation, presence of a breathing tube, large fluctuations in blood pressure, hypoxia, severe anaemia, large fluctuations in blood sugar, and septic shock (43,55-58). Precipitating factors also include the environment (noise, light ...) and psychological and social factors (e.g. isolation due to microbiological reasons). It is important to know the possible precipitating factors, minimize them or even prevent them.

Monitoring and recording the occurrence of signs of delirium in each nursing shift is recommended to detect delirium as well. The American guidelines consider the recommendation to be a recommendation of good clinical practice because of the weak evidence of a better outcome in patients due to the diagnosis and treatment of delirium (7). Without targeted checking, as much as 2/3 of the signs of delirium are overlooked (6,7). The most commonly used scoring systems are: The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) shown in Figure 1 and the Intensive Care Delirium Screening Checklist (ICDSC), shown in Table 5. To use them, staff must be properly trained (6,7,59,60). With the CAM-ICU, the presence of delirium can be confirmed or ruled out, but the degree of delirium cannot be determined. There is a simpler scoring system called the Nursing Delirium Screening Scale (Nu-DESC). If signs of delirium (1 point or more) are detected with the Nu-DESC, a more accurate assessment with a CAM-ICU or ICDSD is required (6,61).

Contrary to popular belief, delirium rarely occurs exclusively as agitation, with 2/3 of patients having hypoactive delirium and approximately 1/3 patients having a mixed form (6). This raises the question of what effect the level of awakeness/alertness has on the assessment of delirium with the aforementioned scoring systems. So far, there is little data in the literature on the influence of awakeness/alertness on the reliability of delirium assessment; it is only clear that in deeply sedated patients (RASS –4 or –5) assessment is not possible (6,7).

6 Assessment of stress, fear and sleep disorders

There are not many proven tools for measuring stress, fear and sleep quality that are suitable for everyday use. Stress is one of the most common symptoms in critically ill patients. Not only does it have psychological consequences, but it also affects cognitive functions, the neuroendocrine system and the mechanisms of inflammation (62). Mental and cognitive consequences, in particular, may persist long after treatment at the ITU and require long-term treatment.

Figure 1: Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). In the case of deep sedation (-4 or -5 according to the RASS), the presence of delirium cannot be assessed. It is always necessary to look for the cause of anxiety, sedation and/or somnolence. Adapted from Ely et al., 2001 (59).

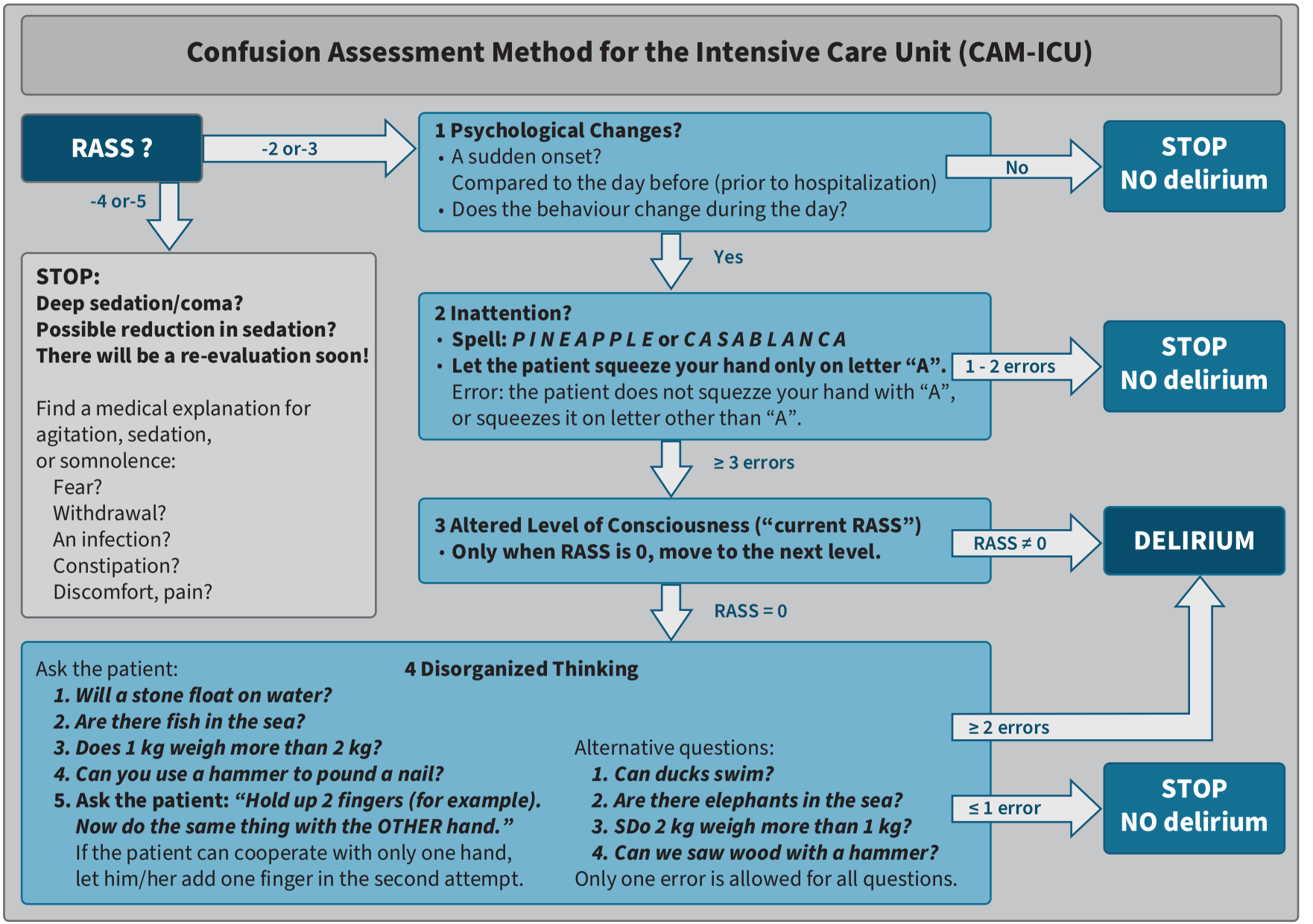

Table 5: Intensive Care Delirium Screening Checklist (ICDSC). Adapted from Bergeron et al., 2001 (58).

Description
1. Altered Level of Consciousness. Choose one of the answers from A to E:
A. exaggerated response to normal stimulation (RASS +1 do +4) ***1 point***
B. normal wakefulness (RASS 0) ***0 points***
C. responds to mild or moderate stimulation (obeys commands) (RASS -1 do -3) ***1 point***
D. oresponds only to intense repeated stimulation (e.g. strong voice, pain) (RASS -4) ***stop assessment****
E. no response (RASS -5) ***stop assessment****
2. Inattention (*1 point for each positive answer*):
A. difficulty following commands *or*
B. the patient is easily distracted by external stimuli *or*
C. difficulty transferring focus
Does the patient follow you with their eyes?
3. Disorientation (*1 point* for each deviation):
A. disorientated to time or place *or* does not recognize people
Does the patient recognize ITU caregivers who have cared for him/her and not recognize those who have not? Does he/she recognize the place they're in? (let them list the caregivers, place ...)
4. Hallucinations or delusions *(1 point for each positive answer)*:
A. equivocal evidence of hallucinations or behaviour due to hallucinations *(hallucination is a perception of something that is not there with no stimulus) or*
B. delusions or gross impairment of the perception of reality *(delusion is a false belief that is fixed/ unchanging)*
Does the patient currently have or have they had any hallucinations over the past 24 hours? Are they afraid of people or things around them? (fear that is inappropriate to the clinical situation)
5. Psychomotor agitation or retardation *(1 point for each positive answer)*:
A. hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential danger (e.g. pulling catheters out, hindering the staff ...) *or*
B. inactivity *or* clinically noticeable psychomotor slowing *or* retardation
Based on observation and documentation of the caregiver who cares for the patient over a shift.
6. Inappropriate speech or mood *(1 point for each positive answer)*:
A. inappropriate, disorganized, or incoherent speech *or*
B. inappropriate mood related to events or situation
Is the patient apathetic to current clinical situation? (e.g. lack of emotion) ***Any gross abnormalities in speech or mood? Is the patient inappropriately demanding?***

Description
7. Sleep/wake cycle disturbance? (*1 point for each abnormality*):
A. sleeping less than 4 hours at night *or*
B. waking frequently at night (no disturbances by the staff or noise) *or*
C. sleeping more than 4 hours during day
Based on the caregiver assessment.
8. Symptom fluctuation (*1 point for each item that changes*):
Fluctuation of any of the above items (under points 1–7) over 24 hours
Based on the caregiver assessment.

Notes:
If the patient scores 4 points or more, it is delirium (99% sensitivity). RASS (Richmond Agitation-Sedation Scale, RASS).
* In patients who are stuporous or comatose, assessment of delirium is not possible.

We do not currently have validated scoring systems or useful commercial monitors for stress detection. It is indirectly determined by monitoring vegetative functions and vital parameters, which are not a reliable measure of stress level. It is also possible to measure the concentration of cortisol and interleukins in the blood, which is less useful for everyday clinical practice (63).

For measuring the level of fear there are two validated scoring systems available: The State-Trait Anxiety Inventory (STAI) and the anxiety subscale of the Brief Symptom Inventory (BSI) (64). Both scoring systems go beyond the nature of this article. At this point, let me emphasize that deeper sedation, despite popular belief, is not associated with a reduced incidence of fear (65).

Lack of sleep and poor sleep quality is a very common problem in critically ill patients and is one of the main stressors. To date, the duration and effectiveness of sleep have been found to be normal in critically ill patients in most cases (7). However, a severe sleep disorder often occurs due to sleep fragmentation (frequent awakenings), disrupted day-night (circadian) rhythm (more sleep during the day, less at night), as well as a greater presence of shallow sleep phases (N1 and N2) and a lower proportion of deep sleep phases (N3, N4 and REM) (66). Normally, the phases of REM (rapid eye movement) and non-REM alternate at approximately 90-minute intervals, while in critically ill patients the phase of REM, especially, is missing (67). The frequent occurrence of atypical sleep patterns in the electroencephalogram has also been described in the literature; patients are often pathologically awake (7).

Patients who had had trouble sleeping before the onset of the critical illness and those who had been using sleeping pills are particularly prone to poor sleep quality during ITU treatment (7). In addition, pain, disturbing environmental factors such as noise, light, bed quality, staff intervention (care, recording vital signs, therapeutic interventions), psychological factors (e.g. fear, disorientation, foreign environment), breathing problems (dyspnoea, coughing) and certain medicines contribute to the poor quality of sleep of critically ill patients (7,68).

Lack of sleep and poor sleep quality

have a number of undesired effects. Quality sleep accelerates cellular immunity and wound healing, there is less chance of delirium and neurological-cognitive dysfunction, and there is less chance of a prolonged need for mechanical ventilation (7). Poor sleep quality increases the chance of developing delirium. The onset of delirium, however, concludes a vicious circle because it negatively affects the quality of sleep. Patients with delirium have a lower proportion of the REM sleep phase. Their day-night rhythm is also disrupted as they sleep more during the day. The exact effect of delirium on individual stages of sleep is not yet known (7,69). According to the limited data from the literature, inadequate mechanical ventilation is also likely to negatively affect sleep quality, day-night rhythm, and sleep architecture. On the other hand, properly adjusted mechanical ventilation in certain patients with respiratory insufficiency is expected to improve sleep quality. The actual impact of poor quality and lack of sleep on the patient's treatment outcome is currently unknown (7).

The only well-validated objective method for measuring sleep quality (90-minute REM and non-REM sleep cycles) is polysomnography, which is too demanding for everyday use in the ITU (6). In the literature, single-channel EEG, BIS monitor, and continuous measurement of skin potential are mentioned as possible methods for measuring sleep. Due to the lack of reliable data, the guidelines do not recommend any of these methods (6). The American guidelines recommend that patients who are able to respond and are oriented be asked how they slept, or that their sleep be assessed using the Richards-Campbell Sleep Questionnaire shown in Table 6 (7,70).

Contrary to popular belief, the use of sedatives further disrupts the already poor sleep structure of the critically ill patient (7).

The effect of sleep quality during treatment at the ITU on the patient's treatment outcome is unknown (7).

7 Non-pharmacological measures for preventing pain, fear, stress, insomnia, discomfort and delirium

Nonpharmacological measures are too often an underestimated part of preventing pain, fear, stress, insomnia, discomfort, and delirium. These are mostly inexpensive measures and do not require additional equipment, but require properly educated and motivated staff. Simpler nonpharmacological measures logically follow the assessment of pain, delirium, and sedation.

According to the recommendations, nonpharmacological measures are the basis for preventing the occurrence of delirium (9,71,72). More than the implementation of a single measure, it is recommended to implement a combination of different measures, which mostly have a beneficial effect on several of the patient's problems at the same time (e.g. better sleep, less pain, less delirium) (7). One important measure is to maintain a day-night (circadian) rhythm (73). This is helped by reducing noise (establishing a quiet environment) and light at night. A patient who does not have delirium should be offered the option of using sleeping mask and earplugs at night. In doing so, we take into account his or her wishes (75). The American guidelines recommend that the assist-control mode of mechanical ventilation be used in patients who require invasive mechanical ventilation overnight. This should improve the quality of sleep. Due to a lack of data, there are currently no recommendations for the use of

Table 6: Richards Campbell Sleep Questionnaire. Adapted from Rivosecchi et al., 2016 (70).

Indicator	Response
Sleep depth	My sleep was: Very light **(0)** ... very deep **(100)**
Sleep latency	Last night I fell asleep: I just never could fall asleep **(0)**... I fell asleep immediately **(100)**
Awakenings	Last night: I was awake all night **(0)** ... I rarely woke up **(100)**
Return to sleep	Last night, when I woke up or was awakened: I couldn't get back to sleep **(0)** ... I got back to sleep immediately **(100)**
Sleep quality	I would describe my sleep last night as: bad **(0)** ... good **(100)**

Note: The closer a patient gets to 100, the better he or she slept.

adaptive breathing methods. It is also recommended to use non-invasive forms of mechanical ventilation (NIV – non-invasive ventilation) overnight in patients who are suitable for NIV (7).

During the day, the patient should be adequately stimulated and activated (74). Cognitive stimulation and diversion of attention are important. The assistance of staff and relatives in orienting the patient in time and space is recommended (53). The patient should start using his or her glasses, hearing aid, denture and other aids as soon as possible (72). It also makes sense to use different media, e.g. radio, television, computer, or newspaper, taking into account the patient's wishes and needs (76). The presence of relatives who, according to some experts, could be included in the patient's treatment process (e.g. conversation with the patient, care assistance) also has a beneficial effect (6,7). The latter requires a significant mental and organizational shift in each ITU.

During the day, it is important that the patient is exposed to daylight, which consists of more blue light of shorter wavelengths. The light from the blue spectrum affects the melatonin system, which helps to maintain a state of wakefulness (76).

When planning the construction of an intensive care unit or its renovation, it is essential to provide an adequate number of windows that allow a sufficient amount of daylight (77).

If possible, it is recommended that all invasive and non-invasive procedures be performed on the patient in the morning shift (6). This allows them more time for quiet and uninterrupted rest in the afternoon and at night. A peaceful environment is easier to ensure in large enough single rooms, which is also a recommendation of the ITU spatial planning guidelines (77).

There is growing evidence in the literature of the beneficial effect of early mobilization on the reduced incidence of delirium and a better overall treatment outcome in the ITU (78). Early mobilization (in bed and out of bed) and rehabilitation are also recommended by the American guidelines (7). Despite the accumulation of data on the positive effects of early rehabilitation in the literature, some questions remain open. Given the contraindications, early rehabilitation has no serious side effects (78).

Removal of drains, venous cannulas and enteral feeding tubes has been shown

to reduce the risk of delirium, discomfort and often pain (72,79). It is recommended to assess the need for these devices on a daily basis and to remove them as soon as the patient no longer needs them.

As soon as possible, a switch to enteral or oral feeding is also recommended (6).

A comfortable position of the patient in bed is important, especially in patients who cannot position themselves (sedated, plegic, immobilized). Positions that reduce pain are also important.

The literature mentions the beneficial effects of massage, aromatherapy, acupressure and various relaxation techniques on the patient's general comfort. All of these techniques should be performed throughout the day, taking into account the patient's wishes. These techniques are mentioned with a low level of recommendation in both the American and the German guidelines (6,7). Massage and relaxation techniques can also be used as an additional measure to prevent pain during procedures. These two approaches have virtually no serious side effects. The main problem is that the current research in the literature is very poorly comparable due to the use of different techniques in individual studies. There is also a problem in practice that there is often a shortage of staff in the ITU, but this technique must also be properly taught.

Unlike massage and relaxation techniques, the American guidelines do not recommend virtual reality and hypnosis therapy due to a lack of evidence (7).

The beneficial effect of music therapy is described. When choosing music, the patient's wishes are taken into account whenever possible, otherwise it is recommended to choose calmer, slow music without lyrics, which should not be too loud. The American guidelines recommended music therapy primarily as an additional measure for reducing pain, especially during procedures, although the level of evidence for its effectiveness in the literature is low. The main problem in performing music therapy is the need for appropriate devices (headphones, music source), which must also meet hygienic or microbiological standards (possibility of disinfection).

To prevent pain during procedures, the American guidelines recommend the use of cooling (low level of evidence). It is therefore recommended to cool the drain area for 10 minutes before removing the drains. The method, while taking precautions to prevent frostbite (cooling through a cloth), has no serious side effects, is inexpensive, and can be quickly taught to staff (7).

The view of the use of physical restraint on a patient is highly controversial in the literature. According to the American guidelines, physical restraints are not used at all in some European countries, and in North America they are used in up to 75% of all ITUs (7). Physical restraint involves various measures, e.g. tying the patient's limbs to the bed, wrapping the patient's fingers in a "boxing glove", fastening the patient to the bed with a band tied over the chest. The reasons for the use of physical restraint are different: one of the most important in everyday practice is a lack of staff (7). The latter is the main reason that physical restraint is still present in Slovenian ITUs. The historical purpose of physical restraint is to "calm down" restless and aggressive patients (they are often delirious) and to prevent potential harm to the patient and staff. However, we know from everyday clinical practice that patients are often even more restless when physically restrained. There is also some information in the literature that physical restraint results in even more adverse events, such as e.g., accidental removal of the airway, catheters, drains and other devices, occurrence of pressure ulcers,

prolonged ITU treatment, increased agitation, increased use of benzodiazepines, opioids and antipsychotics, and increased risk of developing delirium (7,80). All of the above contradicts the results that staff expect from the use of physical restraint. Last but not least, the question of the ethics of physical restraint also arises. The personal opinion of the author of this article is that it is necessary to take all possible measures to minimize the need to use physical restraint or make sure there is no need for it at all. At the same time, the abandonment of physical restraint should not result in excessive use of sedatives, opioids and antipsychotics.

8 Conclusion

In addition to the underlying disease, patients usually have a number of other problems during treatment at the ITU. These can arise from the underlying disease (e.g. pain, delirium), from the environment (noise, insomnia, bed rest), as a result of various invasive procedures or as a result of previous illnesses and addiction to certain active ingredients (e.g. alcohol). Pain, insomnia, fear, delirium, fatigue and thirst are important stressors that negatively affect the patient's treatment. As these stressors can potentially be mitigated or completely prevented, it is extremely important to identify them promptly and take appropriate action. It is crucial to communicate with the patient, if he or she is able to do so, and to take his or her needs into account. However, in unconscious or unfocused patients, it is essential to know the appropriate validated assessment tools.

In addition to all the above, we must not forget that in addition to satisfying basic physiological needs (e.g. feeding, bowel movements and urination), patients often want to talk about their distress, pain, and fear. They also want staff nearby who, in addition to their professional skills, are also empathetic and attentive to their problems.

References

1. Puntillo KA, Arai S, Cohen NH, Gropper MA, Neuhaus J, Paul SM, et al. Symptoms experienced by intensive care unit patients at high risk of dying. Crit Care Med. 2010;38(11):2155-60. DOI: 10.1097/CCM.0b013e3181f267ee PMID: 20711069
2. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al.; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306-16. DOI: 10.1056/NEJMoa1301372 PMID: 24088092
3. Sricharoenchai T, Parker AM, Zanni JM, Nelliot A, Dinglas VD, Needham DM. Safety of physical therapy interventions in critically ill patients: a single-center prospective evaluation of 1110 intensive care unit admissions. J Crit Care. 2014;29(3):395-400. DOI: 10.1016/j.jcrc.2013.12.012 PMID: 24508202
4. Nelson BJ, Weinert CR, Bury CL, Marinelli WA, Gross CR. Intensive care unit drug use and subsequent quality of life in acute lung injury patients. Crit Care Med. 2000;28(11):3626-30. DOI: 10.1097/00003246-200011000-00013 PMID: 11098964
5. Wade D, Hardy R, Howell D, Mythen M. Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. Minerva Anestesiol. 2013;79(8):944-63. PMID: 23558761
6. Bürkle H, Eggers V, Horter J, Kessler P, Kleinschmidt S, Meiser A, et al. Analgesie, Sedierung und Delirmanagement in der Intensivmedizin (DAS-Leitlinie 2015). Nürnberg: Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin; 2015 [cited 2020 Mar 20]. Available from: https://www.awmf.org/uploads/tx_szleitlinien/001-012p_S3_Analgesie_Sedierung_Delirmanagement_Intensivmedizin_2015-08-abgelaufen.pdf.

7. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJ, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46(9):e825-73. DOI: 10.1097/CCM.0000000000003299 PMID: 30113379
8. Jakob SM, Lubszky S, Friolet R, Rothen HU, Kolarova A, Takala J. Sedation and weaning from mechanical ventilation: effects of process optimization outside a clinical trial. J Crit Care. 2007;22(3):219-28. DOI: 10.1016/j.jcrc.2007.01.001 PMID: 17869972
9. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371(9607):126-34. DOI: 10.1016/S0140-6736(08)60105-1 PMID: 18191684
10. Whipple JK, Lewis KS, Quebbeman EJ, Wolff M, Gottlieb MS, Medicus-Bringa M, et al. Analysis of pain management in critically ill patients. Pharmacotherapy. 1995;15(5):592-9. DOI: 10.1002/j.1875-9114.1995.tb02868.x PMID: 8570431
11. Loeser JD, Treede RD. The Kyoto protocol of IASP basic pain terminology. Pain. 2008;137(3):473-7. DOI: 10.1016/j.pain.2008.04.025 PMID: 18583048
12. Al Sutari MM, Abdalrahim MS, Hamdan-Mansour AM, Ayasrah SM. Pain among mechanically ventilated patients in critical care units. J Res Med Sci. 2014;19(8):726-32. PMID: 25422657
13. de Jong A, Molinari N, de Lattre S, Gniadek C, Carr J, Conseil M, et al. Decreasing severe pain and serious adverse events while moving intensive care unit patients: a prospective interventional study (the NURSE-DO project). Crit Care. 2013;17(2):R74. DOI: 10.1186/cc12683 PMID: 23597243
14. Chanques G, Viel E, Constantin JM, Jung B, de Lattre S, Carr J, et al. The measurement of pain in intensive care unit: comparison of 5 self-report intensity scales. Pain. 2010;151(3):711-21. DOI: 10.1016/j.pain.2010.08.039 PMID: 20843604
15. Twining J, Padula C. The measurement of pain in intensive care unit: comparison of 5 self-report intensity scales. Pain Manag Nurs. 2019;20(5):462-7. DOI: 10.1016/j.pmn.2019.02.005 PMID: 31103512
16. Gordon DB. Acute pain assessment tools: let us move beyond simple pain ratings. Curr Opin Anaesthesiol. 2015;28(5):565-9. DOI: 10.1097/ACO.0000000000000225 PMID: 26237235
17. McGuire DB, Kaiser KS, Haisfield-Wolfe ME, Iyamu F. Pain assessment in non-communicative adult palliative care patients. Nurs Clin North Am. 2016;51(3):397-431. DOI: 10.1016/j.cnur.2016.05.009 PMID: 27497016
18. Osterbrink J. Pain management in nursing care—experts standard. MMW Fortschr Med. 2005;147(15):34. PMID: 15884501
19. Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258-63. DOI: 10.1097/00003246-200112000-00004 PMID: 11801819
20. Gélinas C, Klein K, Naidech AM, Skrobik Y. Pain, sedation, and delirium management in the neurocritically ill: lessons learned from recent research. Semin Respir Crit Care Med. 2013;34(2):236-43. DOI: 10.1055/s-0033-1342986 PMID: 23716314
21. Rijkenberg S, Stilma W, Endeman H, Bosman RJ, Oudemans-van Straaten HM. Pain measurement in mechanically ventilated critically ill patients: Behavioral Pain Scale versus Critical-Care Pain Observation Tool. J Crit Care. 2015;30(1):167-72. DOI: 10.1016/j.jcrc.2014.09.007 PMID: 25446372
22. Rahu MA, Grap MJ, Ferguson P, Joseph P, Sherman S, Elswick RK. Validity and sensitivity of 6 pain scales in critically ill, intubated adults. Am J Crit Care. 2015;24(6):514-23. DOI: 10.4037/ajcc2015832 PMID: 26523009
23. Severgnini P, Pelosi P, Contino E, Serafinelli E, Novario R, Chiaranda M. Accuracy of Critical Care Pain Observation Tool and Behavioral Pain Scale to assess pain in critically ill conscious and unconscious patients: prospective, observational study. J Intensive Care. 2016;4(1):68. DOI: 10.1186/s40560-016-0192-x PMID: 27833752
24. Dehghani H, Tavangar H, Ghandehari A. Validity and reliability of behavioral pain scale in patients with low level of consciousness due to head trauma hospitalized in intensive care unit. Arch Trauma Res. 2014;3(1):e18608. DOI: 10.5812/atr.18608 PMID: 25032173
25. Paulus J, Roquilly A, Beloeil H, Théraud J, Asehnoune K, Lejus C. Pupillary reflex measurement predicts insufficient analgesia before endotracheal suctioning in critically ill patients. Crit Care. 2013;17(4):R161. DOI: 10.1186/cc12840 PMID: 23883683
26. Gélinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420-7. DOI: 10.4037/ajcc2006.15.4.420 PMID: 16823021
27. Aïssaoui Y, Zeggwagh AA, Zekraoui A, Abidi K, Abouqal R. Validation of a behavioral pain scale in critically ill, sedated, and mechanically ventilated patients. Anesth Analg. 2005;101(5):1470-6. DOI: 10.1213/01.ANE.0000182331.68722.FF PMID: 16244013

28. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21-6. DOI: 10.1097/00000542-200601000-00005 PMID: 16394685
29. Shehabi Y, Bellomo R, Kadiman S, Ti LK, Howe B, Reade MC, et al.; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: A multinational prospective longitudinal cohort study. Crit Care Med. 2018;46(6):850-9. DOI: 10.1097/CCM.0000000000003071 PMID: 29498938
30. Burry L, Rose L, McCullagh IJ, Fergusson DA, Ferguson ND, Mehta S. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. Cochrane Database Syst Rev. 2014;7(7):CD009176. DOI: 10.1002/14651858.CD009176.pub2 PMID: 25005604
31. Mehta S, Burry L, Cook D, et al. SLEAP Investigators; Canadian Critical Care Trials Group: Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: A randomized controlled trial. JAMA. 2012;308:1985-92. DOI: 10.1001/jama.2012.13872 PMID: 23180503
32. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003;289(22):2983-91. DOI: 10.1001/jama.289.22.2983 PMID: 12799407
33. Sessler CN, Grap MJ, Brophy GM. Multidisciplinary management of sedation and analgesia in critical care. Semin Respir Crit Care Med. 2001;22(2):211-26. DOI: 10.1055/s-2001-13834 PMID: 16088675
34. Vivien B, Di Maria S, Ouattara A, Langeron O, Coriat P, Riou B. Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant. Anesthesiology. 2003;99(1):9-17. DOI: 10.1097/00000542-200307000-00006 PMID: 12826836
35. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62(10):1743-8. DOI: 10.1212/01.WNL.0000125184.88797.62 PMID: 15159471
36. American Psychiatric AssociationDiagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, D.C.: APA; c2013.
37. Lipowski ZJ. Update on delirium. Psychiatr Clin North Am. 1992;15(2):335-46. DOI: 10.1016/S0193-953X(18)30240-5 PMID: 1603727
38. Korošec Jagodič H, Jagodič K, Pregelj P. Obravnava bolnika z delirijem. Zdrav Vestn. 2009;78:473-80.
39. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis. Age Ageing. 2014;43(3):326-33. DOI: 10.1093/ageing/afu022 PMID: 24610863
40. Pisani MA, Murphy TE, Van Ness PH, Araujo KL, Inouye SK. Characteristics associated with delirium in older patients in a medical intensive care unit. Arch Intern Med. 2007;167(15):1629-34. DOI: 10.1001/archinte.167.15.1629 PMID: 17698685
41. Van Rompaey B, Elseviers MM, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for delirium in intensive care patients: a prospective cohort study. Crit Care. 2009;13(3):R77. DOI: 10.1186/cc7892 PMID: 19457226
42. Hirsch J, DePalma G, Tsai TT, Sands LP, Leung JM. Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. Br J Anaesth. 2015;115(3):418-26. DOI: 10.1093/bja/aeu458 PMID: 25616677
43. van den Boogaard M, Schoonhoven L, Maseda E, Plowright C, Jones C, Luetz A, et al. Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study. Intensive Care Med. 2014;40(3):361-9. DOI: 10.1007/s00134-013-3202-7 PMID: 24441670
44. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. J Trauma. 2008;65(1):34-41. DOI: 10.1097/TA.0b013e31814b2c4d PMID: 18580517
45. Zhang WY, Wu WL, Gu JJ, Sun Y, Ye XF, Qiu WJ, et al. Risk factors for postoperative delirium in patients after coronary artery bypass grafting: A prospective cohort study. J Crit Care. 2015;30(3):606-12. DOI: 10.1016/j.jcrc.2015.02.003 PMID: 25708120
46. Slooter AJ, Van De Leur RR, Zaal IJ. Delirium in critically ill patients. Handb Clin Neurol. 2017;141:449-66. DOI: 10.1016/B978-0-444-63599-0.00025-9 PMID: 28190430
47. Ely EW, Girard TD, Shintani AK, Jackson JC, Gordon SM, Thomason JW, et al. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. Crit Care Med. 2007;35(1):112-7. DOI: 10.1097/01.CCM.0000251925.18961.CA PMID: 17133176
48. Skrobik Y, Ahern S, Leblanc M, Marquis F, Awissi DK, Kavanagh BP. Protocolized intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. Anesth Analg. 2010;111(2):451-63. DOI: 10.1213/ANE.0b013e3181d7e1b8 PMID: 20375300

49. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753-62. DOI: 10.1001/jama.291.14.1753 PMID: 15082703
50. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010;38(7):1513-20. DOI: 10.1097/CCM.0b013e3181e47be1 PMID: 20473145
51. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med. 2010;38(12):2311-8. DOI: 10.1097/CCM.0b013e3181f85759 PMID: 20838332
52. Inouye SK, Bogardus ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340(9):669-76. DOI: 10.1056/NEJM199903043400901 PMID: 10053175
53. Schiemann A, Hadzidiakos D, Spies C. Managing ICU delirium. Curr Opin Crit Care. 2011;17(2):131-40. DOI: 10.1097/MCC.0b013e32834400b5 PMID: 21301333
54. González-López A, Albaiceta GM, Talbot K. Newly identified precipitating factors in mechanical ventilation-induced brain damage: implications for treating ICU delirium. Expert Rev Neurother. 2014;14(6):583-8. DOI: 10.1586/14737175.2014.915743 PMID: 24852225
55. Bilotta F, Lauretta MP, Borozdina A, Mizikov VM, Rosa G. Postoperative delirium: risk factors, diagnosis and perioperative care. Minerva Anestesiol. 2013;79(9):1066-76. PMID: 23511351
56. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet. 2010;375(9716):773-5. DOI: 10.1016/S0140-6736(09)61158-2 PMID: 20189029
57. Hopkins RO, Suchyta MR, Snow GL, Jephson A, Weaver LK, Orme JF. Blood glucose dysregulation and cognitive outcome in ARDS survivors. Brain Inj. 2010;24(12):1478-84. DOI: 10.3109/02699052.2010.506861 PMID: 20858026
58. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27(5):859-64. DOI: 10.1007/s001340100909 PMID: 11430542
59. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29(7):1370-9. DOI: 10.1097/00003246-200107000-00012 PMID: 11445689
60. Gélinas C, Bérubé M, Chevrier A, Pun BT, Ely EW, Skrobik Y, et al. Delirium assessment tools in adult critically ill: A psychometric analysis and systematic review. Crit Care Nurse. 2018;38(1):38-49. DOI: 10.4037/ccn2018633 PMID: 29437077
61. Egeland M, Zunszain PA, Pariante CM. Molecular mechanisms in the regulation of adult neurogenesis during stress. Nat Rev Neurosci. 2015;16(4):189-200. DOI: 10.1038/nrn3855 PMID: 25790864
62. Tipping CJ, Young PJ, Romero L, Saxena MK, Dulhunty J, Hodgson CL. A systematic review of measurements of physical function in critically ill adults. Crit Care Resusc. 2012;14(4):302-11. PMID: 23230880
63. Perpiñá-Galvañ J, Richart-Martínez M. Scales for evaluating self-perceived anxiety levels in patients admitted to intensive care units: a review. Am J Crit Care. 2009;18(6):571-80. DOI: 10.4037/ajcc2009682 PMID: 19880959
64. Treggiari MM, Romand JA, Yanez ND, Deem SA, Goldberg J, Hudson L, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med. 2009;37(9):2527-34. DOI: 10.1097/CCM.0b013e3181a5689f PMID: 19602975
65. Gabor JY, Cooper AB, Crombach SA, Lee B, Kadikar N, Bettger HE, et al. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. Am J Respir Crit Care Med. 2003;167(5):708-15. DOI: 10.1164/rccm.2201090 PMID: 12598213
66. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. Am J Respir Crit Care Med. 2001;163(2):451-7. DOI: 10.1164/ajrccm.163.2.9912128 PMID: 11179121
67. Elliott R, Rai T, McKinley S. Factors affecting sleep in the critically ill: an observational study. J Crit Care. 2014;29(5):859-63. DOI: 10.1016/j.jcrc.2014.05.015 PMID: 24973105
68. Trompeo AC, Vidi Y, Locane MD, Braghiroli A, Mascia L, Bosma K, et al. Sleep disturbances in the critically ill patients: role of delirium and sedative agents. Minerva Anestesiol. 2011;77(6):604-12. PMID: 21617624
69. Richards KC, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. J Nurs Meas. 2000;8(2):131-44. DOI: 10.1891/1061-3749.8.2.131 PMID: 11227580
70. Rivosecchi RM, Kane-Gill SL, Svec S, Campbell S, Smithburger PL. The implementation of a nonpharmacologic protocol to prevent intensive care delirium. J Crit Care. 2016;31(1):206-11. DOI: 10.1016/j.jcrc.2015.09.031 PMID: 26596509

71. Colombo R, Corona A, Praga F, Minari C, Giannotti C, Castelli A, et al. A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study. Minerva Anestesiol. 2012;78(9):1026-33. PMID: 22772860
72. Patel J, Baldwin J, Bunting P, Laha S. The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. Anaesthesia. 2014;69(6):540-9. DOI: 10.1111/anae.12638 PMID: 24813132
73. Nannapaneni S, Lee SJ, Kashiouris M, Elmer JL, Thakur LK. 2015;34(2):94-100. DOI: 10.1080/21548331.2015.1015389 PMID: 25687293
74. Alway A, Halm MA, Shilhanek M, St Pierre J. Do earplugs and eye masks affect sleep and delirium outcomes in the critically ill? Am J Crit Care. 2013;22(4):357-60. DOI: 10.4037/ajcc2013545 PMID: 23817826
75. Taguchi T, Yano M, Kido Y. Influence of bright light therapy on postoperative patients: a pilot study. Intensive Crit Care Nurs. 2007;23(5):289-97. DOI: 10.1016/j.iccn.2007.04.004 PMID: 17692522
76. Hoyer EH, Friedman M, Lavezza A, Wagner-Kosmakos K, Lewis-Cherry R, Skolnik JL, et al. Promoting mobility and reducing length of stay in hospitalized general medicine patients: A quality-improvement project. J Hosp Med. 2016;11(5):341-7. DOI: 10.1002/jhm.2546 PMID: 26849277
77. Thompson DR, Hamilton DK, Cadenhead CD, Swoboda SM, Schwindel SM, Anderson DC, et al. Guidelines for intensive care unit design. Crit Care Med. 2012;40(5):1586-600. DOI: 10.1097/CCM.0b013e3182413bb2 PMID: 22511137
78. Nydahl P, Sricharoenchai T, Chandra S, Kundt FS, Huang M, Fischill M, et al. Safety of patient mobilization and rehabilitation in the intensive care unit. Systematic review with meta-analysis. Ann Am Thorac Soc. 2017;14(5):766-77. DOI: 10.1513/AnnalsATS.201611-843SR PMID: 28231030
79. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911-22. DOI: 10.1016/S0140-6736(13)60688-1 PMID: 23992774
80. Bregar B, Možgan B. Posebni varovalni ukrepi – primerjava s tujino. In: Bregar B, Novak JP. Posebni varovalni ukrepi v teoriji in praksi. Ljubljana: Zbornica zdravstvene in babiške nege Slovenije; 2012. pp. 13-21.