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Review

Management of delirium in acute stroke patients: a position paper by the Austrian Stroke Society on prevention, diagnosis, and treatment

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Markus Kneihsl, Natalie Berger, Stefan Sumerauer, Susanne Asenbaum-Nan, Franz Stefan Höger, Thomas Gattringer, Christian Enzinger, Martin Aigner, Julia Ferrari* and Wilfried Lang*

***Abstract*:** Delirium is a common complication in acute stroke patients, occurring in 15–35% of all stroke unit admissions and is associated with prolonged hospital stay and a poor post-stroke prognosis. Managing delirium in acute stroke patients necessitates an intensive and multiprofessional therapeutic approach, placing a significant burden on healthcare staff. However, dedicated practical recommendations for delirium management developed for the population of acute stroke patients are lacking. For this purpose, the Austrian Stroke Society, in cooperation with the Austrian Society of Neurology, the Austrian Society of Neurorehabilitation, and the Austrian Society of Psychiatry, Psychotherapy, and Psychosomatics has formulated an evidence-based position paper addressing the management of delirium in acute stroke patients. The paper outlines practical recommendations on the three pillars of care in stroke patients with delirium: (a) Key aspects of delirium *prevention* including stroke-specific delirium risk factors and delirium prediction scores are described. Moreover, a non-pharmacological delirium prevention bundle is presented. (b) The paper provides recommendations on timing and frequency of delirium screening to ensure early *diagnosis* of delirium in acute stroke patients. Moreover, it reports on the use of different delirium screening tools in stroke populations. (c) An overview of non-pharmacological and pharmacological *treatment* strategies in patients with delirium and acute stroke is presented and summarized as key recommendation statements.

Keywords: acute stroke, delirium, intervention bundles, prevention, risk scores

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Correspondence to:
Markus Kneihsl
Department of Neurology, Medical University of Graz, Auenbruggerplatz 22, Graz A-8036, Austria

Division of Neuroradiology, Vascular and Interventional Radiology, Department of Radiology, Medical University of Graz, Graz, Austria
markus.kneihsl@medunigraz.at

Natalie Berger
Stefan Sumerauer
Christian Enzinger
Department of Neurology, Medical University of Graz, Graz, Austria

Susanne Asenbaum-Nan
Department of Neurology, General Hospital Amstetten, Amstetten, Austria

Franz Stefan Höger
Department of Neurology, LKH Graz II, Graz, Austria

Thomas Gattringer
Department of Neurology, Medical University of Graz, Graz, Austria

Division of Neuroradiology, Vascular and Interventional Radiology, Department of Radiology, Medical University of Graz, Graz, Austria

Martin Aigner
Department of Psychiatry and Psychotherapy, Karl Landsteiner University for Health and Science, Tulln, Austria

Julia Ferrari
Department of Neurology, Hospital Barmherzige Brüder Vienna, Vienna, Austria

Introduction and background

Delirium is a clinical syndrome characterized by acute disturbances in consciousness, attention, and cognition, typically exhibiting a fluctuating course.[1,2] It is a common complication in stroke, occurring in 15–35% of all stroke unit admissions, and is associated with a prolonged hospital stay, an increased rate of post-stroke disability, and mortality.[3–11] Moreover, managing delirium necessitates an intensive and multiprofessional therapeutic approach, placing a significant burden on healthcare staff.[10] Although guidelines for delirium management have been established for postoperative and intensive care unit (ICU) settings,[12] recommendations specifically developed for the population of acute stroke patients are scarce. This gap is notably disadvantageous, considering that prior studies have elucidated the limitations of extrapolating delirium screening and management strategies from non-stroke cohorts to stroke populations.[13]

For this purpose, the Austrian Stroke Society, in cooperation with the Austrian Society of

Wilfried Lang
Medical Faculty, Sigmund Freud University, Vienna, Austria
*Shared senior authorship

Neurology, the Austrian Society of Neurorehabilitation, and the Austrian Society of Psychiatry, Psychotherapy, and Psychosomatics has formulated an evidence-based position paper addressing the management of delirium in acute stroke patients. The paper aimed to provide a practical guidance for clinicians and a scientifically sound foundation on (a) prevention, (b) diagnosis, and (c) treatment of delirium in patients with acute stroke.

Methods

The key topics addressed in this position paper were developed by a core team comprising representatives from the Austria Stroke Society (JF and WL), the Austrian Society of Neurology (CE), the Austrian Society of Neurorehabilitation (MK), and the Austrian Society of Psychiatry, Psychotherapy, and Psychosomatics (MA).

To ensure the comprehensive coverage of the current knowledge on delirium in acute stroke patients, a literature search was conducted in February 2024 across two databases: PubMed/MEDLINE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry). The search utilized a combination of the following keywords: 'stroke', 'delirium', 'prevention', 'risk factors', 'prediction', 'non-pharmacological prevention', 'pharmacological prevention', 'screening', 'delirium subtypes', 'non-pharmacological interventions', 'pharmacological therapy'. Only publications in English and from peer-reviewed journals were considered.

The initial draft of the paper was formulated by a core team of authors (MK, NB, and SS), and recommendations were reconciled in several conferences. The position statement underwent further refinement during an inclusive process involving all authors, leading to a consensus on the core statements.

The evidence strength (class I–IV) and the rating of recommendation (level A–C) were assessed based on an evaluation of the underlying study data, following a system analogous to that proposed by Brainin *et al.*[14] If no evidence supporting levels A–C was available, we used 'good clinical practice points' (GCP) to recommend best practices, drawing upon the collective experience of the guideline development group.[14] All recommendations reflect a consensus within the author group.

Delirium prevention

Delirium is primarily triggered by multiple prodelirogenic factors, collectively defining the occurrence and extent of the syndrome.[4,7] Despite its complex pathophysiology, previous studies in non-stroke cohorts postulated that up to one-third of all delirium cases might be preventable through timely recognition and modification of established delirium risk factors.[15]

Pathophysiological aspects

Delirium is a typical syndrome of advanced age and can be explained by shifts in the neuroendocrine balance.[5] While various (systemic) processes contribute to these changes,[5,7] two neurotransmitters were identified to play a crucial role in the onset of delirium[16,17]:

(1) Acetylcholine: Numerous studies have established a correlation between reduced acetylcholine levels and the severity of delirium. Acetylcholine plays a crucial role in central nervous system processes associated with wakefulness, attention, sensory processing, learning, and memory.[18–20] Moreover, it is implicated in initiating rapid eye movement sleep and exerts influence over mood and behavior. The availability of acetylcholine diminishes with age, immobilization, and in dementia promoting delirium in these people.[18–20]
(2) Dopamine is involved in various neuronal processes: Beyond its role in reward and motor activity, dopamine plays a significant part in attention and working memory.[18] Elevated dopamine levels seem to be linked to hyperactive delirium symptoms, including agitation, distraction, and aggression.[18]

These aspects should be taken into consideration when initiating or adjusting the dosage of anticholinergic or dopaminergic drugs.[18–20]

The onset and severity of delirious states seem to be influenced not solely by acetylcholine and dopamine but also by additional neurotransmitters, such as serotonin, glutamate, and gamma-Aminobutyric acid (GABA).[21,22] Moreover, the

involvement of inflammatory markers, including interleukins and interferons, is noteworthy, as their influence on the blood–brain barrier may elucidate the well-established connection between infection and delirium.[21,23]

Delirium risk factors and prediction

The first studies on delirium risk factors in non-stroke cohorts were conducted in the 1990s.[15,24] Factors most commonly associated with delirium include advanced age, preexisting dementia, and infections. Disturbances in electrolyte and water balance (especially dehydration) and the severity of the acute illness were also strongly associated with delirium onset and severity.[7,15,24]

This is also reflected in studies on stroke patients, where, in addition to older age and preexisting cognitive impairment, the severity of stroke measured by the National Institutes of Health Stroke Scale was reported to be the most important non-modifiable risk factor for delirium.[11,25–28] Patients with the highest stroke-associated delirium risk were those with an intracranial hemorrhage, large infarct size, and involvement of the frontal cortex. Conversely, patients with small lacunar strokes were significantly less likely to exhibit delirious states.[26–31]

In stroke patients, infections were the most frequently identified modifiable risk factors for stroke-related delirium, underscoring the importance of prevention, early detection, and treatment of infections.[11,25,31] The duration of indwelling catheters, particularly urinary catheters, should be minimized, as suggested by recent data published by Fleischmann *et al.*[32]

The influence of premedication on the development of delirium appears to be less substantial than anticipated from a pathophysiological perspective.[9,25] Long-term medications that are well tolerated should not be abruptly discontinued or dose adjusted in the acute stroke setting, even if they possess potential prodelirogenic effects. Conversely, caution is recommended when initiating medications with delirogenic potential, particularly anticholinergics, L-Dopa/Dopamine agonists, and corticosteroids.[9,25] Table 1 shows an overview of delirium risk factors in stroke patients.

Delirium prediction models have been developed for early identification of stroke patients with a high risk for delirium and to identify stroke subgroups who would benefit from targeted delirium prevention strategies.[31] However, the investigation of these models in stroke research has been limited to date. Two studies, constrained by their design and the small cohort size, failed to provide significant conclusions.[31,33] Therefore, the internally validated model by Oldenbeuving *et al.*[34] provides the only valuable score for identifying stroke patients with a high delirium risk. This model, which incorporates the variables age, stroke severity, stroke location, and infections, exhibited robust discriminative performance in predicting subsequent delirious states in a general stroke population (area under the curve: 0.85; sensitivity: 76%; specificity: 81%). The score, however, is constrained by the small size of the delirium group ($n = 58$) and requires external validation in a larger cohort before it can be unequivocally recommended.[34]

Future studies investigating delirium prediction in stroke cohorts should explore previously neglected risk factors, such as chronic substance abuse (i.e. alcohol, nicotine, benzodiazepines), visual/hearing impairment, and the influence of urinary catheters and nasogastric tubes. Although current evidence does not support the use of a single biomarker for delirium prediction,[35] emphasis should be placed on inflammatory laboratory biomarkers (e.g. leukocytes, C-reactive protein, and interleukin-6) that have already been linked to the development of delirium.[22,32,35]

Another promising field is of machine learning models, which have already been demonstrated to generate accurate prediction models for delirium onset in non-stroke cohorts using automated algorithms.[36,37] Although these models are often constrained by missing external reproducibility and validation, such endeavors could be particularly advantageous in syndromes of complex multifactorial origin, such as delirium in acute stroke patients.

Recommendations

- Delirium risk factors should be evaluated in all acute stroke patients at admission (IV, GCP).
- The necessity for medical catheters (such as urinary catheters and nasogastric tubes) should be evaluated on a daily basis, and their duration should be minimized (IV, GCP).
- The initiation of corticosteroids, anticholinergic, and dopaminergic drugs is linked to an

Table 1. Overview of predictors for delirium in acute stroke patients.

Demographics	Strength of the association	Studies	Comments
Age	+++	Miu and Yeung[9] Oldenbeuving *et al.*[11] Gustafson *et al.*[25] Alvarez-Perez and Paiva[26] Fleischmann *et al.*[32]	# Delirium risk increases with age # Substantial risk increases after the age of 70 years (odds ratio >2)
Clinical risk factors			
Infarct location	++	Miu and Yeung[9] Oldenbeuving *et al.*[11] Alvarez-Perez and Paiva[26]	# Infarcts in the anterior circulation are associated with an increased risk of delirium. # Small lacunar brain infarcts are linked to a lower delirium risk. # Limited evidence supports an elevated delirium risk in right hemispheric strokes
Intracerebral hemorrhage	+++	Gustafson *et al.*[25] Alvarez-Perez and Paiva[26]	# Significant increase in the risk of delirious states in patients with intracerebral hemorrhage (odds ratio >3) # Intraventricular bleeding is most strongly correlated with delirium risk
Stroke severity and symptoms	++	Miu and Yeung[9] Oldenbeuving *et al.*[11]	# Increased delirium risk observed in moderate to severe stroke syndromes (NIHSS ⩾5 points) # Specific stroke symptoms (aphasia, neglect) are likely associated with higher delirium risk
Comorbidities			
Dementia/ mild cognitive impairment	+++	Oldenbeuving *et al.*[11] Gustafson *et al.*[25] Alvarez-Perez and Paiva[26]	# Significantly increased risk of delirium in individuals with known dementia (odds ratio >2) # Mild cognitive impairment is associated with a significantly elevated risk → Screening at admission is advisable
Previous delirium	++	Gustafson *et al.*[25]	# Possible underestimated risk factor, as mostly not included in previous studies
Atrial fibrillation/ cardiac disease	+	Kotfis *et al.*[8] Miu and Yeung[9] Gustafson *et al.*[25]	# Positive, albeit weak association # The underlying pathophysiological mechanisms remain largely unclear
Medication	+	Gustafson *et al.*[25]	# An overall low level of association is reported → Exercise caution when initiating anticholinergic and dopaminergic medications
Infections/fever	+++	Miu and Yeung[9] Oldenbeuving *et al.*[11] Alvarez-Perez and Paiva[25] Fleischmann *et al.*[32]	# Strong association with emerging delirium # Monitor early indicators, such as rising leukocytes or C-reactive protein levels
Catheters	++	Fleischmann *et al.*[32]	# Indwelling urinary catheters appear to elevate the risk of delirium
Previously unexplored factors with strong delirogenic potential in non-stroke cohorts		# Visual and/or auditory impairment[22] # Substance abuse[22] # Electrolyte imbalances[7,11] # Dehydration[11,24]	

NIHSS, National Institutes of Health Stroke Scale.

increased risk of delirium occurrence and should be avoided in acute stroke patients whenever possible (IV, GCP).

Non-pharmacological delirium prevention

Multimodal non-pharmacological prevention strategies have demonstrated positive effects to reduce delirium rates in hospitalized non-stroke cohorts in several randomized studies.[38] This evidence is corroborated by a Cochrane review, encompassing clinical investigations involving a total of 16,000 patients.[39] Intervention bundles included components such as early mobilization, monitoring of fluid and electrolyte balance, cognitive and sensory stimulation, and adjustment of environmental factors such as light and noise, or optimized sleep hygiene.[38–40] Within the Hospital Elder Life Program a systematically applied intervention bundle including the aforementioned factors resulted in a 30% reduction in delirium in geriatric patients aged ⩾70 years.[15] The current UK National Institute for Health and Care Excellence guideline provides an overview for delirium prevention and management in non-stroke patients and emphasizes the importance of interprofessional coordination among medical teams, nursing staff, and therapists in speech pathology, occupational therapy, and physiotherapy.[12,38,40] Notably, the cost-effectiveness of these programs has been investigated and confirmed.[41]

Within the specific population of acute stroke patients, only one small randomized controlled trial tested a multicomponent delirium prevention strategy. However, the very low number of delirium in both the treatment and the control group (three *versus* seven patients) does not allow to draw significant conclusions.[42] Based on the available literature, the present position paper provides a recommendation on non-pharmacological delirium prevention strategies.[38–43] These include recommendations on mobilization, body perception, family members, communication, orientation, sleep, pain, and medical catheters as outlined in Table 2.

Table 2. Overview of a non-pharmacological intervention bundle for preventing and treating delirium in acute stroke patients.[35–41,44–47]

Mobilization	# Conduct mobilization at least twice daily, adjusting intensity based on the underlying medical condition # Effective for delirium prevention and for reducing delirium severity
Body perception	# Early support for body perception in the stroke unit/neurological intensive care unit encompasses multidisciplinary care, involving nursing, occupational therapy, physiotherapy, and speech language therapy # The intervention is applied on a daily basis in tandem with cognitive stimulation
Family members	Might be involved in patient's therapy: # Offer orientation-promoting voice messages from relatives regarding the situation and the environment # Endorse frequent visits and adjusted visiting hours (caution: avoid overstimulation/restlessness)
Communication	# Reorienting communication by healthcare personnel # Use of communication boards in cases of artificial ventilation or aphasia # Endorse early involvement of speech therapists
Orientation	# Daylight, clear illumination # Provide artificial warm light during the night # Use of glasses and hearing aids (consider patient-owned aids upon admission) # Provide calendars/clocks and newspapers # Establish contact and trust through repeated questioning
Sleep	# Minimize ambient noise during nighttime (e.g. from monitors) # Implement a noise indicator system for employees # Limit nursing activities to essential tasks during nighttime # Avoid disruptions to the sleep–wake cycle # Provide sleep masks and earplugs
Pain	# Use repeated pain screenings # Provide multimodal therapy [including positioning, physiotherapy/occupational therapy, (neuro)psychology] if needed
Catheters/ restraints	# Use restraints only in case of self-endangerment or endangerment of others in accordance with legal requirements # Evaluate necessity of urinary catheters or nasogastric tubes daily

Recommendation

- Multimodal non-pharmacological prevention strategies (i.e. early mobilization, fluid/electrolyte balance, visual/hearing aids, sleep regulation, pain therapy, etc.) may be effective for delirium prevention in hospitalized stroke patients (III, C).

Pharmacological delirium prevention

Various studies have explored the efficacy of antipsychotic medications in preventing delirium. While specific data on stroke patients is lacking, a meta-analysis of data from 14 randomized controlled trials found no significant effect of haloperidol or second-generation antipsychotics in delirium prevention among hospitalized patients.[48] Similarly, there is insufficient evidence to recommend the routine use of melatonin for preventing delirium by influencing the sleep–wake cycle.[39,49] Nevertheless, a recent propensity score-matched analysis in a German acute stroke cohort showed a reduction of delirium rates in people who received melatonin.[50] The pharmacological regulation of circadian rhythms, particularly in intensive and intermediate care as well as stroke unit settings, therefore remains a promising area of delirium research. For details on pharmacological delirium treatment, see section "Pharmacological therapy".

Recommendation

- The use of antipsychotics for primary delirium prevention is not recommended in hospitalized patients (I, A).

Diagnosing delirium in stroke patients

Delirium screening

The timely detection of delirious states is crucial to avoid delays in the delirium-specific therapy. For this purpose, several delirium screening tools have been developed, each possessing distinct strengths and weaknesses.

The most widely used delirium screening tool is the confusion assessment method (CAM),[51] which conveys an improved version for critically ill patients (CAM-ICU).[52] Other frequently used tests include the Intensive Care Delirium Screening Checklist (ICDSC),[53] the 4 A's test (4AT),[54] the Nursing Delirium-Screening (Nu-DESC),[55] and the Delirium Observation Scale (DOS).[56] Meta-analyses in non-stroke cohorts have shown that CAM-ICU and ICDSC are effective screening tests for delirium in critically ill patients.[52,53]

However, there is limited research on delirium screening in acute stroke patients.[7,13,57,58] Typical signs and symptoms of the stroke event limit the clinical use of most of the aforementioned delirium risk scores in stroke patients, as these tools were not designed to be used in patients with neurological deficits/disorders. Therefore, a recent small study aimed to validate the 4AT in an Italian stroke cohort. Despite excluding patients with aphasia and severe cognitive impairment, this work presented a low specificity of 65% to identify delirium in the early phase after stroke when compared to the gold standard Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) diagnosis.[59] Another study validating the CAM-ICU and ICDSC tools in a central European population of neurointensive care and stroke unit patients again showed low sensitivities of 67% and 70%, respectively, underlining the fact that results from non-stroke cohorts cannot be translated to stroke patients in many occasions.[58]

The sole available work to date that has assessed delirium screening tools in an unselected stroke cohort was carried out by Fleischmann *et al.*[13] This study investigated the efficacy of the CAM, 4AT, and Nu-DESC, with CAM demonstrating superior accuracy in detecting delirium in stroke patients. CAM exhibited a sensitivity of 82% and specificity of 80% when compared to the gold standard DSM-V diagnostic criteria. In contrast, 4AT and Nu-DESC showed lower specificities of 74% and 66%, respectively.[11] Although CAM had the best performance, its sensitivity was notably lower compared to non-stroke cohorts.[4,11] This discrepancy may be attributed to the weakness of the model in identifying delirium in patients with severe stroke syndromes including impairments of lobar higher cortical brain functions, such as speech disorders or neglect.[4,11]

A stroke-specific delirium risk score might therefore be of high clinical importance, especially in the setting of severely affected patients. In this context, Reznik *et al.*[60] have recently developed a delirium risk score for specific use in acute stroke patients, namely the Fluctuating Mental Status Examination (FMSE). The screening tool can be nonverbally used and combines five binary items:

attention, orientation, consciousness, activity, and thought content. In a dedicated cohort of patients with acute intracerebral hemorrhage, the FMSE had an area under the curve of 0.82 for a delirium diagnosis (sensitivity 88%, specificity 83%) and might therefore represent a promising tool for delirium screening in acute stroke patients for the future.[60] However, FMSE needs external validation/replication in larger cohort as the pilot study was small, with only 40 patients.[60,61]

Given the limited available data on delirium screening instruments in acute stroke, it is currently not possible to make recommendations for a specific delirium screening test. Therefore, Table 3 aims to present a comprehensive overview of delirium screening instruments, highlighting their respective advantages and disadvantages for stroke patients.

A systematic delirium screening was endorsed for all acute stroke patients.[62–64] This was based on observations that the early detection of delirium followed by an optimized management was associated with a reduction of the delirium severity.[8,27]

Delirious states typically manifest within the first 72 h after stroke and the risk steadily decreases thereafter.[62,63] McManus *et al.*[62] identified 92% of all delirious states within 7 days of hospital admission in acute stroke patients. It is crucial to note that environmental changes, such as a transfer from the stroke unit to the rehabilitation unit or general wards, are known well to trigger delirium. We therefore recommend a continuous delirium screening for the first 5–7 days after admission (documented by every shift) and for 24–48 h after transfer to another ward.[61–64]

Recommendations

- The implementation of routine delirium screening (nursing staff and/or physicians) is recommended for all stroke patients (IV, GCP).
- The delirium screening should be conducted during the initial 5–7 days following hospital admission and within 24–48 h after transfer to another ward (IV, GCP).

Diagnostic criteria and delirium subtypes

The diagnosis of delirium can be made using either the DSM-V or the International Classification of Diseases, Tenth Revision (ICD-10) criteria.[1,2] A DSM-V-based delirium diagnosis must fulfill all the following criteria to diagnose delirium: (A) disturbance in attention and awareness, (B) disturbance develops acute and fluctuates over time, (C) disturbance in cognition, (D) Criteria A and C must not be explained by a preexisting disease/evolving neurocognitive disorder and must not occur in the context of a severely reduced level of arousal, and (E) there must not be any evidence that the disturbance is a direct physiological consequence of another medical condition.[1]

Compared to DSM-V, the diagnostic criteria of ICD-10 require the presence of at least one additional characteristic feature of a sleep–wake rhythm disorder (such as sleep disturbance, increasing symptoms at night, and/or hallucinations upon awakening).[2] Direct comparisons between ICD-10 and DSM classifications are limited,[44] largely because the vast majority of clinical studies utilize DSM-V for diagnostic assessments.[58–60] Consequently, DSM-V criteria are widely regarded as the gold standard for delirium assessment, and we also recommend their use to ensure optimal comparability in clinical and study settings.

Delirium can further be subclassified according to the impairment of psychomotor activity[1,2,45,46]:

(a) Hyperactive delirium: Hyperactive delirium, which represents a third of all delirious states, is the most easily identified subtype. It manifests with increased motor activity, restlessness, and agitation progressing to aggression. Without prompt intervention, it can escalate to psychosis, endangering self and others.[45,46] Vegetative symptoms like sweating and a gradual rise in blood pressure may signal its onset, especially in the vulnerable phase of stroke. Timely monitoring is crucial to prevent complications and ensure swift diagnosis and therapy.
(b) Hypoactive delirium: The diagnosis of the hypoactive delirium subtype (50% of all deliriums) can be difficult as typical symptoms including reduced motor activity and apathy are easily overlooked in stroke patients.[46,47,65] This also explains the lower sensitivity of previously described delirium screening tests in stroke cohorts supporting the need for stroke-specific screening tools. In this context, electroencephalography

Table 3. Overview of various delirium screening tools.

Tool	Items	Characteristics	Content	Pros and cons
CAM score[51]	Short version: 5 Long version: 9	Assessment: <5 min	Acute onset, attention deficits, disorganized thinking, fluctuating vigilance, orientation impairment, memory issues, perceptual disturbances, psychomotor agitation, psychomotor slowing, disrupted sleep–wake cycle	+ Most robust evidence of all presented tools to diagnose delirium in acute stroke – Requires orientation and additional cognitive testing for valid results – Binary outcomes diminish the value of longitudinal assessments – Unsuitable for patients with aphasia
CAM-ICU[52]	4	Assessment: 2 min (only for ICU setting)	Acute onset, attention deficits, disorganized thinking, fluctuating vigilance	+ Optimized for the ICU setting – Unsuitable for aphasic patients – Mandatory training phase
DOS[56]	13	Documentation: 1 min (individual observation period, typically one shift)	Wakefulness, attention, thinking, psychomotor disturbances, orientation, memory, agitation, perceptual disturbances	+ Simple criteria, no training required + Feasible in patients with aphasia/ neglect – Low sensitivity for hypoactive delirium – Positive screening should prompt the use of a more specific scale/ evaluation
ICDSC[53]	8	Documentation: 1 min (individual observation period)	Altered consciousness, attention deficits, orientation impairment, hallucinations, agitation/slowness, inappropriate speech/mood, sleep disturbance, fluctuating symptoms	+ Optimized for ICU setting + Suitable for aphasic patients – Relatively low sensitivity – Requires a training phase
Nu-DESC[55]	5	Documentation <2 min (individual observation period)	Orientation, behavior, communication, hallucinations, psychomotor slowing	+ Designed for nursing staff + Short documentation time – Attention disorder is not assessed
4AT[54]	4	Documentation <2 min (individual observation period)	Wakefulness, orientation, attention, fluctuating symptoms	+ Simple, no elaborate training required + Patients with aphasia are assessable – Moderate specificity in stroke cohorts
FMSE[60]	5	Documentation 1 min (individual observation period, typically one shift)	Consciousness, orientation, activity, thought content, and attention	+ Developed for stroke populations + Easy and fast documentation – Only data from a small pilot study available – No external validation

4AT, 4 A's test; CAM, confusion assessment method; CAM-ICU, confusion assessment method-intensive care unit; DOS, Delirium Observation Scale; FMSE, Fluctuating Mental Status Examination; ICDSC, Intensive Care Delirium Screening Checklist; Nu-DESC, Nursing Delirium Screening Scale.

(EEG) holds the potential to aid in diagnosing delirium in clinically complex scenarios. While a normal EEG suggests a low likelihood of delirium, additional research is warranted to elucidate typical EEG findings indicative of specific delirium subtypes.[66] Hypoactive delirium is associated with a worse prognosis, which might be attributed to delays in diagnosis and treatment.[46]

If hypo- and hyperactive delirious phases alternate, a diagnosis of mixed delirium may be established.[45]

Recommendation

- To enhance comparability with previous studies, we recommend to diagnose delirium in stroke patients based on the criteria of the DSM-V classification (IV, GCP).

Delirium treatment

The treatment of delirious states consists of (a) addressing modifiable individual risk factors, (b) improving non-pharmacological interventions and, in case of imminent risk to the patient and/or personnel, (c) initiating specific pharmacological therapy.

Non-pharmacological interventions

Non-pharmacological multicomponent interventions have been utilized in non-stroke cohorts to treat ongoing delirium, leading to a substantial reduction in both the duration and severity of delirious states.[67–70] In the intensive care setting, early mobilization has been specifically linked to a decreased duration of delirium. However, effect sizes were smaller in comparison to preventive non-pharmacological intervention bundles.[71]

In stroke populations, a sole prospective study has investigated the impact of non-pharmacological interventions in a central European cohort: Nydahl *et al.*[72] applied a bundle of interventions, addressing metabolic disturbances, early infection treatment, mobilization, sleep optimization, noise adaptation, and avoiding prodelirious medication. While the main results showed a trend toward a lower Nu-DESC score in the intervention group (Nu-DESC median postintervention: 3.0 *versus* Nu-DESC median preintervention: 3.5), there was no effect on the disability or mortality after stroke.[72] However, the results must be interpreted cautiously, as the study was largely limited by a small sample size.[72] Similar intervention bundles should be specifically investigated in the population of acute stroke patients, offering a promising possibility for reducing delirium rates and severity after stroke (Table 2). While most non-pharmacological interventions have not been associated with negative side effects, early mobilization within the first 24h after stroke, as observed in the A Very Early Rehabilitation Trial after stroke (AVERT) trial, was linked to increased dependency and mortality.[73] Therefore, mobilization should always be based on a balanced benefit–risk analysis in the early phase after a stroke.

The use of force to exert an action contrary to an individual's desires, or the limitation of an individual's freedom of movement, regardless of the individual's resistance, is defined as physical restraint.[74] It should be exclusively used in patients with endangerment of their selves or the treating personnel and must be always in line with legal requirements. In previous studies, physical restraint has been positively correlated with delirium severity especially in the early stages of delirium, and should be strictly avoided whenever possible.[74,75]

Recommendation

- Non-pharmacological intervention bundles are associated with a reduction in the duration and severity of delirium and are recommended for stroke patients (IV, GCP).

Pharmacological therapy

The utilization of pharmacological therapies, including sedative and antipsychotic medication, is a common approach for managing patients with delirium (Table 4). However, the supporting evidence for their efficacy is limited.[76] It was hypothesized that the fluctuating nature of delirium poses challenges in objectively assessing the treatment effect of pharmacological therapies and could have explained negative study results.[77]

Despite these challenges, a general lack of significant effects of pharmacological therapy on the duration and severity of delirium suggests an overestimation of the impact of medication on delirium treatment.[76] Only two substances have evidence from placebo-controlled trials.[78,79]

Alpha-2 agonists. Dexmedetomidine and clonidine are frequently used sedative drugs in daily clinical routine.[76,77] While evidence supporting the use of clonidine in patients with delirium is limited,[77] a beneficial effect of dexmedetomidine on the severity and progression of delirium in critically ill patients has been documented in multiple studies. Dexmedetomidine exhibited superior effectiveness and safety when compared to haloperidol in a cohort of non-intubated patients experiencing delirium in the ICU.[79] Subsequently, a Cochrane review by Burry *et al.*[80] in 2018 supported these findings, linking the use of dexmedetomidine to a reduced duration of delirium.

Of importance, the use of dexmedetomidine is confined to intensive care or intermediate care units, primarily due to its pharmacodynamics and the requirement for intravenous continuous infusion.[76,77,79] Furthermore, it is important to note that higher doses of dexmedetomidine in adults under 65 years of age have been linked to increased mortality.[81] This should be taken into consideration when treating patients in this age group. Despite its common clinical usage, no data on the efficacy of dexmedetomidine in stroke patients are currently available.

Antipsychotics. Antipsychotics have been extensively studied for their effectiveness in delirium,[48,77] with only one study showing a positive effect.[78] In this small placebo-controlled trial ($n = 36$), Devlin *et al.* identified a reduction in median delirium duration (36 *versus* 120 h) and a higher chance to discharge patients to further rehabilitation (89% *versus* 56%) in the quetiapine group. No influence on mortality or duration of ICU stay could be demonstrated.[78] However, larger trials could not confirm a positive treatment effect to date, and there is no data available in acute stroke populations.[48,77]

Therefore, the available evidence does not support routine use of antipsychotics in all patients with delirium, a position also reflected in 'Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU'.[82] However, in cases of imminent danger to patients or treating personnel, which predominantly occurs in hyperactive or mixed delirium subtypes, antipsychotic medication may be applied.[78] As previous studies included high numbers of patients with hypoactive delirium, which could have possibly offset positive effects,[48,76,77] future studies are crucial regarding the effect of antipsychotic substances, especially in (stroke) cohorts with hyperactive or mixed delirium.[77]

Benzodiazepines. Benzodiazepines play a subordinate role in delirium treatment. There is no evidence for a therapeutically positive effect on delirium severity and course. Especially in older/geriatric stroke patients, benzodiazepines should not be used due to their high potential for side effects.[83,84]

The only exception is the specific entity of delirium due to alcohol withdrawal ('delirium tremens'): A recently published community-based pooled cohort of more than 100,000 European adults revealed that every eighth person exhibits a daily alcohol consumption with the potential for dependence.[85] Therefore, the medical history of alcohol consumption should be assessed at every admission of a stroke patient to identify risk factors for delirium tremens.[86] If typical symptoms are present, benzodiazepines are the first-line medication in such patients. In addition, all patients with suspected increased alcohol consumption should receive thiamine (Vitamin B1) substitution for 3–5 days to prevent Wernicke encephalopathy and Korsakoff syndrome.[86]

In recent years, research has explored the potential of various drugs across different classes for preventing and treating delirium. However, studies on melatonin, antiepileptics such as valproic acid, or thiamine have failed to provide sufficient data justifying their widespread use.[77,87]

Practical guidance for pharmacological management of delirium

As a first step, the patient's medication should be reviewed to identify any newly introduced drugs or potential interactions, especially in cases of polypharmacy with a potential prodelirogenic effect. For instance, the initiation of substances such as anticholinergic and dopaminergic agents, as well as corticosteroids, should be avoided.[9,25] In this context, consultation with a geriatrician may be beneficial.

While there is currently neither evidence nor expert recommendations for pharmacological treatment in patients with hypoactive delirium,[48] in cases of hyperactive/mixed subtype with probable self-endangerment, endangerment of others, or vegetative symptoms, the initiation of sedative and antipsychotic therapy is advisable. This initiation should adhere to the principle of 'start low, go slow'.[76,77]

Orally administered antipsychotics for delirium treatment include Quetiapine, Risperidone, and Melperone.[77,88] The decision on which of these medications to use should be based on delirium symptoms and comorbidities. Melperone

Table 4. Pharmacological therapies for the treatment of delirium.[69–83]

Antipsychotics	Sedative effect	Antipsychotic effect	Extrapyramidal motor side effect	Anticholinergic effect	Comments
Melperone	++(+)	(+)	++	(+)	# Good tolerability # Beneficial for geriatric patients # Low antipsychotic effect
Quetiapine	++	+(+)	–	+(+)	# Preferred treatment in patients with Parkinson's disease # Combination with Risperidone in case of insufficient antipsychotic effect
Risperidone	(+)	+++	+	(+)	# Preferred treatment for prominent psychotic symptoms # Minimal to no sedation
Haloperidol	+	+++	+++	+	# Second-line agent # Use only in the presence of predominant psychotic symptoms **Caution:** extrapyramidal motor side effects; significant QTc prolongation
Benzodiazepines	+++	–	–	(+)	# Avoid in geriatric patients # Use in alcohol withdrawal delirium or an alcohol-induced delirium
Alpha-2 receptor agonists					
Dexmedetomidine	+++	(+)	–	–	# Use restricted to monitored patients # Continuous infusion required # Contraindicated in second- or third-degree atrioventricular block
Clonidine	+++	(+)	–	–	# Different administration forms available (intravenous, oral) # Contraindicated in second- or third-degree atrioventricular block

QTc = corrected QT interval.

combines a good sedative effect with excellent tolerability and negligible cardiovascular and anticholinergic effects, making it particularly suitable for predominant symptoms of restlessness, agitation, and vegetative symptoms.[72] In cases of psychotic symptoms including hallucination or delusion, a medication with a stronger antipsychotic effect is preferable with Risperidone showing the strongest effect.[65] Since Risperidone lacks sedation, combining it with Melperone or alternatively with Quetiapine could be useful.[77] In cases of severe psychotic conditions, Haloperidol, with its strong Dopamine D2 receptor binding, may be an alternative. However, due to its potential for severe extrapyramidal side effects and association with cardiac conduction disorders, Haloperidol should be used only as a second-line medication.[77,89] In patients with Parkinson's syndrome, Quetiapine is the preferred choice due to its minimal extrapyramidal side effects. It is important to note the QTc-prolonging effect of these medications (Haloperidol ≫ atypical antipsychotics), and hence, ECG assessment is recommended before initiation and regularly during the course of treatment.[89]

For individuals experiencing severe delirium, continuous monitoring is imperative. The administration of intravenous substances, specifically alpha-2 agonists, under controlled monitoring is the most effective treatment option.[76] In cases of chronic substance abuse, it is advisable to avoid

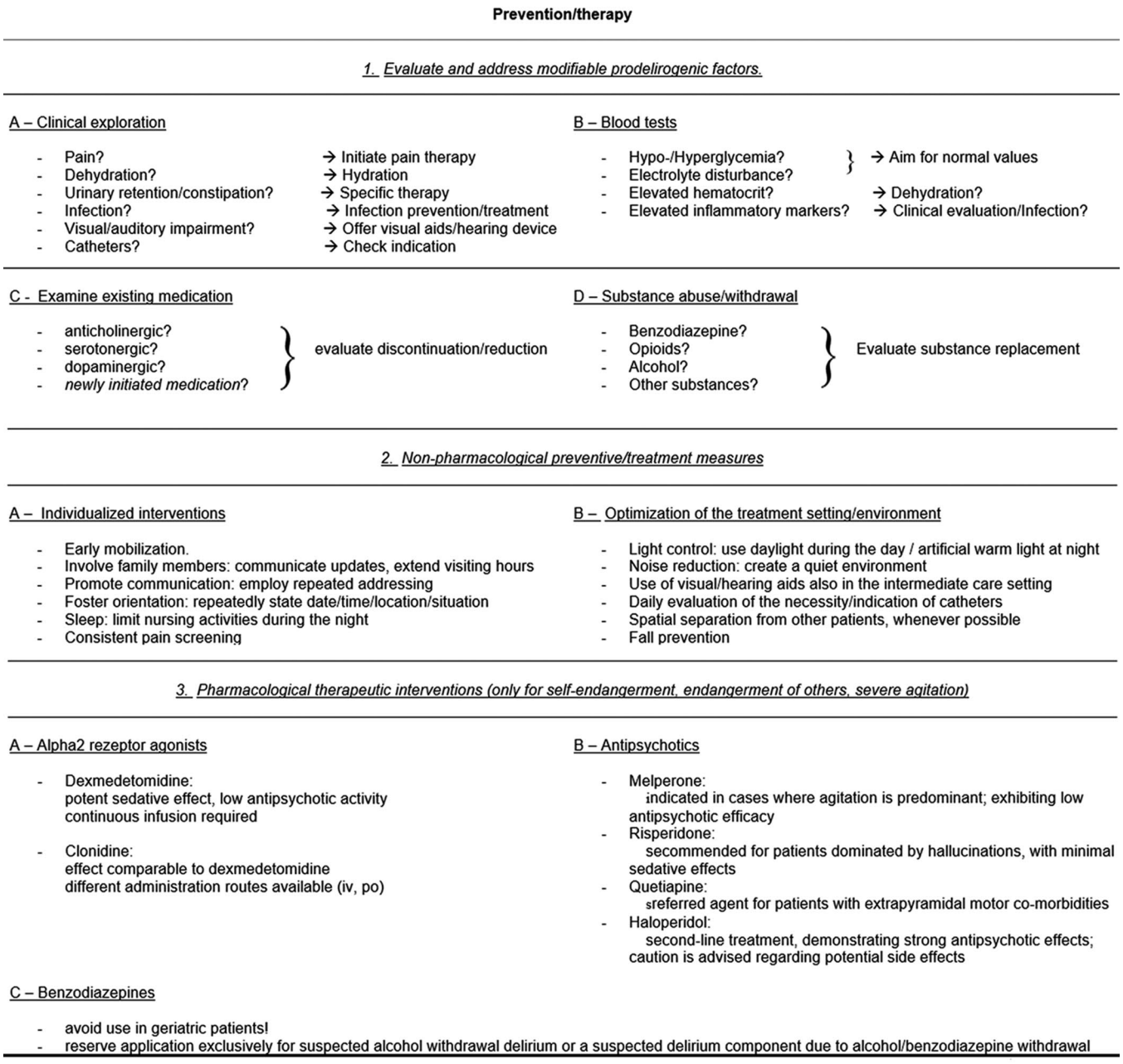

Figure 1. Delirium in acute ischemic stroke patients – a proposed prevention and treatment pathway.

abrupt discontinuation of the substance or provide a suitable substitute.

The data obtained from ICU patients indicate that approximately one in five patients diagnosed with delirium is discharged with specific antipsychotic drugs prescribed.[90,91] It is imperative that medications tailored for delirium management are consistently monitored throughout the hospitalization period and gradually tapered at the earliest opportunity.[90] Furthermore, in cases where a patient is discharged with such medication, it is advisable to undergo reassessment by a psychiatrist or geriatrician.

Figure 1 presents a proposed prevention and treatment pathway in patients with delirium and acute stroke.

Recommendations

- Pharmacological treatment should be considered only in patients exhibiting delirium with probable self-endangerment, endangerment of others, or vegetative/psychotic symptoms (IV, GCP).
- The use of alpha-2 agonists, particularly dexmedetomidine, is recommended for stroke patients with delirium under monitoring conditions (II, B).
- The utilization of (atypical) antipsychotics may be considered in patients with delirium of the hyperactive or mixed type (IV, GCP).
- The use of benzodiazepines is generally not recommended in geriatric patients. Exception: In cases of (presumed) alcohol or benzodiazepine withdrawal, benzodiazepines constitute the preferred therapeutic approach (II, B).

Prognosis and rehabilitation

There is substantial evidence regarding the adverse effects of delirium on the prognosis of patients following a stroke.[5–9] Although delirium is generally considered a transient condition, studies have demonstrated that stroke patients with delirium have an increased risk of deterioration in functional outcomes (according to the Modified Rankin Scale) not only at discharge but also at 90 days and 1 year after stroke.[5–9] Particularly in the early phase after stroke, delirium is associated with increased mortality with a more than 30% higher likelihood of death during hospitalization in an American stroke population.[5] The delirium cohort also exhibited higher rates of additional complications such as pneumonia during the hospital stay, leading to extended hospitalizations by an average of 5–9 days. Recent research further indicated a significantly elevated 5-year mortality risk for stroke patients with delirium in the acute phase (3.3-fold increased risk).[6,8,9]

It is noteworthy that cognitive impairment following a stroke is more prolonged in patients who initially presented with delirium. A study found a more than twofold increased likelihood of cognitive impairment 1-year post-stroke when delirium was present.[6] Whether cognitive dysfunction after delirium is a consequence of persistent central nervous system damage or delirium-related reduced/ineffective neurorehabilitation during the crucial early phase of neuronal regeneration is currently unclear and warrants further investigations.

Nevertheless, rehabilitative therapies should be continued in patients with (at least mild-moderate) delirious states whenever possible. Positive effects on delirium have been demonstrated, not only for physical activity but also for cognitive stimulation.[9] In this context, additional neuropsychological/psychiatric care might be beneficial as persistent neuropsychiatric symptoms, particularly anxiety is frequently observed in the long term (>3 months) following an acute delirium in stroke patients.[92]

Conclusion

Delirium in acute stroke patients is a complex syndrome that requires an optimized multiprofessional management to reduce the negative impact on outcome. Three factors appear to be crucial for optimal care (Figure 2).

Prevention

Delirium risk factors and comorbidities should be evaluated and – if modifiable – treated upon admission in all stroke patients. Clinical risk scores could assist clinicians in identifying patients at high risk of delirium and in developing individual prevention regimens.

Early diagnosis

Routine delirium screening is strongly recommended during the initial 5–7 days following hospital admission and an additional 24–48 h after transfer to another ward for all stroke patients. Given the absence of validated stroke-specific delirium screening tools, local teams are advised to select one from various established instruments used in non-stroke cohorts, based on their preferences. In severely affected patients, stroke-specific delirium screening tools might have the potential to enhance delirium diagnosis in the future.

Multiprofessional treatment

Delirium therapy involves a complex interplay of physicians, nurses, and therapists. Non-pharmacological intervention bundles have been demonstrated to be highly effective in prevention and treatment of delirious states in non-stroke cohorts. The development of standardized

Recommendations - Summary	
	Evidence classification according to EFNS criteria Evidence class (I-IV), rating of recommendation (A-C; general best practice point, GCP)*
Delirium Prevention	
Delirium risk factors should be evaluated in all acute stroke patients at admission.	IV, GCP
Multimodal non-pharmacological prevention strategies (including early mobilization, fluid/electrolyte balance, etc.) may be effective for delirium prevention in hospitalized stroke patients.	III, C
The indication for installations (e.g., urinary catheters) must be assessed daily, and the duration of their retention should be minimized whenever possible.	IV, GCP
The initiation of anticholinergic and dopaminergic agents, as well as the administration of corticosteroids, is associated with an increased risk of delirium occurrence. This should be considered in the benefit-risk assessment prior to initiating these medications.	IV, GCP
The use of antipsychotics for primary delirium prevention is not recommended in hospitalized patients.	I, A
Diagnosis of Delirium	
To enhance comparability with previous studies, we recommend to diagnose delirium in stroke patients based on the criteria of the DSM-V classification.	IV, GCP
The implementation of routine delirium screening (nursing staff or physicians; e.g., using the Delirium Observation Screening tool) is recommended for all stroke patients.	IV, GCP
The delirium screening should be conducted during the initial 5-7 days following hospital admission and within 24-48 hours after transfer to another ward.	IV, GCP
Delirium therapy	
Non-pharmacological intervention bundles are associated with a reduction in the duration and severity of delirium and are recommended for stroke patients.	IV, GCP
Pharmacological treatment should be considered only in patients exhibiting delirium with probable self-endangerment, endangerment of others, or vegetative symptoms.	IV, GCP
The use of alpha-2 agonists, particularly dexmedetomidine, is recommended for stroke patients with delirium under monitoring conditions.	II, B
The utilization of (atypical) antipsychotics may be considered in patients with delirium of the hyperactive or mixed type.	IV; GCP
The use of benzodiazepines is generally not recommended in geriatric patients. Exception: In cases of (presumed) alcohol or benzodiazepine withdrawal, benzodiazepines constitute the preferred therapeutic approach.	II, B
*Brainin M et al., Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol 2004; 11(9):577–81	

Figure 2. Summary of evidence-based recommendations on prevention, diagnosis, and treatment of patients with delirium and acute ischemic stroke.

intervention concepts for the specific population of stroke patients is highly warranted to reduce the burden of delirium on patients and healthcare staff.

Declarations

Ethics approval and consent to participate

The position paper involved the analysis of previously published and publicly available literature, and no direct involvement with human subjects or sensitive data occurred. Therefore, the study is considered exempt from ethical review.

Consent for publication

Not applicable.

Author contributions

Markus Kneihsl: Conceptualization; Methodology; Writing – original draft.

Natalie Berger: Conceptualization; Writing – original draft.

Stefan Sumerauer: Conceptualization; Writing – original draft.

Susanne Asenbaum-Nan: Conceptualization; Writing – review & editing.

Franz Stefan Höger: Conceptualization; Writing – review & editing.

Thomas Gattringer: Conceptualization; Writing – review & editing.

Christian Enzinger: Conceptualization; Writing – review & editing.

Martin Aigner: Conceptualization; Writing – review & editing.

Julia Ferrari: Conceptualization; Writing – review & editing.

Wilfried Lang: Conceptualization; Writing – review & editing.

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ORCID iDs

Markus Kneihsl https://orcid.org/0000-0002-6334-9432

Thomas Gattringer https://orcid.org/0000-0002-6065-6576

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Appendix

Abbreviations

4AT	4 A's test
CAM	confusion assessment method
DOS	Delirium Observation Scale
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEG	electroencephalography
FMSE	Fluctuating Mental Status Examination
GCP	good clinical practice points
ICDSC	Intensive Care Delirium Screening Checklist
ICD-10	International Classification of Diseases, Tenth Revision
ICU	intensive care unit
NIHSS	National Institutes of Health Stroke Scale
Nu-DESC	nursing delirium-screening