Review Article

Acute Confusional States in Hospital

Norbert Zoremba, Mark Coburn

Summary

Background: Acute confusional state (delirium) is an acute disturbance of brain function. The incidence of such states varies according to the group of patients concerned: it ranges from 30% to 80% among patients in intensive care and from 5.1% to 52.2% among surgical patients, depending on the type of procedure. The earlier German term “Durchgangssyndrom” (usually rendered as “transitory psychotic syndrome”) tended to imply a self-limited and thus relatively harmless condition. In fact, however, delirium is associated with longer hospital stays, poorer treatment outcomes, and higher mortality. Approximately 25% of patients who have experienced an acute confusional state have residual cognitive deficits thereafter.

Methods: This review is based on publications retrieved by a selective search in MEDLINE, PubMed, the Cochrane Library, and in the International Standard Randomised Controlled Trial Number (ISRCTN) registry.

Results: Validated instruments are available for the reliable diagnosis of an acute confusional state, e.g., the Confusion Assessment Method for the ICU (CAM-ICU) for patients in intensive care and the 3D-CAM or CAM-S for patients on regular hospital wards. The prevention and treatment of this condition are achieved primarily by a nonpharmacological, multidimensional approach including early mobilization, reorientation, improvement of sleep, adequate pain relief, and the avoidance of polypharmacy. A meta-analysis has shown that these measures lower the incidence of delirium by 44%. The authors find no basis in the current literature for recommending prophylactic medication, although current data promisingly suggest that the incidence of delirium in surgical patients can be lowered by the perioperative administration of dexmedetomidine (odds ratio 0.35). The pharmacotherapy of acute confusional states involves a careful choice of drug based on the clinical manifestations in the individual case.

Conclusion: The key elements of success in the treatment of acute confusional states in the hospital are adequate prevention, rapid diagnosis, the identification of precipitating factors, and the rapid initiation of both causally oriented and symptom-directed treatment.

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Acute confusional state, also referred to as delirium, is an acute impairment of brain function. Its multifactorial etiology is not yet fully understood. The incidence of delirium varies depending on the patient collective investigated. Whereas a third of internal medicine patients over the age of 70 years develop delirium in hospital, the incidence among surgical patients depends on the intervention performed and is put at between 5.1% following small interventions and 52.2% following larger surgical interventions (e.g., aortic surgery). Delirium occurs in 30%–80% of intensive care patients depending on disease severity (1, 2).

Delirium during a hospital stay is prognostically relevant. In medical parlance, delirium has long been referred to as a “transitory psychotic syndrome.” This created the impression that this form of cerebral dysfunction was temporary and resolved without sequelae. However, delirium is associated with an increase in mortality from 3.9% to 22.9%, hospital stays prolonged by up to 10 days, and worse treatment outcomes (3, 4). Not only the occurrence of delirium but also its duration is prognostically significant for the patient.

An investigation in intensive care patients showed that the 1-year survival probability went down by approximately 10% per day of delirium (5). In addition, both the severity and the duration of delirium affect cognitive performance. Delirium results in greater post-inpatient care requirements, while impaired cognitive function comparable to mild Alzheimer’s disease affects approximately 25% of patients following delirium (6, 7).

There is no doubt that delirium is a medical emergency that needs to be either prevented or diagnosed and treated promptly. The German Joint Federal Committee (*Gemeinsamer Bundesausschuss*, G-BA) has included the “prevention of postoperative delirium in elderly patients” as one of its four service areas to test quality contracts (www.g-ba.de/informationen/beschluesse/2960/).

Methods

A selective literature search was conducted in MEDLINE, PubMed, the Cochrane Library, and the International Standard Randomised Controlled Trial Number (ISRCTN) registry. Search terms are listed in the *eBox*.

Diagnosis of delirium

Prompt diagnosis of delirium is challenging, since the clinical picture and symptoms vary considerably. The

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FIGURE

Possible forms of delirium and clinical treatment outcomes. Delirium is caused by a combination of predisposition and exposure to delirogenic factors. The full clinical picture of delirium can be classified into five possible forms. The main forms include hyperactive, hypoactive, and mixed delirium. The catatonic variant is an extreme form of hypoactive delirium and the excited variant is an extreme form of hyperactive delirium. Delirium ends either in fully restored or in impaired cognitive function (modified from [8, 11, 12]).

TABLE 1

Validated test methods to detect delirium*

Diagnosis of delirium	
CAM-ICU	Assessment of attention, consciousness, and cognitive disorders using test questions
ICDSC	Assessment of consciousness, attention, orientation, hallucinations, agitation, speech, sleep, and symptoms (1 = present, 0 = absent); assessment based on total score
Nu-DESC	Assessment of orientation, behavior, communication, hallucinations, and psychomotor retardation (score of 0–2 based on severity); assessment based on total score
3D-CAM	Assessment of attention, consciousness, and cognitive disorders using test questions
CAM-S	Assessment of course of the disorder, attention, cognition, consciousness, orientation, memory, psychomotor agitation, retardation, and sleep using tests; severity determination (0–2). Assessment based on total score.

*These include: Confusion Assessment Method for the ICU (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), Nursing Delirium Screening Scale (Nu-DESC), 3-Minute Diagnostic Interview for CAM-defined delirium (3D-CAM), and Confusion Assessment Method Severity (CAM-S) (13–16).

main symptom of delirium in the current Diagnostic and Statistic Manual of Mental Disorders (DSM-5) is impaired awareness and attention, which can be accompanied by a disturbance in cognition. The disorder is one of acute onset and follows a fluctuating course. When diagnosing delirium, it is essential to establish that the disorder is not due to other neurocognitive causes (e.g., dementia) and that it cannot be explained by the pathophysiological effects of a physical disease. Delirium is highly variable in terms of incidence and clinical picture; therefore, it appears to develop as a result of a combination of increased vulnerability (pre-

disposition) and simultaneous exposure to delirogenic factors (8).

A distinction is made between three phenotypes depending on the clinical picture (9, 10):

- Hypoactive delirium (30%)
- Hyperactive delirium (5%)
- Mixed delirium (65%).

In addition to this distinction, the catatonic variant can be defined as an extreme form of hypoactive delirium and the excited variant as an extreme form of hyperactive delirium (11). A cohort study found that cognitive function was fully restored in 19% at 3 months following delirium, while reduced cognitive performance was observed in 52% (Figure) (12). Hyperactive delirium can be rapidly diagnosed in clinical practice on the basis of symptoms. Hypoactive delirium and mixed delirium, on the other hand, are far more challenging to identify. Therefore, defined tests are the only method of detection in clinical practice, particularly in the case of hypoactive delirium.

Despite a number of potential approaches, instrumental or laboratory diagnostic methods are not reliably feasible and are currently the subject of research (e.g., BioCog). The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are two of the validated delirium screening tools for the intensive care unit. All test methods mentioned here are available in German and can be used free of charge.

The CAM-ICU is the most reliable score for detecting delirium in intensive care patients. It has a sensitivity of 0.79 and a specificity of 0.97 (13). The ICDSC, with its high sensitivity of 0.99 and specificity of 0.64, represents a possible alternative to the CAM-ICU in intensive care patients (13). The ICDSC takes only a few minutes to perform, is suitable for ventilated intensive care patients, and enables the identification of subsyndromal delirium (14).

In addition to the Nursing Delirium Screening Scale (Nu-DESC), the 3D-CAM is a validated measurement tool for the general medical unit, with a sensitivity of 0.95 and a specificity of 0.94 (15). The CAM-S represents a more recent test method, which, compared to the 3D-CAM and CAM-ICU, is additionally able to determine delirium severity (Table 1) (16).

To date, unfortunately, close delirium screening has not been performed to a sufficient extent in European hospitals and intensive care units. Luetz et al. were able to show that a validated method of delirium detection was used in only 27% of patients on intensive care units (17). What is more, the clinically unremarkable course of hypoactive delirium is associated with a higher mortality rate compared to hyperactive delirium (33% versus 15%) (18). The S3 guideline on analgesia, sedation, and delirium management in intensive care medicine recommends performing delirium screening at least every 8 h on the intensive care unit (1).

Due to the close interaction between delirium, agitation, and pain, these domains should be additionally determined using a validated screening instrument, e.g., the numeric rating scale (NRS) or the Richmond Agitation–Sedation Scale (RASS). The time investment required for this is comparatively modest, totaling approximately 5 min. Likewise, delirium screening, pain determination, and agitation measurement should be performed in the same manner in non-intensive care patients.

It has become apparent in clinical practice in recent years that screening on the intensive care unit has increased significantly. However, delirium screening on peripheral units still requires considerable improvement.

Delirium prevention strategies

Multiple factors can have an impact on the occurrence and severity of delirium and, as such, should be taken into account in the context of delirium prevention (19). As early on as 1999, Inouye et al. provided early evidence in their controlled non-randomized study that non-pharmacological, multidimensional delirium prevention was able to significantly reduce delirium rates (20). These multidimensional prevention strategies include (*Box 1*):

- Early mobilization
- Reorientation
- Optimized fluid and nutritional intake
- Sleep improvement
- Adequate pain management
- Avoidance of polypharmacy.

According to a meta-analysis, this approach can reduce the incidence of delirium by 44% (odds ratio [OR]: 0.56; 95% confidence interval [CI]: [0.42; 0.76]) (21). This multidimensional prevention strategy is also effective in postoperative patients and reduced the rate of delirium from 20.8% [11.3; 32.1] to 4.9% [0.0; 11.5] (22). Adequate pain treatment (“analgesia first”) is absolutely crucial to the implementation of this multicomponent treatment. Freedom from pain is an essential treatment component in the eCASH concept, since only then can one initiate the various preventive measures. As part of this, stimulation measures should be performed during the day and sleep-promoting measures at night (23). The avoidance of excessive sedation (RASS < −1) in intensive care medicine is also a crucial factor in the prevention of delirium (1).

Reorientation

For most patients, a stay in hospital is a considerable disruption to their normal way of life. They find themselves in a strange environment, which can result in markedly impaired orientation (24). Therefore, reorientation measures should begin promptly following hospital admission, the most important of which include:

- Optimizing vision and hearing
- Making clocks and calendars clearly visible
- Involving family members

BOX 1

Non-pharmacological treatment options in delirium prevention and management*

- **Reorientation**
 - Use of patients’ own glasses and hearing aids
 - Clearly visible clocks and calendars
 - Current newspapers
 - Avoiding room changes
 - Ensuring nighttime peace
 - Light reduction at night
 - Ensuring a high level of personnel continuity
- **Anxiety avoidance**
 - Adequate pain therapy
 - Early involvement of family members
 - Noise reduction
 - Cold stimuli reduction
 - Explaining painful examinations and signaling that they are about to begin
- **General measures**
 - Early mobilization
 - Occupational therapy and physiotherapy
 - Encouraging mental activity
 - Adequate oxygenation
 - Sufficient nutrition and fluid intake
 - Avoidance of polypharmacy

*Reorientation measures, anxiety reduction, and early mobilization play a crucial role here (modified from [24])

- Avoiding room changes
- Ensuring a high level of continuity in terms of care providers.

Optimizing individual areas of reorientation is not sufficient to ensure effective delirium prevention. Subgroup analysis in a controlled study showed that insufficient reorientation measures due to lack of personnel and poor patient adherence influence the delirium rate. Failure to implement measures stringently resulted in a delirium rate of 24%. If reorientation was intensified, the rate dropped to 13% and went down to 7% when tightly implemented (25).

A simple but indispensable initial measure is to promote vision and hearing with the patient’s own glasses and hearing aid—according to the authors’ clinical experience, only then is the patient able to adequately perceive their environment and communicate with the treating physicians, nurses, and family members.

Involving family members early on in the course of treatment makes for a somewhat more familiar environment. For this reason, hospitals as well as intensive care units are introducing ever more generous visiting times. Visiting times should only be reduced in the late evening and night in order to ensure an adequately peaceful nighttime environment.

TABLE 2

Possible causes of delirium (35)

Differential diagnoses and causes	
D	Drugs (medication or substance withdrawal)
E	Eyes, ears (sensory disorders)
L	Low O ₂ status (hypoxia)
I	Infection, sepsis
R	Retention (of urine or stool)
I	Ictal state (liver dysfunction)
U	Underhydration and undernutrition (hypovolemia and malnutrition)
M	Metabolic causes
(S)	Subdural hematoma (CNS pathology)

BOX 2

Possible vegetative symptoms of delirium (e1, e2)

- Tachycardia and heart problems
- Arterial hypertension
- Agitation and tremor
- Insomnia
- Increased perspiration
- Nausea
- Hyperthermia

Early physical and occupational therapy

Since mobility is reduced during a hospital stay, patients often rapidly lose muscle mass and consequently muscle strength. The resulting immobility is associated with longer hospital stays and a higher incidence of neuropsychiatric dysfunction (26). A randomized controlled study demonstrated that early physical and occupational therapy during hospital stays reduces the delirium rate from 41% to 28% and significantly increases the likelihood of a return to independent living (27). This applies not only to ICU patients—all inpatients benefit from early and intensive physiotherapy. One study showed that the delirium rate was 14% in the case of less intensive physiotherapy and went down to 3% in the case of intensive physiotherapy performed several times a day (25). Intensive physiotherapy during the daytime also results in physical fatigue and, as a result, a good night's sleep.

Appropriate sleep–wake rhythm

Sleep disruption occurs more frequently in hospital due to nursing and medical interventions, inappropriate lighting, and the failure of patients, visitors or personnel to adjust the volume of their conversations. Particu-

larly on the intensive care unit, high noise levels cause stress and sleeplessness and can trigger delirium as a result. Therefore, one needs to take a conscious approach to this problem in hospitals and place special emphasis on ensuring adequate nighttime peace. Eye masks and earplugs go a long way towards minimizing noise and light exposure in oriented and non-delirious patients, thereby improving sleep quality (28). A cohort study demonstrated that a reduction in sleep disruption was associated with a drop in the incidence of delirium from 33% to 14% (29).

Avoidance of polypharmacy

Many, in particular elderly patients take multiple medications to treat pre-existing diseases. The number of drugs used often increases during a hospital stay. An interaction with the choline, dopamine, or serotonergic system can trigger delirium. Even one highly potent substance (e.g., lorazepam) can lead to this. However, a combination of several low-grade delirium-inducing drugs can also add to the risk of delirium in the setting of polypharmacy. A cohort study showed that delirium occurred in 69% of patients using six or more drugs, whereas the incidence of delirium was only 30% in the comparison group (fewer than six drugs) (relative risk = 2.33) (30). Therefore, it is essential to continuously monitor drugs and discontinue unnecessary medication in order to prevent delirium. The Priscus list can be particularly helpful here (e3).

Pharmacological prophylaxis

Attempts are repeatedly made to reduce the incidence of delirium by means of pharmacological prophylaxis. However, a recently published randomized placebo-controlled study revealed that the administration of haloperidol in critically ill patients at high risk of delirium neither reduced the delirium incidence nor improved treatment outcome (31). A meta-analysis on the prophylactic administration of cholinesterase inhibitors and antipsychotic agents also found no clear evidence to support pharmacological delirium prevention (32).

The prophylactic administration of melatonin is also controversial. For example, exogenous melatonin administration in elderly non-surgical patients shows a preventive effect on delirium, which, however, cannot be reproduced in surgical patients (33). Therefore, pharmacological delirium prevention cannot be generally recommended at this point in time. The selective α_2 -agonist dexmedetomidine appears to be a promising substance for delirium prevention. A meta-analysis was able to show that the perioperative administration of dexmedetomidine significantly reduces the incidence of delirium in surgical patients (OR: 0.35; 95% CI: [0.24; 0.51]; $p < 0.01$) (34).

Treatment of delirium

If delirium develops, the first step should be to identify possible causes. Infections, substance withdrawal, electrolyte disorders, blood sugar imbalance, pain, and hypoxia are particularly common causes (Table 2). If

symptoms persist despite the elimination of possible triggers, non-pharmacological treatment should be initiated immediately. In addition to early mobilization, encouraging cognitive activity, and reorientation, this also includes improving the patient's sleep. These measures are not only of crucial importance in the prevention but also in the treatment of delirium (36).

Depending on the clinical picture, a variety of substances are available for the symptom-oriented, pharmacological treatment of delirium. However, many of these substances can only be used under intensive care monitoring due to their side-effect profiles.

α_2 -Agonists and short-acting benzodiazepines should be used in a guideline-compliant manner to manage agitation and the possible effect of delirium (1). Long-working benzodiazepines (e.g., lorazepam), in contrast, are not indicated for agitation and evidently harbor their own significant delirogenic potential (37). The administration of neuroleptic drugs is likewise not indicated for agitation without productive psychotic symptoms. In the case of drug and substance withdrawal delirium, long-acting benzodiazepines such as diazepam and lorazepam are indicated in accordance with the guidelines (1, 38). Should vegetative symptoms develop (*Box 2*), adrenergic symptoms can be managed with α_2 -agonists and, where appropriate, β -blockers.

Low-dose haloperidol or atypical neuroleptic agents are recommended in the case of productive psychotic symptoms—irrespective of whether delirium is hyperactive or hypoactive (1). If haloperidol is selected, it should be administered in low doses. Administering high-dose haloperidol can result in an overdose and is associated with a greater likelihood of delirium on the following day (1). Furthermore, intravenous haloperidol administration needs to be titrated under cardiac monitoring, since the use of haloperidol can cause QT interval prolongation as well as torsade de pointes tachycardia.

Atypical neuroleptic agents (risperidone, olanzapine, and quetiapine) represent alternatives to haloperidol. Their efficacy is comparable to low-dose haloperidol (39). Although atypical neuroleptics cause fewer extrapyramidal disorders compared to haloperidol, they necessitate close monitoring of blood count and liver values.

Summary

The management of delirium in hospital requires a multifactorial approach. Prevention and prompt diagnosis by means of validated screening methods are crucial. If delirium is diagnosed, treatment must be initiated swiftly, with non-pharmacological treatment options playing an extremely important role. Only in this way is it possible to correctly treat the medical emergency that delirium represents and achieve the best treatment outcome for the patient (40).

Key messages

- Since delirium results in increased mortality irrespective of the clinical picture, treatment needs to be initiated promptly.
- Reorientation strategies, physiotherapy, maintaining a sleep-wake rhythm, as well as other non-pharmacological treatment options are able to reduce the incidence of delirium.
- A validated delirium screening test should be performed several times a day in order to ensure early diagnosis of delirium. Screening is recommended at least every 8 h on the intensive care unit.
- The identification and causal treatment of the underlying etiology of delirium is mandatory prior to any symptom-oriented pharmacological or non-pharmacological treatment.
- The selection of drugs to be used must be based on clinical symptoms.

Conflict of interests

PD Dr. Zoremba received congress fee and travel cost reimbursement, as well as lecture honoraria from Orion Pharma and MD Horizonte GmbH.

Prof. Coburn received congress fee and travel cost reimbursement, as well as lecture honoraria from Orion Pharma and MD Horizonte GmbH.

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► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref0719

eTable:
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Supplementary material to:

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eBOX

Search terms used for research

The authors used the following terms for their literature search:

“delirium,” “definition,” “detection,” “diagnosis,” “screening,” “pathophysiology,” “prevention,” “therapy,” “treatment,” “physiotherapy,” “sleep,” “ICU,” “general practice,” “postoperative,” “haloperidol,” “dexmedetomidine,” “polypharmacy,” “benzodiazepine,” and “melatonin.”

These terms were used in various combinations to filter sources according to search focus.