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Review article

Delirium: Guidelines for general hospitals

Laurent Michaud[a,b], Christophe Büla[c], Alexandre Berney[b], Vincent Camus[d,e], Rachel Voellinger[a,b], Friedrich Stiefel[b], Bernard Burnand[a,*], the Delirium Guidelines Development Group[1]

[a]*Clinical Epidemiology Center, Institute of Social and Preventive Medicine, University Hospital, Lausanne, Switzerland*
[b]*Psychiatry Service, University Hospital, Lausanne, Switzerland*
[c]*Service of Geriatric Medicine, CHUV and CUTR Sylvana, Epalinges, Switzerland*
[d]*Service of Old Age Psychiatry, University Hospital, Lausanne, Switzerland*
[e]*Clinique Psychiatrique Universitaire, Centre Hospitalier Régional Universitaire and Faculté de Médecine, Université François-Rabelais, Tours, France*

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Abstract

Objective: Delirium is highly prevalent in general hospitals but remains underrecognized and undertreated despite its association with increased morbidity, mortality, and health services utilization. To enhance its management, we developed guidelines covering all aspects, from risk factor identification to preventive, diagnostic, and therapeutic interventions in adult patients. **Methods:** Guidelines, systematic reviews, randomized controlled trials (RCT), and cohort studies were systematically searched and evaluated. Based on a synthesis of retrieved high-quality documents, recommendation items were submitted to a multidisciplinary expert panel. Experts scored the appropriateness of recommendation items, using an evidence-based, explicit, multidisciplinary panel approach. Each recommendation was graded according to this process' results. **Results:** Rated recommendations were mostly supported by a low level of evidence (1.3% RCT and systematic reviews, 14.3% nonrandomized trials vs. 84.4% observational studies or expert opinions). Nevertheless, 71.1% of recommendations were considered appropriate by the experts. Prevention of delirium and its nonpharmacological management should be fostered. Haloperidol remains the first-choice drug, whereas the role of atypical antipsychotics is still uncertain. **Conclusions:** While many topics addressed in these guidelines have not yet been adequately studied, an explicit panel and evidence-based approach allowed the proposal of comprehensive recommendations for the prevention and management of delirium in general hospitals.

Keywords: Diagnosis; Treatment; Clinical epidemiology; Confusional state; Delirium; Nonpharmacological therapy; Prevention; Screening; Systematic review

* Corresponding author. Institut Universitaire de Médecine Sociale et Préventive (IUMSP), Bugnon 17, CH-1005 Lausanne, Switzerland. Tel.: +41 21 314 7255; fax: +41 21 314 4954.
E-mail address: bernard.burnand@chuv.ch (B. Burnand).

[1] The members of the Delirium Guidelines Development Group are as follows: Laurent Michaud, MD (Clinical Epidemiology Center, Institute of Social and Preventive Medicine, University Hospital, Lausanne, Switzerland; Psychiatry Service, University Hospital, Lausanne, Switzerland); Alexandre Berney, MD (Psychiatry Service, University Hospital, Lausanne, Switzerland); Christophe Büla, MD (Service of Geriatric Medicine, CHUV and CUTR Sylvana, Epalinges, Switzerland); Vincent Camus, MD (Service of Old Age Psychiatry, University Hospital, Lausanne, Switzerland; Clinique Psychiatrique Universitaire, Centre Hospitalier Régional Universitaire and Faculté de Médecine, Université François-Rabelais, Tours, France); Rachel Voellinger MD (Clinical Epidemiology Center, Institute of Social and Preventive Medicine, University Hospital, Lausanne, Switzerland; Psychiatry Service, University Hospital, Lausanne, Switzerland); Friedrich Stiefel, MD (Psychiatry Service, University Hospital, Lausanne, Switzerland); Bernard Burnand MD, MPH (Clinical Epidemiology Center, Institute of Social and Preventive Medicine, University Hospital, Lausanne, Switzerland); Thierry Buclin, MD (Division of Clinical Pharmacology, University Hospital, Lausanne, Switzerland); François Chevalley, MPH (Orthopedic Department, University Hospital, Lausanne, Switzerland); Olivier Lamy, MD (Service of Internal Medicine, University Hospital, Lausanne, Switzerland); Yves Dorogi, RN (Psychiatry Service, University Hospital, Lausanne, Switzerland); Mauro Oddo, MD (Intensive Care Department, University Hospital, Lausanne, Switzerland); Patrick Schoettker, MD (Department of Anesthesiology and Prehospital Emergency Medicine University Hospital, Lausanne, Switzerland); Joseph Ghika, MD (Service of Neurology, University Hospital, Lausanne, Switzerland); Armin von Gunten, MPhil, MD (Service of Old Age Psychiatry, University Hospital, Lausanne, Switzerland).

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Introduction

Delirium is an acute change in cognition with altered consciousness and impaired attention that fluctuates over time [1]. It is a frequent condition seen in general hospitals. Its prevalence ranges from 11% to 33% on admission [2–4], and its incidence during hospital stay ranges between 3% and 56% [2,3,5,6]. Delirium is associated with adverse outcomes, including increased morbidity, increased mortality, and increased health services utilization [7–15]. Despite these observations, delirium recognition rates are low (12–43%) [4,16–18], and its management remains inadequate in up to 80% of patients [16]. This suggests lack of preventive and screening activities, missed diagnoses, and inappropriate management of diagnosed delirium. Beneficial changes following guidelines implementation have been demonstrated in several domains [19]. Following the adaptation [20] and implementation [21] of guidelines for depression in general hospitals, we undertook the development of new specific guidelines covering all relevant aspects of the management of delirium among adult patients in general hospitals.

Methods

We chose to start with a strategy of adapting published guidelines, where available, in order not to perform anew valid high-quality work that had been previously conducted [22]. Thus, we first searched to identify high-quality clinical practice guidelines and completed our sources of information with systematic reviews and, in the absence of such documents, clinical trials and cohort studies, when appropriate. The main steps of guidelines development were: (a) a systematic literature search; (b) the rating of each basic element of recommendation (recommendation item) derived from the literature by a multidisciplinary expert panel, using nominal group technique [23]; (c) the incorporation of approved recommendation items in specific recommendations; and (d) a review of the final recommendations by international experts. This process was conducted by the first author, a psychiatry resident, assisted by a development team (senior psychiatrist and senior clinical epidemiologist), in collaboration with a multidisciplinary expert panel representative of the future users of the guidelines. The panel included 14 experts: four psychiatrists (two specialized in old age psychiatry), one geriatrician, one psychiatric nurse, one neurologist, one intensive care clinician, one intensive care nurse, one general internist, one anesthetist, one orthopedic surgeon, one clinical epidemiologist, and one pharmacologist.

Literature search

The aim of this search was to identify existing guidelines and systematic reviews on delirium in adults and in the elderly. Delirium in children was beyond the scope of this research project. Two different search strategies were performed, based on a previously developed and tested strategy (www.chuv.ch/cepic/RPC_strat.html). Medline, PsychINFO, Web of Knowledge, EMBASE, and the Cochrane Library databases were used to identify publications in English and French from 1997 to August 2004 with the keywords "delirium," "confusion," "hallucination," and "delusion." Articles were selected through a three-step screening process based on reviews of the title, abstract, and content of the paper. Additional references from bibliographies were reviewed and included if considered of relevance. The sites of the National Guideline Clearinghouse (www.guideline.gov), the Guidelines International Network (www.g-i-n.net), the National Institute for Clinical Excellence (www.nice.org.uk), the New Zealand Guidelines Group (www.nzgg.org.nz), the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk), and national psychiatric associations were examined. In addition, specific searches were developed for topics (such as risk factors for delirium, prevention of delirium, and physical restraints) not covered by recent guidelines or systematic reviews. Medline, PubMed, EMBASE, and the Cochrane Library were used without time limitations for these searches. Detailed literature search strategies are available from the authors on request. The literature search was updated for the submission of this article. It was repeated using the same methodology for the period from January 2004 to February 2006.

Results of literature search

Searches on guidelines identified 1550 papers, including 519 articles in Medline, 67 articles in PsychINFO, 724 articles in the Web of Knowledge, and 240 articles in EMBASE. Four guidelines were identified in Medline [24–27]. No additional guidelines were found in PsychINFO, the Web of Knowledge, or EMBASE. One additional guideline was identified on an Internet site [28], and another was identified through contacts with delirium experts [29]. Searches on systematic reviews identified 3178 papers, including 2099 articles in Medline, 334 articles in PsychINFO, 724 articles in the Web of Knowledge, and 21 articles in the Cochrane Library. Sixteen systematic reviews [7,12,30–43] were found in Medline, one in the Web of Knowledge [44], one in EMBASE, [45] and one in the Cochrane Library [46]. No additional systematic review was found in PsychINFO. One systematic review was identified on an Internet site [47]. Altogether, 5 guidelines and 19 systematic reviews were therefore identified. The results of literature search update are not detailed here because of space limitations but are available from the authors on request. No new guidelines were retrieved by updating. Five systematic reviews were identified [48–52]. The quality of retrieved guidelines was evaluated with the Appraisal of Guidelines for Research and Evaluation instrument (www.agreetrust.org) by two independent raters (L.M. and R.V.). Systematic reviews were evaluated by the first author using the Cochrane Library criteria [53] and existing references [54,55]. The six most important domains assessed were: (a) clarity of the clinical

question examined; (b) quality and extent of the literature search; (c) inclusion criteria; (d) quality of the methodological evaluation of retrieved studies; (e) review method; and (f) meta-analysis, if present. Based on this evaluation, their results were considered relevant or not to drawing related recommendation items.

Development of recommendations

The retrieved literature was synthesized by selecting, for each topic (i.e., prevention, risk factors, screening, diagnosis, and management), the most appropriate source of evidence, according to the quality of the study and the level of evidence. Based on the quality of available literature, the level of evidence according to the Oxford classification (see Table 1 and www.cebm.net/levels_of_evidence.asp) was determined for each recommendation item. Drafts of recommendation items were reviewed by and discussed with the expert panel. About 400 recommendation items, covering risk factors, prevention, identification, diagnoses, and management of delirium, were identified. In the first round, the appropriateness of recommendation items was rated separately by each member of the expert panel, using an adapted RAND appropriateness method [23]. The experts scored each recommendation item on a Likert scale ranging from 1 (*extremely appropriate*) to 9 (*extremely inappropriate*). The experts were asked to take into account in their vote both the result of literature synthesis (with its level of evidence) and their clinical experience. Votes were aggregated into four categories (*appropriate*, *uncertain*, *inappropriate*, and *disagreement*) according to the median vote of the experts and the level of intrapanel disagreement. Disagreement was defined as the occurrence of at least 4 of 14 experts voting in one to three categories and at least four others voting in seven to nine categories. In the absence of disagreement, a recommendation item was classified as appropriate (median=1–3), uncertain (median=4–6), or inappropriate (median=7–9). All items on which disagreement occurred were classified as uncertain. After analyzing the first round of ratings, the experts received an individualized feedback document featuring their own initial rating and the panel median rating for each recommendation item. Recommendation items with disagreement were discussed by the experts at two additional panel meetings and were subsequently rated individually a second time.

Following this process, recommendations were graded for each recommendation item through a rating that combined the level and quality of evidence, and the degree of appropriateness and consensus among the experts. The grade of recommendation was based on the level of evidence (i.e., Oxford classification: Level I=*Grade A*; Levels II and III=*Grade B*; Levels IV and V=*Grade C*). In the case of a very high appropriateness rating (defined by a median vote of 1, i.e., extremely appropriate) and consensus among the experts, a superior grade of recommendation was chosen (e.g., Level II on the Oxford classification with very high appropriateness rating and consensus among panelists implies a Grade A recommendation). Grading definitions are shown in Table 1. The final draft was reviewed by two international experts in delirium and revised according to their comments. The results of literature update were synthesized by the first author and discussed with all authors. Some changes were introduced in the text, and relevant modifications were submitted to the expert panel. Changes in recommendations resulting from the update are mentioned in the tables.

Presentation of guidelines

The guidelines consist of a full-text document and a summary algorithm developed for implementation, which are both accessible to hospital staff through the intranet system of the University Hospital of Lausanne. To enhance readability, the present paper focuses on the most important recommendations, while the entire guidelines are summar-

Table 1
Levels of evidence and grades of recommendation

Levels of evidence*	Grades of recommendation
Level I RCT Systematic reviews of RCT (homogeneous) Systematic reviews	Grade A: Based on fair evidence or on acceptable evidence with a high consensus between experts (Level I evidence, or Level II/III evidence with high consensus)
Level II Non-randomized controlled trials Level III Prospective cohort studies	Grade B: Based on acceptable evidence or on sufficient evidence with a high consensus between experts (Level II/III evidence, or Level IV/V evidence with high consensus)
Level IV Retrospective cohort studies and case–control studies Level V Case reports and published expert opinions	Grade C: Based on acceptable evidence (Level IV/V evidence with sufficient consensus between experts)
	Grade I (i): There is no sufficient evidence or no sufficient consensus to formulate any recommendation (i.e., studies or expert opinions are contradictory) (Note: In this case, the decision must be made by considering particular circumstances and the clinical experience of the practitioner.)

* Data from the Oxford classification (www.cebm.net/levels_of_evidence.asp).

ized in Tables 2–8. References could not be included in the current tables for publication, but the full-text document indicates references for every recommendation (available from the authors on request).

Results

The 392 recommendation items on delirium that were submitted to the expert panel resulted in about 5500 ratings (response rate=94%). Most recommendation items had a low level of evidence (Level I, 1.3%; Level II, 6.1%; Level III, 8.2%; Level IV, 6.6%; Level V, 77.8%). However, of the recommendation items, 71.1% were considered by the experts as appropriate, 21.7% were considered uncertain, and 7.2% were considered inappropriate. A permanent disagreement remained among the experts in only 3.8% of propositions, which were classified into the uncertain recommendation. The dispersion of votes was shown to be related to the level of evidence, with interquartile range (IQR) being 1 for Level I, 4 for Level V, and between 2 and 3 for Levels II–IV. On the other hand, this dispersion was similar between the experts working in the field of psychiatry and those practicing somatic medicine (IQR=4). The frequency and usefulness of screening for delirium, the role of physical restraints, the benefits of electroencephalogram (EEG) and lumbar puncture (LP), and selected indications for benzodiazepines in agitated delirium in younger adults were the most controversial topics among the panelists.

Risk factors

One systematic review studied risk factors for delirium [30]. Since this publication, 21 prospective studies have

Table 2
Risk factors for delirium

	Predisposing factors (on admission)	Grade	Precipitating factors (during stay)	Grade	Aggravating factors	Grade
General factors	Age >70 years	A				
	Severity of illness	A				
Central nervous system factors	Cognitive impairment	A	Stroke	A		
	Depression in the elderly	B	Central nervous system pathological process	B		
	Sensory impairment	B				
	Previous stroke	B				
Metabolic factors	Preoperative electrolyte disturbances	B	Metabolic, electrolyte, and endocrine disturbances	A		
	Preoperative dehydration	B	Fever	C		
	Dehydration	C				
Other systemic factors			Infections	A		
			Pain	B		
			Traumatism	C		
			Hypoperfusion, hypoxia, and cardiac or pulmonary failure	B		
			Organ failure	C		
Substance-related factors	Alcohol abuse	B[a]	Drug or toxic withdrawal	A		
	Number of drugs before admission	B	Number of drugs and number of psychotropic drugs	B		
	Number of psychotropics before admission	B	Anticholinergic drugs	B		
			Opioids	C		
Environmental factors				B	Intensive care unit	B
	Sensory deprivation or overload	C[a]	Physical restraints	B		
					High number of room changes	B
					Absence of a clock	B
					Absence of glasses	B

Please refer to Table 1 for grading definitions.
Patients who are older (>70 years), severely ill, or cognitively impaired are most vulnerable to delirium. They should be first targeted for the identification of other risk factors (B).
Whenever possible, cognitive impairment, fever, dehydration, pain, and electrolytic disturbances should be systematically detected using, for example, a checklist (B).
New drug treatments should be introduced with caution (C).
Any treatment change should be considered with caution, especially with regard to psychotropic drugs, anticholinergic drugs, and opioids (C).
Pain should be adequately managed (C).
Physical restraints should be avoided (C).
In surgical patients, postoperative perfusions and transfusions should be used cautiously (C).
[a] Recommendation modified by the updating of guidelines.

Table 3
Recommendations for the prevention of delirium

General recommendations	Specific recommendations	Grade
Detect and treat cognitive impairment	Routine screening of cognitive functions and delirium, whenever possible, using standardized instruments (e.g., MMSE or BOMC on admission, and CAM during hospital stay)	A
	Cognitively stimulating activities adapted to the patient	C
Favor high-quality sleep	Nonpharmacological sleep promotion	A
	Noise reduction; use of low-level lighting; avoidance of constant lighting	A
	Maintenance of a normal sleep–wake cycle	A
Minimize drug side effects	Limitation of the total number of drugs	C
	Avoidance or cautious use of the following medications: • Psychotropics, especially hypnosedatives and benzodiazepines • Anticholinergic drugs • Opioids	C
Prevent/correct electrolytic disturbances and dehydration	Stimulation of adequate hydration; use of fluid balance charts	A
	Biochemical screening; early management of electrolyte disturbances	B
	Hypodermoclysis if oral intake is inadequate	C
Improve communication and orientation	Regular verbal communication; use of short sentences; frequent information on place, reason for hospitalization, and daily activities; whenever possible, involvement of patient in the process of care; information and reassurance about medical procedures	B
	"On-time" clocks and calendars; familiar artifacts, whenever possible (i.e., posters); avoidance of ward or room transfers; continuity of care	B
Limit sensory underload or overload	Screening for visual and hearing impairment; provision of visual and hearing aids; adequate lighting; use of nightlights; avoidance of blind rooms (without windows)	A
Involve and inform significant others	Information of proxies regarding delirium; encouragement of visits to the patient and involvement in orientation; nursing and feeding; support of proxies	C
Avoid malnutrition and vitamin deficiencies	Nutritional support and/or vitamin supplements for high-risk groups (i.e., B vitamins for alcoholic abusers)	B
Prevent or treat withdrawal	If middle-aged adults are at high risk for alcohol withdrawal, prevention with benzodiazepines	A
	Clomethiazole for prevention of withdrawal in the elderly	B
	Systematic screening for alcohol abuse	B
Do not use physical restraints	Protocol for physical restraints	A
Favor mobilization	Avoidance of immobilization; education regarding hazards of bed rest	A
	Limiting the use of catheter and intravenous line; avoidance of the use of Foley catheter	B
	Early mobilization protocol; evaluation by physiotherapist, whenever necessary	B
	Stimulation of mobility; performance of self-care and daily activities	B
Optimize operative conditions	Adequate analgesia; patient-controlled analgesia, if feasible	B
	Prevention of postoperative hypotension/hypoxemia	C
	Maintenance of postoperative hematocrit level at >30%	C
Consider interventions on the system	Staff education	A
	Development and implementation of guidelines regarding harmful procedures (i.e., physical restraints, polymedication, unnecessary catheters)	B
	Adequate staff allocation	B
	Involvement of volunteers and family	C

Please refer to Table 1 for grading definitions.

investigated this topic [17,56–75]. In addition, one systematic review studied postoperative risk factors for delirium [76]. According to Inouye and Charpentier [59] and Inouye [77], risk factors were grouped into predisposing and precipitating factors. Predisposing factors are baseline conditions that increase the risk of delirium, while precipitating factors are triggers that cause delirium. Although this distinction may seem artificial, it was adopted because it clarifies the potential contribution of these conditions to the multifactorial pathway leading to delirium. This classification also provides a framework for preventive interventions, one of the aims of the development of the present guidelines. The contribution of drugs, most often considered as precipitating factors, was examined by means of a specific literature search [59,78–82]. In one study, environmental factors were found to aggravate diagnosed delirium [83]. Table 2 summarizes the risk factors for delirium and the general recommendations for identification.

Table 4
Standardized instruments for delirium

	Screening on admission	Grade	Screening during stay	Grade	Diagnosis	Grade	Rating of severity	Grade
Instrument	MMSE	C	CAM/BOMC	C	CAM	C	DRS or MDAS	C
Use	On admission	C	Depending on the situation, at least twice a week	C	To assist in diagnosis	C	To rate severity	C
Users	Medical or nursing staff with adequate training	C	Medical or nursing staff with adequate training	C	Medical or nursing staff with adequate training	C	Medical or nursing staff with adequate training	C

Please refer to Table 1 for grading definitions.
Diagnosis may be based on *DSM-IV* or *ICD-10* criteria, a standardized instrument, or both (B).

Prevention

Systematic reviews [7,31,39,47,51] and recent studies on delirium prevention [5,84–90] led to the examination of a series of potential interventions. Multicomponent intervention strategies based on a specialized delirium consultation team and/or specific staff training were shown to prevent delirium in surgical and medical inpatients [5,7,31,39,47,51,84–89], while pharmacological prevention through haloperidol was unable to lower its incidence [90]. Patients at risk for delirium, such as elderly persons (≥70 years), severely ill individuals, and patients with cognitive impairment, should be the target of nonpharmacological preventive interventions (Table 3). However, only a few interventions are based on sound evidence, and cost concern is an important barrier to their implementation.

Screening and diagnosis

Screening for delirium may improve its detection, as suggested by several studies and previous guidelines [24,26,28,91]. However, only a few studies of variable methodological quality investigated this issue [92–94]. Despite this relative lack of evidence, a consensus was reached

Table 5
History, physical examination, and additional investigations

		Grade
History	Full drug history, including over-the-counter drugs	B
	Substance abuse (e.g., alcohol, recreational drugs, etc.)	B
	Previous delirium	B
	Sensory deficits and/or aids (e.g., hearing aid, glasses, etc.)	B
	History by proxies	B
Status	Neurological examination	B
	Evidence of alcohol abuse or withdrawal	B
	Nutritional status	C
First-step investigations	Full blood count	B
	Electrolytes (sodium, potassium, and calcium)	B
	Renal function (blood urea nitrogen and creatinine)	B
	Urine analysis	B
	Blood gases	C
	Liver function tests (alanine amino transferase, aspartate amino transferase, and bilirubin)	C
	Glucose	C
Investigations for selected indications	HIV serology	B
	Blood levels of drugs	B
	Blood and urine cultures	B
	Urinal screening for toxics	B
	Vitamin B_{12} and folate serum levels	B
	Antinuclear antibodies	B
	Screening for heavy metals	C
	Systemic lupus	C
	Urinary porphyries	C
	Ammonium	C
	Magnesium and phosphate	I
	Albumin	I
	Alkaline phosphatase	I

Please refer to Table 1 for grading definitions.
The identification and treatment of underlying causes is the cornerstone of delirium management (B).
Potentially involved drugs should be stopped early, biochemical disturbances should be corrected, and antibiotic treatment should be rapidly introduced for infections (B).
History by proxies should be determined to differentiate delirium from dementia and to document previous cognitive status (B).

Table 6
Indications for standard EEG, brain imaging, and LP

	Indications	Grade
EEG	Differentiation of delirium from nonconvulsive or temporal lobe epilepsy	C
	Identification of encephalitis	C
	No cause identified in refractory and persistent delirium	C
	Usefulness of EEG in differentiating delirium from dementia	I
Brain imaging	Cerebral CT	
	Focal neurological signs	C
	Development of delirium after head injury or fall	C
	Patients with pathology potentially associated with intracranial processes (e.g., metastatic cancer)	C
	No cause identified in refractory and persistent delirium	C
	Magnetic resonance imaging	
	Patients with pathology potentially associated with intracranial processes (e.g., metastatic cancer)	C
	Other indications[a]	I
LP	Meningism and fever and/or headache	A
	Meningism only	B
	If headache and meningism only, or if no cause is identified in refractory and persistent delirium[a]	I

Please refer to Table 1 for grading definitions.
[a] In these indications, the usefulness of magnetic resonance imaging and LP is uncertain and should be appreciated by a specialist.

to recommend systematic screening for delirium in at-risk patients. Screening should be conducted with standardized validated tools [37]. Instruments identifying cognitive impairment, such as the Mini-Mental State Exam (MMSE) [95] and the Blessed Orientation–Memory–Concentration (BOMC) [96,97], show the best clinimetric properties for delirium screening (Table 4). Moreover, the MMSE proved to be helpful in monitoring the development and resolution of delirium in geriatric patients [98]. The gold standards for diagnosing delirium are the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) or *International Classification of Diseases, Tenth Revision* (*ICD-10*) criteria, but their

Table 7
Pharmacological treatment

	Recommendations	Grade
Indications for drug treatment	Avoidance of systemic pharmacological treatment	B
	Uncontrollable agitation despite nonpharmacological interventions	B
	Danger to the patient, staff, or others	B
	Anxiety in agitated or hallucinating patients	B
	Need to control agitation, to perform an investigation, or to provide treatment	C
	Uncertain indication	
	Hypoactive delirium	I
Type of drugs	Haloperidol	B
	Risperidone[a]	C
	Quetiapine[a]	C
	Clomethiazole	C
	Clozapine[a]	C
	Olanzapine[a,b]	C
	Benefit of chlorpromazine uncertain	I
Indications for atypical antipsychotics	Contraindication to classical antipsychotics	C
	Side effects of classical antipsychotics	C
Combinations with benzodiazepine	No benzodiazepine in the elderly (>70 years)	C
	Indications in younger adults	
	Uncontrollable agitation while on antipsychotic treatment	C
	Caution required given the potential side effects of these substances in delirium	C
	Uncertain indications	
	Lack of response to antipsychotic treatment	I
	Tolerance to only low doses of antipsychotics	I

Please refer to Table 1 for grading definitions.
Electrocardiogram of patients treated with antipsychotics should be monitored to detect QT interval prolongation (risk of "torsade de pointes") (B).
Benzodiazepines as monotherapy are reserved for delirium caused by alcohol or benzodiazepine withdrawal as single cause. Whenever another cause is suspected, a combination of haloperidol and benzodiazepines should be used (B).
Vitamin supplements should be instituted in patients with possible B-vitamin deficiencies (i.e., alcohol abuser or malnourished) (B).
Sedation may be indicated in end-of-life care (B).
Cholinergics, such as physostigmine, may be useful in delirium caused by anticholinergic medications (I).
[a] Clinicians should pay attention to possible cerebrovascular events induced by these medications in the elderly.
[b] Recommendation modified by the updating of guidelines.

Table 8
Other recommendations

	Recommendations	Grade
Dangerous patients	Physical restraint is an exceptional measure that may be indicated if • Other less restrictive means have failed *and* • The patient's behavior puts self and/or staff and/or others at risk Restraints should be used only after discussion with the patient, proxies (including those with durable power of attorney), and nursing staff. The use of a restraint protocol is mandatory to monitor evolution over time. Reevaluation of restraint use should occur periodically, as frequently as every 15 min in the acute phase.	C
Specialized referral	Referral to a specialist (psychiatrist, old age psychiatrist, geriatrician, neurologist, etc.) may be required if: • Delirium is unresponsive to treatment • There is important agitation with possible need for physical restraint • There are doubts about management	C
Informed consent	Informed consent should not be signed by a delirious patients as one's competency is altered	C

Please refer to Table 1 for grading definitions.

external validity does not seem satisfying [99]. *ICD-10* criteria are considered more specific but less sensitive than *DSM-IV* criteria [100,101], but both classifications identify conditions that seem to share a similar prognosis [102]. Other instruments may also be useful in diagnosing delirium [103]. Among them, the Confusion Assessment Method (CAM) has been validated and extensively studied [104], and a special version for use in the intensive care unit (Confusion Assessment Method for the Intensive Care Unit) is available [105]. The Delirium Rating Scale (DRS) [106,107] or the Memorial Delirium Assessment Scale (MDAS) [108] may be useful in rating the severity of delirium. Table 4 summarizes recommended instruments and their proposed use.

Investigation and treatment

The management of delirium includes: (a) the identification and treatment of all potential underlying causes (precipitating factors); (b) the provision of supportive care; and (c) the selection of appropriate pharmacological treatment for behavioral symptoms, when necessary. The identification and treatment of underlying causes is the cornerstone of delirium management. Medical history should be gathered from patients and proxies, and physical examination should be conducted in every patient [7,24,26,91,109,110]. Depending on information and clinical examination, additional investigations may be considered. Some investigations are recommended for every patient, while others are proposed in selected indications (Table 5). The utility of EEG, LP, and brain imaging (CT/MRI) is a much debated topic in the literature and has also been a subject of controversy in the expert panel (Table 6). Supportive care interventions include all preventive interventions listed in Table 2 [5,111–113]; their aim is to restore physiological conditions and to reorient the patient. These interventions should be considered for all delirious patients. Specific therapeutic interventions and nurse-directed care seem to have a beneficial effect on the evolution of delirium in surgical [7,44,47] and medical [5,51,88,89,114] inpatients.

Sound evidence supporting specific indications for drug treatment in delirium is still lacking (Table 7) [52]. A consensus to avoid systemic drug treatment of delirious patients was reached by the experts. When pharmacological treatment seems appropriate, antipsychotics are considered first-choice medications. Haloperidol has been shown to be efficient in treating symptoms of delirium [115] and to have a positive effect on the severity and duration of delirium [90]. For safety reasons, an electrocardiogram should be obtained as soon as feasible (risk of QT interval prolongation and arrhythmia) [116,117]. The usefulness of new atypical antipsychotics has been debated in the literature. Some evidence indicate that olanzapine [118–121] and quetiapine [122] have efficacy similar to that of haloperidol, with fewer side effects, in delirious patients; risperidone showed similar efficacy and side effects [123]. Numerous authors advocate that results from trials in dementia patients suffering from behavioral and psychological symptoms allow the recommendation of new atypical antipsychotics in delirium. These drugs have been associated with a potential increased risk of cerebrovascular events and mortality in dementia patients [124,125], leading the Food and Drug Administration to issue a warning advising avoidance of their use for this indication (www.fda.gov/cder/drug/infopage/antipsychotics/default.htm). However, the results of numerous randomized controlled trials (RCT) on this subject were recently studied by high-quality systematic reviews [48–50], yielding no definitive answer on this potential risk. Moreover, an additional retrospective study showed a higher risk of death associated with the use of conventional versus atypical antipsychotics [126]. Given these conflicting data and considering the fact that the studied population included patients with dementia rather than patients with delirium, haloperidol was considered to be the preferred pharmacological treatment for delirium. Taking into account that several atypical antipsychotics have also been reported to cause delirium, probably because of their anticholinergic effect [127–129], they were recommended with a lower grade of recommendation. New data available in the future might affect this specific recommendation. Benzodiazepines

are not as efficient as antipsychotics and may even precipitate confusion [78–80,130]. They are only recommended as first-choice drugs for alcohol-related or benzodiazepine-related withdrawal [131]. Following the American Psychiatric Association guidelines, young patients who tolerate only minimal doses of antipsychotics could benefit from a combination of benzodiazepines and antipsychotics [91]. Cholinergics [114,132,133], mianserine [134], ondansetron [135], and melatonin [136] have also been studied and could be useful in some situations, while donepezil seems to have no beneficial effect [137]. Clomethiazole is advocated by some authors [138,139] and recommended as a second-line treatment by the experts, based on their positive clinical experience. The pharmacological treatment of delirium is summarized in Table 7. Recommendations for the management of dangerous patients, referral for specialized consultation, and issues concerning informed consent are presented in Table 8.

Discussion

The development and implementation of guidelines is an important preliminary step to improve delirium management, given its high occurrence in patients hospitalized in general hospitals and highly variable care practices. A recent survey showed that only two countries in Europe possess a guideline for the diagnosis and treatment of delirium [140]. The present guidelines thus constitute a significant contribution from several perspectives. First, from a methodological standpoint, these guidelines are important because they were developed using rigorous methodology based on an extensive literature review and appraisal that included a formal evaluation of existing guidelines and covered all aspects of delirium management. This methodology also included formal consultation with an expert panel of diverse professional and specialty backgrounds that completed a structured appropriateness rating by means of nominal group technique, which is especially well-suited for areas of uncertainty. The guidelines were finally reviewed by international experts, and the literature update conducted just before submission confirmed most recommendations. Second, this work is also important because, to our knowledge, these guidelines are the first to cover, in English, the entire spectrum of delirium management in general hospitals: risk factors identification, preventive and diagnostic strategies, and pharmacological and nonpharmacological treatments. Finally, another contribution of this work is to identify several topics that need to be investigated in future research, such as the usefulness of systematic screening in different populations, the effectiveness of nonpharmacological management, and the place of drugs of anecdotic use (i.e., cholinergics).

Despite the rigorous methodology used, some areas remain with uncertainty, and several key recommendations deserve further comments. First, there exists consensus among the experts to emphasize the prevention of delirium. Emerging data support this strategy, and efforts should be made to implement prevention programs in at-risk populations in general hospitals. Second, atypical antipsychotics, which have been increasingly used over the past years and have been supported by some empirical evidence, were not recommended as first-choice drugs mainly because of recent data on cerebrovascular adverse events in the elderly. This position might be modified once additional data are available. Third, pharmacological treatment is not systematically recommended to treat delirious patients. Consensus was reached about when and under which circumstances pharmacological treatment is appropriate; that is, in situations where the patient's condition (e.g., agitation) prevents adequate care (e.g., pulling out a central intravenous line) or puts the patient or the nursing staff at risk (e.g., physical aggressiveness).

Several difficulties were encountered while developing these guidelines. First, only a few and incomplete guidelines on delirium existed. A simple adaptation of previous high-quality guidelines was therefore considered not adequate, and the literature search was extended to systematic reviews, RCT, and cohort studies. Levels of evidence were frequently not specified in the guidelines and had to be evaluated from source studies. Finally, most of the topics discussed in these guidelines had not been adequately studied. Therefore, only low levels of evidence appeared in the literature, and diverging strategies were recommended by different authors. To overcome these difficulties, the multidisciplinary panel approach allowed an explicit and systematic examination of proposed recommendation items, which were developed based on existing evidence. This strategy, combining evidence-based knowledge and the consultation of an expert panel, is increasingly being used in the field of psychiatry [141] and somatic medicine [142]. Our literature search retrieved a high proportion of low levels of evidence, thus highlighting the benefits of the experts' consultation. Moreover, the consultation triggered discussions of topics on which diverging expert opinions were found in the literature. During the formalized meetings and voting process, recommendation items often had to be clarified within the expert panel. This certainly improved the quality of our guidelines, but involved heavy logistic support and strong commitment from all the experts.

These guidelines will be implemented in several wards at our university general hospital, and their ability to change practice will be evaluated. A recent review on adherence to mental health guidelines showed that interventions such as academic detailing (visiting of practitioners by colleagues or specially trained staff to present and discuss guidelines), continuous quality improvement, or feedback may not be sufficient to change practice [143]. Additional clinical resources and redesigning of the system seem to be necessary to improve practice, according to current evidence on guidelines implementation [19]. Moreover, changes tend

to return to preintervention level after the cessation of intervention. Recent interventions to improve the management of delirium highlighted the need to enhance guidelines [144] or educational package [145] implementation by follow-up and teaching sessions. We intend to take into account our previous experiences on the implementation of guidelines on depression in general hospitals [21] and the results of the abovementioned studies when implementing these guidelines on delirium.

In conclusion, the development of these guidelines required an extensive literature search and a formalized multidisciplinary expert panel approach to achieve consensus on topics not yet adequately investigated by research. Major efforts will be needed to implement these guidelines in clinical practice, to enhance the application of evidence-based recommendations, and, thus, to improve patient care. Initiatives such as those from the Cochrane Library's recent protocols [146–148] and additional clinical research are mandatory to help improve the quality and the evidence base of such guidelines.

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