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Delirium in Older Persons
Advances in Diagnosis and Treatment

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IMPORTANCE Delirium is defined as an acute disorder of attention and cognition. It is a common, serious, and often fatal condition among older patients. Although often underrecognized, delirium has serious adverse effects on the individual's function and quality of life, as well as broad societal effects with substantial health care costs.

OBJECTIVE To summarize the current state of the art in diagnosis and treatment of delirium and to highlight critical areas for future research to advance the field.

EVIDENCE REVIEW Search of Ovid MEDLINE, Embase, and the Cochrane Library for the past 6 years, from January 1, 2011, until March 16, 2017, using a combination of controlled vocabulary and keyword terms. Since delirium is more prevalent in older adults, the focus was on studies in elderly populations; studies based solely in the intensive care unit (ICU) and non–English-language articles were excluded.

FINDINGS Of 127 articles included, 25 were clinical trials, 42 cohort studies, 5 systematic reviews and meta-analyses, and 55 were other categories. A total of 11 616 patients were represented in the treatment studies. Advances in diagnosis have included the development of brief screening tools with high sensitivity and specificity, such as the 3-Minute Diagnostic Assessment; 4 A's Test; and proxy-based measures such as the Family Confusion Assessment Method. Measures of severity, such as the Confusion Assessment Method–Severity Score, can aid in monitoring response to treatment, risk stratification, and assessing prognosis. Nonpharmacologic approaches focused on risk factors such as immobility, functional decline, visual or hearing impairment, dehydration, and sleep deprivation are effective for delirium prevention and also are recommended for delirium treatment. Current recommendations for pharmacologic treatment of delirium, based on recent reviews of the evidence, recommend reserving use of antipsychotics and other sedating medications for treatment of severe agitation that poses risk to patient or staff safety or threatens interruption of essential medical therapies.

CONCLUSIONS AND RELEVANCE Advances in diagnosis can improve recognition and risk stratification of delirium. Prevention of delirium using nonpharmacologic approaches is documented to be effective, while pharmacologic prevention and treatment of delirium remains controversial.

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D elirium, defined as an acute disorder of attention and cognition, is a common, life-threatening, and often preventable clinical syndrome in older persons. Often occurring after acute illness, surgery, or hospitalization, the development of delirium initiates a cascade of events culminating in loss of independence, increased morbidity and mortality, institutionalization, and high health care costs. In the United States, more than 2.6 million adults 65 years and older each year develop delirium and account for an estimated more than $164 billion in annual health care expenditures.[1] Given its adverse effect on function and quality of life, delirium holds significant societal implications for the individual, family, community, and the entire health care system.

Delirium remains underrecognized, and rates of identification have not improved significantly over time. Rates of *unrecognized delirium*, defined as delirium diagnosed by an expert assessor after the diagnosis was not made by the patient's treating physicians and nurses, ranged from 55% to 70% in 2000-2001[2,3] and still remain around 60% in 2015.[4] Delirium is a complex and challenging condition, and a synthesis of current evidence should optimize clinical care. The goals of this review were (1) to summarize the current approaches to diagnosis and treatment of delirium, (2) to highlight recent advances, and (3) to underscore critical gaps in knowledge where future research is needed to advance the field.

Current Approach to Diagnosis and Treatment of Delirium

Delirium remains a clinical diagnosis, and the condition is easily overlooked.[1] Recognition is based on brief cognitive screening and careful bedside observation of key features. The current reference standard diagnostic criteria are the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*) from the American Psychiatric Association[5] and the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* from the World Health Organization.[6] Key diagnostic features, derived from the *DSM-5* and the widely used Confusion Assessment Method (CAM),[7,8] include an acute onset and fluctuating course of symptoms, inattention, impaired level of consciousness, and disturbance of cognition indicating disorganization of thought (eg, disorientation, memory impairment, or alteration in language) (CAM algorithm in eFigure 2 in the Supplement). Other features supportive of the delirium diagnosis include alterations in sleep-wake cycle, perceptual disturbances (eg, hallucinations or misperceptions), delusions, inappropriate or unsafe behavior, and emotional lability.[7] Delirium includes both hypoactive and hyperactive forms. The hypoactive form is more common among older persons, often goes unrecognized, and is associated with higher rates of complications and mortality.[9,10]

The cornerstone of diagnosis is determining the patient's baseline mental status and the acuity of any changes; with delirium, the changes typically occur over hours to days. This step is critical and requires obtaining the history from a knowledgeable informant. Neglecting the baseline mental status assessment is a leading reason for a missed diagnosis, since the acute change might otherwise be missed. Once the baseline mental status is determined, delirium is diagnosed by using brief cognitive screening tests such as the Mini-Cog[11] or the Short Portable Mental Status Questionnaire[12] and rating with a validated delirium instrument.

Conditions that may mimic delirium include dementia, depression, and psychosis (Table 1). As described above, an acute change in mental status from baseline may distinguish delirium from other conditions. Furthermore, inattention, while common in delirium, tends to occur in later stages of dementia. For accurate differential diagnosis, knowledge of the patient's baseline is essential to make the diagnosis. Alteration in the level of consciousness is another feature unique to delirium that is less common with dementia, depression, or psychosis.

The next step is a careful physical and neurologic examination, searching for possible causes. Because delirium can signify an acute medical emergency, all patients presenting with delirium need rapid, targeted evaluation for electrolyte or metabolic derangements, infection, or organ failure. The specific selection of tests should be based on information obtained from the history and physical examination, keeping in mind that delirium is often multifactorial in etiology and can be influenced by a number of predisposing factors (eg, older age, cognitive impairment, multiple comorbidities), precipitating factors (eg, infections, metabolic derangement, drugs), or both. Some conditions presenting with symptoms of delirium, such as hepatic or uremic encephalopathy, acute drug intoxication, alcohol withdrawal delirium (delirium tremens), or Wernicke-Korsakoff syndrome (WKS), have specific treatments (eg, thiamine supplementation for WKS) and therefore should not be overlooked in the evaluation.

Examination of cerebrospinal fluid is not required for most older patients presenting with delirium and fever; however, lumbar puncture[13] should be strongly considered in patients presenting with fever, headache, signs suspicious for meningitis[14] or encephalitis,[15] or when a specific neurologic cause of acute mental status change (such as vasculitis or herpes encephalitis) must be excluded. Neuroimaging can be useful in identifying the etiology of delirium if the history suggests recent falls or examination reveals deteriorating mental status or focal neurologic findings.[16]

Delirium and dementia commonly coexist. It is important not only to distinguish between delirium and dementia diagnostically but also to recognize when delirium is superimposed on a preexisting dementia, which has important prognostic implications, including accelerated rate of cognitive and functional decline,[17] increased length of hospital stay,[18] and higher rates of rehospitalization,[17] institutionalization,[19] and death,[19] compared with dementia alone. Interview with a caregiver for baseline mental status, prior diagnosis of mild cognitive impairment or dementia, and time course of cognitive changes (typically over months for dementia), plus administration of proxy-rated tools, such as the Informant Questionnaire on Cognitive Decline of the Elderly,[20] can help establish the presence of an underlying dementia. The presence of depression should also be ruled out in the interview with the patient and family, using brief depression screening tools such as the Geriatric Depression Scale.[21]

Primary prevention of delirium with nonpharmacologic multi-component approaches has been shown to be effective and has gained widespread acceptance as the most effective strategy for delirium.[22] While many pharmacologic approaches have been evaluated in clinical trials, at present there is no convincing, reproducible evidence that any of these treatments are effective for either prevention or treatment of delirium.[1,23]

Key Points

Question What advances in diagnosis, prevention, and management of delirium in older adults have been introduced in the last 6 years?

Findings Brief screening tools and improved delirium severity measurement tools have been developed for recognition and risk stratification of delirium. Delirium prevention with nonpharmacologic multicomponent strategies is effective. For pharmacologic management of delirium, the benefits do not outweigh the harms, and recommendations are to reserve treatment for patients with severe agitation that poses safety risks.

Meaning Advances in screening and diagnosis of delirium can improve recognition and risk stratification, while implementation of nonpharmacologic delirium prevention strategies can substantially improve outcomes among older patients.

Methods

Search was conducted in Ovid MEDLINE, Embase, and the Cochrane Library from January 1, 2011, through March 16, 2017, using a combination of controlled vocabulary and keyword terms. Concepts were created for the topics of (1) delirium or confusion, (2) diagnosis or prevention or therapy, (3) randomized trials

Table 1. Clinical Features of Diseases That Mimic Delirium

Feature	Condition[a]			
	Delirium	Dementia	Depression	Psychosis
Acute change in mental status	+	−	−	±
Inattention	+	±	±	±
Altered consciousness	+	−	−	−
Disorganized thinking	+	±	−	+
Altered psychomotor activity	+	±	+	+
Chronic duration	±	+	+	±

[a] "±" indicates that the feature may be present.

(using the Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE, sensitivity- and precision-maximizing version, 2008 revision), and (4) elderly adults. The search was limited to articles published in English. In addition to randomized trials, the overall search strategy was also designed to find other types of studies (eAppendix 1 in the Supplement). We identified 2303 titles and abstracts from the electronic search and also found an additional 37 eligible articles from the reference lists of relevant studies. Two hundred fifty-four full-text articles were retrieved for manual review. One hundred twenty-seven articles were used for this review, of which 25 were clinical trials, 42 were cohort studies, 5 were systematic reviews and meta-analyses, and 55 were other categories including methodological papers, clinical guidelines, and biomarker studies that were not cohort studies. A total of 11 616 patients were represented in the treatment studies. The complete list of search strategies and a search flow diagram are provided in eAppendix 1 and eFigure 1 in the Supplement.

Studies based solely in the intensive care unit (ICU) were excluded, since this setting was considered outside the scope of the current review and has been examined in comprehensive reviews.[24,25] In addition, since delirium is more prevalent in older adults, we focused on studies in populations 65 years and older. For selected studies on pharmacologic prevention and treatment, article quality was rated with the Cochrane Collaboration tool for assessing risk of bias.[26]

Results

Clinical Diagnosis

Since 2011, the following new information has become available, and these sections highlight key advances in diagnosis during the past 6 years.

Screening Instruments

The CAM,[7] published in 1990, continues to be the most widely used delirium instrument worldwide, used in more than 4500 original published studies to date and translated into 19 languages. The CAM algorithm is based on the presence of 4 core features of delirium (acute onset and fluctuating course of symptoms, inattention, and either disorganized thinking or altered level of consciousness[7]) and has high sensitivity (94%-100%), specificity (90%-95%), and interrater reliability (κ = 0.92).[8,27] More recently, more than 20 delirium screening tools have been introduced, many of which have been developed in the past 6 years (**Table 2**). These screening tools are used to alert clinicians to the presence of pos-

sible delirium. Since screening tools have varying sensitivity and specificity, a positive screening test result should lead to further investigation for more definitive diagnosis of delirium.

Definitive diagnosis of delirium should be conducted by a trained, experienced clinician and would entail cognitive testing and neurologic examination for fulfillment of key diagnostic features, including disturbance in mental status that represents a change from baseline and fluctuates in severity during the day; inattention (reduced ability to sustain attention and follow conversations); disorganization of thought, such as problems with memory, orientation, or language; and impaired consciousness, such as hypervigilance, drowsiness, or stupor. The presence of an underlying organic etiology or multiple etiologies is also required. The 3-Minute Diagnostic Assessment (3D-CAM) provides a brief assessment (3 orientation items, 4 attention items, 3 symptom probes, and 10 observational items) that facilitates rating of the 4 core CAM features and demonstrated a sensitivity of 95% and specificity of 94% when compared with a clinical reference standard rating in a prospective validation study in hospitalized patients.[28] Another screening tool is the 4A's Test (4AT), which has been validated in various clinical settings.[30] This tool is also brief and easy to administer and has a sensitivity of 89.7% and specificity of 84.1%. The 4AT provides a score range suggestive of cognitive impairment for which more detailed cognitive testing is advised.[30] Both 3D-CAM and 4AT validation studies have high ratings by the Standards for Reporting of Diagnostic Accuracy criteria.[39]

In recent years, many well-established delirium screening tools have been adapted or used in various clinical and research applications. For instance, the CAM[7] is often used as a reference standard in studies of more newly developed delirium screening tools.[40] The Short CAM has been more recently adapted and validated across a large range of patient populations, including medical, surgical, ICU (CAM-ICU), emergency department, nursing home, and palliative care.[40] Other screening tools with more recent validation studies include the Nursing Delirium Symptom checklist (Nu-DESC), which includes assessment of disorientation, inappropriate behavior, inappropriate communication, illusions or hallucinations, and psychomotor retardation. The checklist has sensitivity of 72% and specificity of 80%[41]; however, limitations include the potential for overweighting of hyperactive or agitation symptoms and the risk of missing hypoactive delirium. The Modified Richmond Agitation and Sedation Scale (mRASS), which measures arousal, sedation, and level of consciousness, has been advocated as a screening tool for delirium. However, the mRASS has a low sensitivity of 64% to 70%,[42,43] and the usefulness of the scale depends on the prevalence of decreased mental status in the population. In settings with

Table 2. Characteristics of Delirium Screening Tools (Last 6 Years)[a]

Screening Tool	Setting	No. (% Male)	Age, Mean (SD), y	Assessment Time	Scoring	Sensitivity (Cognitively Impaired), %[b]	Specificity (Cognitively Impaired), %[b]	Interrater Reliability (95% CI)	Description (No. of Question Items)
3D-CAM[28]	Hospital	201 (38)	84 (5.4)	3 min (median)	Possible delirium if (1) acute onset or fluctuation AND (2) inattention AND EITHER (3) disorganized thinking OR (4) altered level of consciousness	95 (96)	94 (86)	95%	Screening tool derived from the CAM (10 PQI, 10 ORI)[c]
CAM-S[29],[d]	Hospital	1219 (41)	77-80[e]	Long form, 10-15 min; Short form, NR	Maximum score: 19 (long form), 7 (short form)	NA[f]	NA	Long form, ICC = 0.88; Short form, ICC = 0.92	Delirium assessment tool derived from the CAM (long form: 4 PQI, 2 CQI, 4 ORI; short form: 1 PQI, 1 CQI, 2 ORI)
4AT[30],[g]	Hospital	234 (36)	84 (5.9)	<2 min	Maximum score = 12; possible delirium when score ≥4	90 (94)	84 (91)	NR	Screening tool for delirium and cognitive impairment (5 PQI, 2 ORI)
DelApp[31]	Hospital	156	85 (delirium group) 87 (dementia group) 75 (control group)	<5 min	Maximum score = 10; median, 6 (IQR, 4-7) in delirium group, 10 (IQR, 10-10) in control group	98	93	NR	Software for objective measurement of attention (9 ORI, 1 PQI)[h]
FAM-CAM[32]	Home[i]	52 (33)[j]	82 (8)	NR	Possible delirium if (1) acute onset or fluctuation AND (2) inattention AND EITHER (3) disorganized thinking OR (4) altered level of consciousness	(88)	(98)	κ = 0.85 (0.65-1.0)	Screening tool for caregivers (11 CQI)
I-AGeD[33]	Hospital	88 (27)[k]	86.4 (8.5)	NR	Maximum score = 10; possible delirium when score >4	77.4[l]	63.2	NR	Caregiver-based questionnaire (10 CQI)
Inter-RAI[34],[m]	Hospital	239 (49)	82 (6.4)	NR	Possible delirium if (1) acute change in mental status and (2) mental function varies over the course of the day	82 (90)	91 (69)	κ = 0.65-0.76	Screening tool for acute care (4 ORI)
MOTYB + signs of confusion[35]	Hospital	265 (51.1)	69 (27)	NR	Possible delirium if the patient failed MOTYB or was confused (subjectively or objectively)	93.8 (87.5)	84.7 (71.4)	NR	Screening tool for acute care (2 PQI, 6 ORI)
RADAR[36]	Hospital, long-term care	193 (40)	80.8 (7.8)	7 s (average)	Maximum score = 3; possible delirium when score ≥1	73 (71.4)	67 (42.9)	κ = 0.34-0.79	Tool for nursing staff (3 ORI)
SQeeC[37]	Hospital	100 (40)	87	30 s to 3 min	Possible delirium if unable to answer first question or provides wrong answer to second question	83 (83)	81 (59)	NR	Tool for evaluating level of consciousness (2 PQI)
Sour Seven[38]	Hospital	80 (36)	81.3 (8.9)	1-2 min (nurses); 2-5 min (caregivers)	Maximum score = 18; possible delirium when score ≥4	89.5	90	64.3%-92.8%[n]	Tool for informal caregivers and untrained nurses (7 ORI)

Abbreviations: CAM, Confusion Assessment Method; CAM-S, CAM-Severity Score; CQI, caregiver questionnaire items; FAM-CAM, Family-CAM; ICC, intraclass correlation coefficient; Inter-RAI, Inter-Resident Assessment Instrument; IQR, interquartile range; I-AGeD, Informant Assessment of Geriatric Delirium scale; MOTYB, Months of the Year Backwards; NA, not applicable; NR, not reported; ORI, observer rating items; PQI, patient questionnaire items; RADAR, Recognizing Acute Delirium as Part of Your Routine; SQeeC, Simple Query for Easy Evaluation of Consciousness; 3D-CAM, 3-Minute Diagnostic Assessment; 4AT, 4 A's Test.

[a] Inclusion criteria: (1) study published during the defined search period, (2) reference standard delirium assessment was completed using *Diagnostic and Statistical Manual of Mental Disorders (DSM)* IV or 5, or DSM-derived criteria such as CAM, Delirium Rating Scale, or Neelon and Champagne Confusion Scale. Exclusion criteria: (1) study of delirium in the critically ill (intensive care unit); (2) validation study of a non-English version of an existing delirium screening tool. [b] Sensitivity and specificity of the screening tool to detect delirium against the gold standard such the *Diagnostic and Statistical Manual of Mental Disorders* criteria. Some studies also determined the sensitivity and specificity of the screening tool for detecting delirium in individuals with cognitive impairment, and those numbers are reported in parentheses. [c] There is a skip pattern option for which if any item in a section is answered incorrectly or endorsed as yes, then the rest of the PQI in that section and corresponding ORI can be skipped, allowing administration of fewer questions (as few as 3). However, the

3D-CAM was validated with administration of all items. [d] The CAM-S is intended to be used in addition to the original CAM algorithm; it will not yield a delirium diagnosis but only quantify the intensity of delirium. [e] CAM-S was validated in 2 different cohorts; mean age was 77 years in the SAGES Study and 80 years in the Project Recovery sample. [f] CAM-S is a tool to quantify the intensity of delirium; therefore, sensitivity and specificity as a delirium screening tool does not apply. [g] Information available at http://www.the4at.com. [h] DelApp is a visual sustained attention counting task and is still in research phase. [i] All patients enrolled in the study had preexisting cognitive impairment. [j] 52 dyads (patient and caregiver). [k] Construction cohort N = 88; 2 validation cohorts of N = 59 and N = 33. [l] The sensitivity and specificity of 77.4% and 63.2% were derived from a cutoff score of greater than 4 on the I-AGeD; sensitivity and specificity in patients without dementia were 100% and 65.2%, respectively. Sensitivity of 2 validation cohorts ranged from 70.0% to 88.9%; specificity ranged from 66.7% to 100%. [m] Delirium screening tool consists of 4 observational delirium items from the Inter-RAI acute care comprehensive assessment system: acute change mental status from baseline, mental function varies over the course of the day, episode of disorganized speech, and easily distracted. [n] Comparison of agreement between untrained nurses and geriatric psychiatrist calculated by each question; comparison of agreement between caregivers and geriatric psychiatrist ranged from 44% to 84% in agreement.

high prevalence of sedation and depressed sensorium, such as the postoperative recovery room and ICU, this approach may be valuable; however, routine use of the mRASS is not recommended outside of these settings, since many cases of delirium will be missed.

Assessment of Delirium Severity

The measurement of delirium severity has assumed increased importance for tracking clinical course and recovery, monitoring response to treatment, and evaluating pathophysiologic mechanisms. Widely used delirium severity measures have included the Delirium Rating Scale–Revised-98 (DRS-R-98)[44] and the Memorial Delirium Assessment Scale.[45] The DRS-R-98 has scale items covering language, thought processes, motor symptoms, and cognition that are designed to capture gradations of symptom intensity.[44] The Memorial Delirium Assessment Scale was designed for use in clinical intervention trials and has scale items for assessing disturbance in arousal, level of consciousness, as well as cognitive function and psychomotor activity.[45]

A recent advance is the development of the CAM-Severity Scale (CAM-S), a new scoring system based on either the short or long version of the CAM. A high-quality validation study involving 2 cohorts totaling more than 1219 patients showed that the CAM-S has strong psychometric properties and high predictive validity for important clinical outcomes related to delirium, including length of stay, hospital costs, nursing home placement, and death.[29] A subsequent study examined the severity of an episode of delirium over the entire hospital stay and compared 9 different measures reflecting intensity, duration, cognitive change, or a combination of these measures. This study demonstrated that episode severity measures including both intensity and duration, such as the sum of all CAM-S scores across the hospitalization, had the strongest association with posthospital outcomes at 30 and 90 days.[46] The Delirium Observation Screening scale is a new nurse-based delirium measure[47] that correlates strongly with DRS-R-98 scores, but validation studies have not yet been completed.

Approaches to Maximize Detection of Delirium

Because of its fluctuating nature and frequent hypoactive presentation, the detection of delirium can be especially challenging. Interview-based methods are sometimes conducted during brief encounters and need to be applied multiple times a day to improve the detection of delirium; however, this may not be feasible in many settings. Standardized chart-based methods,[48] based on identification of keywords (eg, mental status change, disoriented/reoriented) by trained clinician abstractors, can be used in combination with interviews to maximize detection of delirium, particularly episodes occurring during night shifts. These methods have been validated to show sensitivity of 74% and specificity of 83% in comparison with a reference standard rating or clinical consensus panel. Therefore, the combined method of interview plus chart review[48] is the recommended approach when complete and highly sensitive detection of delirium is needed.

Refinement of Approaches for Definitive Diagnosis

One of the problems in comparing different screening tools is that there is no uniform approach to delirium diagnosis by a clinical reference standard. In a recent review,[49] the reference standard was found to range from a single physician's clinical evaluation to

Table 3. American Geriatrics Society Clinical Practice Guidelines for the Prevention and Treatment of Postoperative Delirium[a]

Recommendation	Description
Strong: Benefits Clearly Outweigh Risks or Vice Versa	
Multicomponent nonpharmacologic interventions (for prevention)	Delivered by interdisciplinary team for at-risk older adults Includes mobility and walking, avoiding physical restraints, orienting to surroundings, sleep hygiene, adequate oxygen, fluids, and nutrition
Educational programs	Ongoing, provided for health care professionals
Medical evaluation	Identify and manage underlying organic contributors to delirium
Pain management	Should be optimized, preferably with nonopioid medications
Medications to avoid	Any medications associated with precipitating delirium (eg, high-dose opioids, benzodiazepines, antihistamines, dihydropyridines) Cholinesterase inhibitors should not be newly prescribed to prevent or treat postoperative delirium Benzodiazepines should not be used as first-line treatment of delirium-associated agitation Benzodiazepines and antipsychotics should be avoided for treatment of hypoactive delirium
Weak: Evidence in Favor of These Interventions, But Level of Evidence or Potential Risks Limit Strength of Recommendation	
Multicomponent nonpharmacologic interventions (for treatment)	Delivered by interdisciplinary team when older adults are diagnosed with postoperative delirium to improve clinical outcomes
Pain management	Injection of regional anesthetic at the time of surgery and postoperatively to improve pain control with the goal of preventing delirium
Antipsychotics	The use of antipsychotics (haloperidol, risperidone, olanzapine, quetiapine, or ziprasidone) at the lowest effective dose for shortest possible duration may be considered to treat delirious patients who are severely agitated, distressed, or threatening substantial harm to self, others, or both

[a] Adapted from American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults best practice statement[56] and abstracted clinical practice guideline.[23] Full guideline available at http://www.geriatricscareonline.org.

consensus diagnosis based on comprehensive assessment using information gathered from patients, nurses, family members, and medical records. Since sensitivity and specificity determinations for each screening tool can vary depending on the reference standard used, more standardization will improve the ability to cross-validate and to directly compare different screening tools.

Biomarkers for Delirium

Biomarkers have assumed increasing importance, since they may be useful for identifying patients at higher risk for developing delirium and yield clues to potential underlying pathophysiologic mechanisms. Because delirium can be due to different etiologies, various biomarkers, including inflammatory, neurodegenerative, metabolic, and neurotransmitter-based, have been examined in the past 6 years. Inflammation is thought to play an important role in the pathogenesis of delirium, and recent studies have focused on inflammatory markers, including interleukins and C-reactive protein[50] (eTable 1 in the Supplement). Although numerous biomarkers have been studied, none have yet been validated for clinical application, such as diagnosis or monitoring of delirium.

Novel Uses of Electroencephalography

The current role for electroencephalography (EEG) in the diagnosis of delirium is to aid in differentiating delirium from nonconvul-

Table 4. Multicomponent Nonpharmacologic Approaches
to Delirium Prevention

Approach	Description
Orientation and therapeutic activities	Provide lighting, signs, calendars, clocks Reorient the patient to time, place, person, your role Introduce cognitively stimulating activities (eg, reminiscing) Facilitate regular visits from family, friends
Fluid repletion	Encourage patients to drink; consider parenteral fluids if necessary Seek advice regarding fluid balance in patients with comorbidities (heart failure, renal disease)
Early mobilization	Encourage early postoperative mobilization, regular ambulation Keep walking aids (canes, walkers) nearby at all times Encourage all patients to engage in active, range-of-motion exercises
Feeding assistance	Follow general nutrition guidelines and seek advice from dietician as needed Ensure proper fit of dentures
Vision and hearing	Resolve reversible cause of the impairment Ensure working hearing and visual aids are available and used by patients who need them
Sleep enhancement	Avoid medical or nursing procedures during sleep if possible Schedule medications to avoid disturbing sleep Reduce noise at night
Infection prevention	Look for and treat infections Avoid unnecessary catheterization Implement infection-control procedures
Pain management	Assess for pain, especially in patients with communication difficulties Begin and monitor pain management in patients with known or suspected pain
Hypoxia protocol	Assess for hypoxia and oxygen saturation
Psychoactive medication protocol	Review medication list for both types and number of medications

sive status epilepticus, focal dyscognitive seizures, or psychiatric conditions. Recent studies support the use of EEG in patients with a known history of seizures, findings suggestive of seizures (eg, gaze deviation), history of brain trauma or stroke, or treatment with medications that lower seizure threshold (eg, fluoroquinolones, bupropion).[51,52] In a recent innovation, bispectral EEG monitoring and adjustment of anesthetic depth has been shown to be associated with a marked reduction in postoperative delirium[53,54] and is currently under investigation in a large clinical trial.[55]

Advances in Prevention and Treatment

Development of systematic reviews and guidelines have served to facilitate application of more evidence-based approaches. In 2014, the American Geriatrics Society and the American College of Surgeons jointly released clinical practice guidelines for the prevention and treatment of postoperative delirium.[23] The guidelines, developed in accordance with Institute of Medicine standards, highlight the importance of multicomponent nonpharmacologic prevention strategies, education of health care professionals, medical evaluation of delirium etiology, optimizing pain management with nonopioids, and avoiding high-risk medications (Table 3). New recommendations included avoidance of drug treatment for hypoactive delirium and avoidance of benzodiazepines for treatment of delirium, except in cases of alcohol or benzodiazepine withdrawal.

Prevention

Multicomponent Nonpharmacologic Interventions

Primary prevention with multicomponent nonpharmacologic approaches has been consistently demonstrated to be the most effective strategy for delirium prevention among hospitalized, non-ICU medical and surgical patients. These prevention strategies include early mobilization, adequate hydration, sleep enhancement, orientation to time and place, therapeutic activities such as reminiscence (for cognitive stimulation), and hearing and vision optimization by using hearing and vision aids as needed. Table 4 provides details on these specific approaches to guide clinicians in how to implement delirium prevention strategies.

Because delirium is usually precipitated by multiple factors, effective prevention strategies should be implemented together (typically 3 or more at a time) by a multidisciplinary team. In a meta-analysis of 14 interventional studies based on the Hospital Elder Life Program,[57,58] these approaches significantly reduced the risk of incident delirium by 53% (odds ratio, 0.47 [95% CI, 0.38-0.58), and the risk of falls by 62% (odds ratio, 0.38 [95% CI, 0.25-0.60]) among hospitalized, non-ICU patients 65 years and older.[22]

Multicomponent nonpharmacologic approaches are cost-effective, with 1 study demonstrating an incremental net monetary benefit of £8180 (US $12 852 in 2014), using a cost-effectiveness threshold of £20 000 (US $31 423) per quality-adjusted life year.[59] This study took the novel approach of statistical modeling for patients undergoing surgical hip fracture repair, using decision tree analysis to explore deterministic and probabilistic sensitivity analyses. A Cochrane review of delirium prevention examined 39 trials involving 16 082 patients[60] and found moderate-quality evidence that multicomponent nonpharmacologic interventions are effective for prevention of incident delirium but less robust for decreasing delirium severity or duration.[60] Educating nursing aides and caregivers, specialized geriatric units, and music therapy and psychotherapy have been examined for delirium prevention, but results are not definitive.[61,62] Multicomponent nonpharmacologic approaches for delirium prevention have been examined in specific patient populations. In 1 study of hospitalized patients with dementia, these approaches resulted in noticeable decreases in delirium incidence.[63] Prior to implementation of nonpharmacologic delirium prevention approaches, approximately 20% of patients developed postoperative delirium, whereas after implementation, only 4.9% of patients became delirious.[63]

However, in long-term care, cancer patients, and terminal illness, the effect of these interventions on delirium incidence has been more limited.[64-66] Geriatric consultative approaches have been applied in different settings, but their success is dependent on adherence by the health care staff to recommendations made by the consultants.[1]

Pharmacologic Approaches

Selected pharmacologic delirium prevention studies from the past 6 years are summarized in Table 5. In a recent Cochrane review that examined prophylactic antipsychotics compared with control for preventing delirium in hospitalized non-ICU medical and surgical adult patients 16 years and older, there was no clear benefit of antipsychotics as a group.[60] Some studies suggest that prophylaxis with antipsychotics can prevent postoperative delirium; however, methodologic limitations preclude a definitive recommendation at

Table 5. Selected Delirium Prevention Studies, Last 6 Years[a]

Sources by Category	Study Design	Setting (Study Duration)	Sample Size (Intervention/Control)	Intervention	Control	Outcome	Results, Intervention vs Control, No. (%)	Overall Quality Score[b]
Antipsychotics (Typical and Atypical)								
Fukata et al,[67] 2014	Randomized, open-label, prospective	Elective GI/orthopedic surgery (2007-2012)	119 (59/60)	Haloperidol, intravenous (2.5 mg/d, postoperative days 1-3)	No haloperidol	Delirium incidence	25/59 (42.4) vs 20/60 (33.3) P = .31	5
Hakim et al,[68] 2012	RCT	Cardiac surgery (2007-2010)	101 (51/50)	Risperidone, oral (0.5 mg/12 h postoperative day)	Placebo	Delirium incidence among those with subsyndromal delirium	7/51 (13.7) vs 17/50 (34) P = .03	6
Vochteloo et al,[69] 2011	PCT	Hip fracture surgery (2008-2009)	378 (173/205)	Haloperidol, oral (1 mg/twice daily in high-risk patients)	No haloperidol in lower-risk patients	Delirium incidence	73/173 (42.4) vs 29/205 (14.1) P < .001[c]	3
Wang et al,[70] 2012	RCT	Noncardiac surgery (2009-2010)	457 (229/228)	Haloperidol, intravenous (1.7 mg/d, postoperative day 1)	Placebo	Delirium incidence	35/229 (15.3) vs 53/228 (23.4) P = .03	4
Melatonin or Ramelteon								
Al-Aama et al,[71] 2011	RCT	Hospital, medical (2007-2008)	122 (61/61)	Melatonin, oral (0.5 mg/d)	Placebo	Delirium incidence	2/56 (3.6) vs 10/52 (19.2) P < .02[d]	5
de Jonghe et al,[72] 2014	RCT	Hip fracture surgery (2008-2012)	378 (186/192)	Melatonin, oral (3 mg/d)	Placebo	Delirium incidence	55/186 (29.6) vs 49/192 (25.5) P = .40	6
Hatta et al,[73] 2014	RCT	Hospital, medical (2011-2012)	67 (33/34)	Ramelteon, oral (8 mg/d)	Placebo	Delirium incidence	1/33 (3) vs 11/34 (32) P = .003	6
Perioperative Interventions[e]								
Ashraf et al,[74] 2015	RCT	Elective cardiac cathertization[f]	93 (47/46)	Premedication with diphenhydramine (25 mg) and diazepam (5 mg)	No premedication	Delirium incidence	0/47 (0) vs 0/46 (0) NS	4
Lurati et al,[75] 2012	RCT	Noncardiac surgery (2006-2010)	385 (184/201)	Sevoflurane	Propofol	Delirium incidence	21/184 (11.4) vs 29/201 (14.4) P = .38	6
Oh et al,[76] 2016	Retrospective	Hip fracture surgery (2012-2014)	174 (78/96)	Sugammadex, intravenous (2 mg/kg)	Neostigmine, intravenous (0.05 mg/kg) + glycopyrrolate, intravenous (0.01 mg/kg)	Delirium incidence	26/78 (33.3) vs 35/96 (36.5) P = .75	4
Stoppe et al,[77] 2013	RCT	Cardiac surgery (2011)	30 (15/15)	Xenon	Sevoflurane	Delirium incidence	3/15 (20) vs 4/15 (27) P = .67	4
Whitlock et al,[78] 2015	RCT	Cardiac surgery (2007-2013)	7507 (3755/3752)	Methylprednisolone, intravenous (250 mg at induction and at initiation of cardiopulmonary bypass)	Placebo	Delirium incidence	295/3755 (8) vs 289/3752 (8) P = .80	6
Djaiani et al,[79] 2016	RCT	Cardiac surgery (2011-2014)	183 (91/92)	Dexmedetomidine (0.4 µg/kg bolus, then 0.2-0.7 µg/kg/h)	Propofol (25-50 µg/kg/min)	Delirium incidence	16/91(17.5) vs 29/92 (31.5) P = .03	6
Liu et al[80] 2016	RCT	Orthopedic surgery (2014-2015)	197 (99/98)	Dexmedetomidine (0.2-0.4 µg/kg/h)	Placebo	Delirium incidence	In 65- to 75-year-olds, 7/31 (22.6) vs 16/30 (43.3) P < .01[g]	5

(continued)

Table 5. Selected Delirium Prevention Studies, Last 6 Years[a] (continued)

Sources by Category	Study Design	Sample Size (Intervention/Control)	Setting (Study Duration)	Intervention	Control	Outcome	Results, Intervention vs Control, No. (%)	Overall Quality Score[b]
Li et al,[81] 2017	RCT	285 (142/143)	Cardiac surgery (2014-2015)	Dexmedetomidine (0.6 µg/kg bolus, then 0.4 µg/kg/h)	Placebo	Delirium incidence	7/142 (4.9) vs 11/143 (7.7) $P = .30$	6
Dighe et al,[82] 2014	RCT, post hoc analysis	161 (83/78)	Cardiac surgery (2007-2011)	Gabapentin (200 mg 3 times daily ×4 d)	Placebo	Delirium incidence	10/83 (12) vs 7/78 (9) $P = .53$	4
Marcantonio et al,[83] 2011	RCT	16 (7/9)	Hip fracture surgery (2007-2008)	Donepezil, oral (5 mg/d)	Placebo	Delirium presence over time	7/11 (64) vs placebo 9/14 (64) $P = .94$[h]	6
Papadopoulos et al,[84] 2014	RCT	106 (51/55)	Orthopedic surgery[f]	Ondansetron, intravenous (8 mg/d ×5 d)	Placebo	Delirium incidence	18/51 (35.3) vs 29/55 (52.7) on postoperative day 2 $P = .07$[i]	5
Pesonen et al,[85] 2011	RCT	70 (35/35)	Cardiac surgery (2008-2009)	Pregabalin, oral (150 mg/d on day 1; 75 mg/12 h on postoperative days 1-5)	Placebo	CAM-ICU score[j]	Mean score, postoperative day 1: 24/25 vs 21/25 $P = .04$	5

Abbreviations: CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; GI, gastrointestinal; NS, nonsignificant; RCT, randomized clinical trial.

[a] Some studies were excluded if studies were conducted exclusively in the intensive care unit or the duration of intensive care unit stay could not be determined. Studies with overall quality score less than 2 were also excluded.

[b] The quality rating was based on the Cochrane risk of bias overall quality score, with 1 point assigned for each of 6 domains found to be at low risk of bias. Low risk of bias, 6 (low risk of bias in all domains), unclear risk of bias = not enough information to make a clear judgment (high or unclear risk of bias on 1 or more domains); high risk of bias, less than 4 (high risk of bias on ≥2 domains).

[c] In this study, the patients received prophylactic haloperidol if they were determined to be at high risk based on the Risk Model for Delirium score. Because of protocol violation, there were 26 patients in the high-risk group who did not receive haloperidol, but the delirium incidences in these patients were not significantly different from those of patients who received prophylaxis.

[d] Numerator and denominators calculated after the prevalent delirium cases were subtracted (melatonin n = 5, placebo n = 9).

[e] Delirium incidence was not the primary outcome for some of the perioperative intervention studies (Lurati et al[75] [tertiary end point], Whitlock et al[78] [secondary outcome]). They were included because of the study quality, intervention type, and large study population.

[f] Study duration not reported.

[g] This study examined the effect of dexmedetomidine on patients with amnestic mild cognitive impairment and in individuals with normal cognition, stratified by age. Patients with amnestic mild cognitive impairment: dexmedetomidine vs placebo (normal saline), 22.6% vs 43.3% ($P < .01$) for those aged 65 to 75 years and 37.5% vs 90% ($P < .01$) for those 75 years or older. Patients with normal cognition: dexmedetomidine vs placebo (normal saline) 11.9% vs 30.8% ($P < .01$) for those aged 65 to 75 years and 16.7% vs 36.8% ($P < .01$) for those 75 years or older.

[h] Denominator was number of interviews, more than 1 interview per patient.

[i] Study reports statistical significance on postoperative days 3 to 5, but the total number of individuals who experienced delirium in each group are not reported.

[j] Modified Finnish CAM-ICU score (highest 25 points).

this time (Table 5). The same meta-analysis also found minimal evidence to support the use of medications to prevent delirium, including cholinesterase inhibitors, melatonin, and melatonin-receptor agonist (ramelteon), based on meta-analysis.[60]

Delirium Prevention for the Surgical Patient

Most perioperative measures involving the use of different types of sedation or anesthesia have not effectively reduced the incidence of delirium (Table 5). One study showed that dexmedetomidine may be effective in reducing delirium incidence in patients with mild cognitive impairment, but this finding will need to be replicated in larger studies.[80] Other strategies, including tight control of glucose levels and blood transfusions for delirium prevention in the perioperative setting, have shown varying degrees of benefit.[86,87] Moderate-quality evidence suggests that adjusting the depth of anesthesia according to bispectral index monitoring can decrease the incidence of delirium.[60,88]

Treatment

Nonpharmacologic Approaches

Few recent studies have examined nonpharmacologic approaches for the treatment of delirium. One pilot study involving 143 nursing home patients examined a modified Hospital Elder Life Program in the long-term care setting for prevention and treatment of delirium and found that it was feasible, with high satisfaction rates and decreased hospitalization rates. However, further testing of the intervention in a clinical trial will be needed.[89] A recent clinical trial using daily therapeutic activities such as reminiscence activities for cognitive stimulation in the postacute care setting for delirium superimposed on dementia found no benefit on delirium duration or severity but did demonstrate significantly improved executive function and decreased length of stay.[90] Other studies have focused on specialized delirium rooms or improving sleep to treat delirium with use of earplugs, bright light therapy, and sleep protocols—but with varying and limited results.[91,92]

Pharmacologic Treatment Approaches

Selected pharmacologic delirium treatment studies from the past 6 years are summarized in Table 6. Most studies do not show benefit of antipsychotics in decreasing the duration or severity of delirium. A recent comprehensive, systematic review examined antipsychotic drugs including oral risperidone, oral olanzapine, oral seroquel, intramuscular ziprasidone, and oral, intravenous, and intramuscular haloperidol[100] and concluded that the current evidence does not support the use of antipsychotics for treatment (or prevention) of delirium in hospitalized older adults. There was no significant decrease in delirium incidence among 19 studies and no change in delirium duration, severity, hospital or intensive care length of stay, or reduction in mortality.

Potential harm was demonstrated in 2 studies in which more patients required institutionalization after treatment with antipsychotics. Moreover, in a randomized clinical trial of atypical antipsychotic drugs in palliative care settings, participants receiving oral risperidone or haloperidol had higher delirium symptom scores and were more likely to require breakthrough treatment compared with participants receiving placebo. Participants in the placebo/nonpharmacologic management group also had better overall survival compared with those in the haloperidol group.[99] Only a few limited studies have considered pharmacologic approaches other than antipsychotics for the treatment of delirium, and no definitive recommendations can be made at this time. More research is needed to establish safe and effective pharmacologic treatment approaches.

Discussion

To assist clinicians with the evaluation and treatment of delirium, a detailed suggested algorithm is presented in the **Figure**, which synthesizes recent evidence gleaned from this comprehensive review with all prior evidence. The algorithm entails assessing delirium risk, instituting delirium prevention measures, evaluating and managing delirium once its presence is confirmed, and treating delirium using both nonpharmacologic and, in appropriate cases, pharmacologic strategies. While such an approach has not been validated, it is based on the best available evidence from prior studies and incorporates relevant recent evidence, such as current evidence against the use of antipsychotic medications in the treatment of delirium because of lack of efficacy and increased risk of adverse events and poor outcomes.

Advances in diagnosis have included the development of new brief screening tools (Short-CAM adaptations, 3D-CAM, and 4AT) to improve delirium identification. Delirium severity, such as that measured with the new CAM-S scoring, has been recognized as increasingly important for tracking clinical course, prognosis, and response to treatment. Measures that capture both intensity and duration of an episode of delirium (such as the sum of all CAM-S scores) correlate best with clinical outcomes in a direct, graded relationship. For complete capture of delirium episodes, a combined approach including interview and chart review is recommended. Intraoperative EEG monitoring and bispectral monitoring are emerging strategies that identify delirium risk and help to adjust depth of anesthesia, which may decrease risk.

Primary prevention with multicomponent nonpharmacologic approaches such as reorientation, early mobilization, therapeutic activities, hydration, nutrition, sleep strategies, and hearing and vision adaptations are effective and cost-effective and remain the cornerstone of delirium management. However, these approaches can be labor intensive, and streamlined approaches include the use of volunteers, aides, or nonlicensed professionals to enhance feasibility and reduce costs of implementation. Development of effective treatments have been hindered by multiple challenges, including the multifactorial contributors, diagnostic complexity, multimorbidity, heightened risk of adverse effects (ie, drug interactions), and need for multicomponent approaches. Although promising approaches are emerging, safe and highly effective pharmacologic treatments for delirium have not yet been identified. Antipsychotics are often used for patients with delirium and with severe agitation and safety risks but may contribute to heightened adverse effects and poorer long-term outcomes. Therefore, similar to the initiative by the Centers for Medicare & Medicaid Services to reduce the use of antipsychotics for improved dementia care, a concerted effort to reduce the use of antipsychotics and focus on nonpharmacologic management may improve delirium care.

Several limitations of this review must be acknowledged. The literature search was restricted to the past 6 years; however,

Table 6. Selected Delirium Treatment (Typical and Atypical Antipsychotics) Studies, Last 6 Years[a]

Sources by Category	Study Design	Setting (Study Duration)	Sample Size (Intervention/Control)	Intervention	Control	Outcome	Results, Intervention vs Control, No. (%)	Overall Quality Score[b]
Atalan et al,[93] 2013	RCT	Cardiac surgery (2010-2012)	53 (27/26)	Morphine sulfate, intramuscular (5 mg, up to 20 mg/d)	Haloperidol, intramuscular (5 mg, up to 20 mg/d)	Delirium duration in those with hyperactive delirium	31.56 h vs 33.9 h; P = .61	4
Boettger et al,[94] 2015	Open-label, matched	Hospital, oncology (2000-2006)	84 (21 haloperidol/21 risperidone, 21 aripiprazole, 21 olanzapine)	Haloperidol (5.5 mg)	Risperidone (1.3 mg) Aripiprazole (18.3 mg) Olanzapine (7.1 mg) (mean doses 4-7 d)	Delirium resolution and adverse-effect profiles (typical vs atypical)	16/21 (76.2) vs 18/21 (85.7) [risperidone], 16/21 (76.2) [aripiprazole], and 13/21 (61.9) [olanzapine] P = .42[c]	3
Kishi et al,[95] 2012	Case series	Hospital, cancer[d]	29 (intervention)	Risperidone, oral (0.5-1 mg to start, then titrated)	No control group	Delirium severity (responder, 25% reduction in the DRS-R-98 from baseline to day 7)	No significant differences in the number of treatment responders vs nonresponders, 14/29 (48) vs 15/29 (51)	2
Maneeton et al,[96] 2013	RCT	Hospital, medical (2009-2011)	52 (24/28)	Quetiapine, oral (25-100 mg/d for 1-7 d)	Haloperidol, oral (0.5-2 mg/d for 1-7 d)	Delirium severity by DRS-R-98 (higher score = more severe)	22.9 (6.9) vs 21.7 (6.7) P = .59	5
Schrøder Pedersen et al,[97] 2014	Prospective cohort	Cardiac surgery (2012)	240 (123/117)	Standardized treatment with haloperidol, oral (2.5-5 mg 3 times daily × 1.5 d, then taper)	No standardized treatment protocol	Delirium duration	3 (range, 1-5) d vs 1 (range, 1-4) d P = .23	3
Yoon et al,[98] 2013	Prospective observational	Hospital, medical surgical[d]	80 (23 haloperidol/21 risperidone, 18 olanzapine, 18 quetiapine)	Haloperidol, oral (0.5-10 mg/d)	Risperidone, oral (0.25-4 mg/d) Olanzapine, oral (1-20 mg/d) Quetiapine, oral (25-200 mg/d)	Delirium severity ≥50% reduction from baseline by DRS-K	15/23 (65.2) vs 14/21 (66.6) [risperidone], 12/18 (66.6) [olanzapine], and 13/18 (72.2) [quetiapine] P = .97	2
Agar et al,[99] 2017	RCT	Inpatient hospice, hospital palliative care (2008-2014)	249 (81 haloperidol, 82 risperidone/86 placebo)	Haloperidol, risperidone, oral (0.25 mg every 12 h, up to 2 mg/d)[e]	Placebo	Delirium symptom scores on day 3 (higher score = more severe)	Haloperidol vs placebo: 0.24 U higher in haloperidol group, P = .009 Risperidone vs placebo: 0.48 U higher in risperidone group, P = .02	6

Abbreviations: DRS-K, Korean version of the Delirium Rating Scale–Revised-98 (DRS-R-98); RCT, randomized clinical trial.

[a] Some studies were excluded if studies were conducted exclusively in the intensive care unit or the duration of intensive care unit stay could not be determined. Studies with overall quality score less than 2 were also excluded.

[b] The quality rating was based on the Cochrane risk of bias overall quality score, with 1 point assigned for each of 6 domains found to be at low risk of bias. Low risk of bias, 6 (low risk of bias in all domains), unclear risk of bias = not enough information to make a clear judgment (high or unclear risk of bias on 1 or more domains); high risk of bias, less than 4 (high risk of bias on ≥2 domains).

[c] Adverse effects: extrapyramidal symptoms (haloperidol, 4 of 21 [19%]; risperidone, 1 of 21 [4.8%]), sedation (olanzapine, 6 of 21 [28.6%]).

[d] Study duration not reported.

[e] The study had different loading, initial, and maximum doses for participants 65 years or younger and for participants older than 65 years. Participants 65 years or younger received a 0.5-mg loading dose with the first dose of 0.5 mg, then 0.5-mg maintenance dose every 12 hours. Doses could be titrated by 0.25 to 0.5 mg, with maximum dose of 4 mg. For participants older than 65 years, the loading, initial, and maximum doses were halved.

Figure. Suggested Algorithm for Delirium Evaluation and Treatment[a]
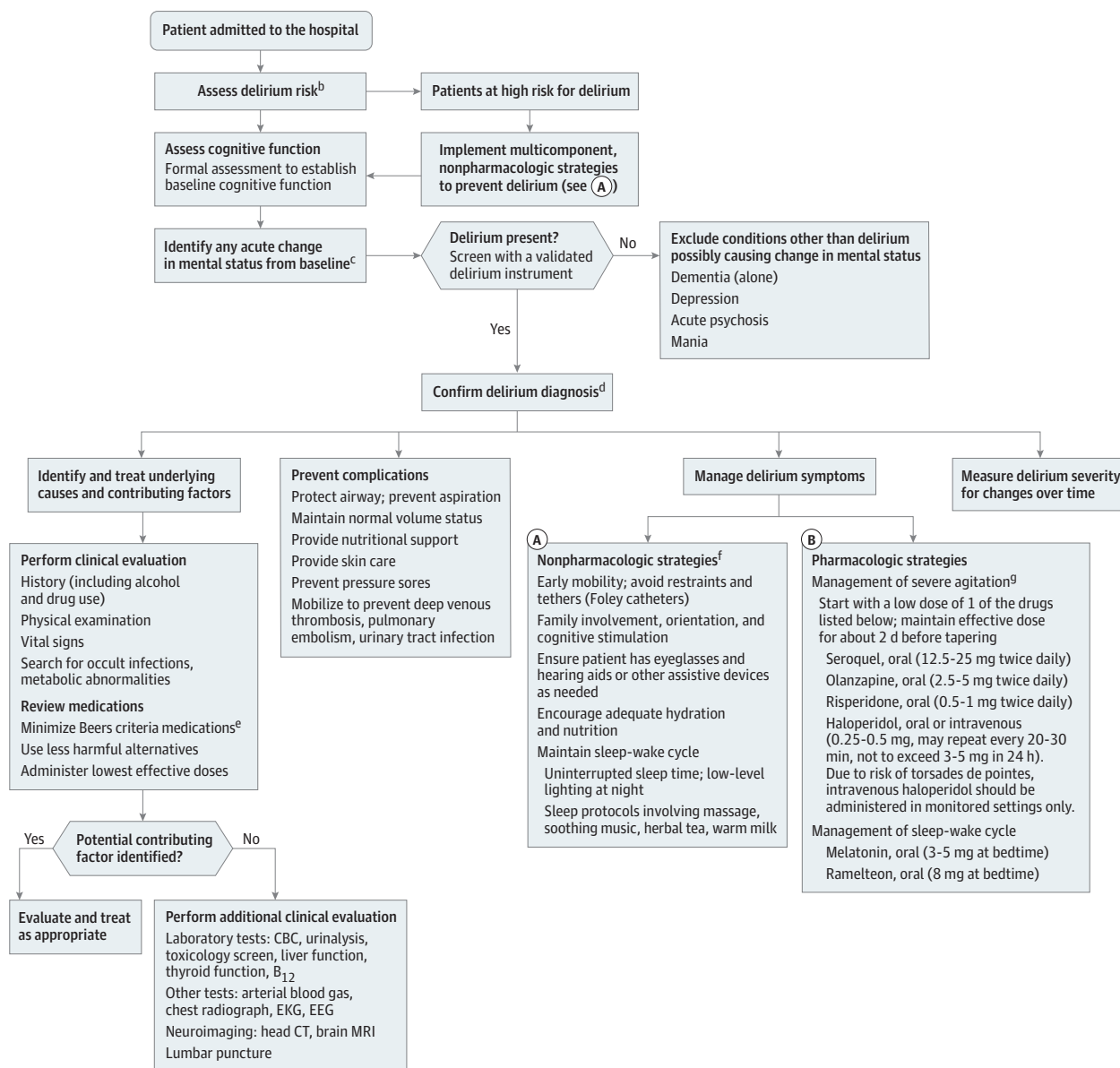
CBC indicates complete blood cell count; CT, computed tomography; EEG, electroencephalogram; EKG, electrocardiogram; MRI, magnetic resonance imaging.

[a] Although the algorithm is evidence-based, it has not been validated.

[b] Common delirium risk factors include dementia or cognitive impairment, functional or mobility impairment, visual or hearing impairment, dehydration, sleep deprivation, history of alcohol misuse, advanced age (>70 years), multiple coexisting medical illnesses, and presence of specific comorbidities (eg, stroke, depression).[1]

[c] Delirium should be considered a life-threatening medical emergency until proven otherwise; therefore, the presence of an acute change in mental status should trigger a rapid evaluation. Increasingly, many hospitals are incorporating delirium pathways (standing order sets for evaluation and treatment of delirium), implementation of delirium screening tools into the electronic medical record, and dedicated delirium wards/services.

[d] Delirium is diagnosed in the presence of the following core features: (1) acute and fluctuating mental status change from baseline; (2) inattention PLUS (3) disorganized thinking OR (4) altered level of consciousness.[10]

[e] The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (Beers Criteria)[34] can help identify medications that should be avoided or used at lowest possible dose. This includes tricyclic antidepressants, anticholinergics, antihistamines (eg, diphenhydramine), benzodiazepines, corticosteroids, H_2-receptor antagonists, meperidine, sedative-hypnotics, thioridizine, and chlorpromazine.

[f] Multicomponent, nonpharmacologic strategies should be used for both delirium prevention and treatment.

[g] Reserve antipsychotic medications for use only when behaviors (ie, agitation, hallucinations) pose a serious safety hazard to patient, staff, or both or when there is risk of interrupting essential medical care.

inclusion of recent systematic reviews allowed incorporation of many additional years of evidence. Studies based solely in the ICU were excluded, because they were considered outside the scope of this review and already covered in recent comprehensive reviews. Moreover, only studies published in English were included. Last, for many areas explored, we found weak to insufficient evidence, which limited

our recommendations. High-quality, adequately powered randomized clinical trials represent an important priority for the field.

Advances in the pathophysiologic understanding of delirium will be critical to advance the diagnosis and treatment of delirium. High-priority areas for future investigation are outlined in eTable 2 in the Supplement. Biomarkers are likely to play an increasing role in confirming diagnosis, stratifying risk, monitoring severity, and providing mechanistic understanding of delirium. Because inflammation is thought to play an important role in the pathogenesis of delirium,[101] inflammatory markers are widely studied for delirium risk stratification and monitoring (eTable 1 in the Supplement). Although several studies have shown the association of elevated levels of inflammatory biomarker levels, including interleukins and C-reactive protein, with delirium, the results are not always consistent and not yet ready for clinical application.[50,102] Similar to biomarker studies in other fields, standardization of assay platforms across laboratories and validation across different clinical populations will facilitate incorporation of biomarkers into clinical practice.

Innovative treatment approaches may include identifying pathophysiologically targeted approaches, boosting cognitive reserve, providing neuroprotection, enhancing sleep, and using multipronged combination approaches. Given the complex and multifactorial etiology of delirium, innovative approaches are greatly needed to break the escalating cycle of brain dysfunction that is the hallmark of the disorder and thereby effectively treat this condition, which is common and a highly morbid condition among older adults.

Conclusions

Delirium is a common, serious condition associated with increased morbidity and mortality in older patients as well as enormous societal costs. Advances in diagnosis can improve recognition and risk stratification of delirium, and many brief delirium screening tools have been developed in the past 5 years to allow improvement in recognition and risk stratification. Along with thorough clinical examination and laboratory testing, additional tools such as imaging and fluid biomarkers are being studied to enhance clinical risk stratification and diagnosis. Pharmacologic prevention and treatment of delirium remains controversial, and nonpharmacologic management of delirium remains the cornerstone of delirium prevention and treatment. Prevention of delirium using nonpharmacologic approaches is documented to be effective, whereas pharmacologic prevention and treatment of delirium remains controversial.

Future high-quality, adequately powered studies of pharmacologic treatment are a priority to identify approaches that are effective and safe.

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