Delirium and long term cognition in critically ill patients

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ABSTRACT

Delirium, a form of acute brain dysfunction, is very common in the critically ill adult patient population. Although its pathophysiology is poorly understood, multiple factors associated with delirium have been identified, many of which are coincident with critical illness. To date, no drug or non-drug treatments have been shown to improve outcomes in patients with delirium. Clinical trials have provided a limited understanding of the contributions of multiple triggers and processes of intensive care unit (ICU) acquired delirium, making identification of therapies difficult. Delirium is independently associated with poor long term outcomes, including persistent cognitive impairment. A longer duration of delirium is associated with worse long term cognition after adjustment for age, education, pre-existing cognitive function, severity of illness, and exposure to sedatives. Interestingly, differences in prevalence are seen between ICU survivor populations, with survivors of acute respiratory distress syndrome experiencing higher rates of cognitive impairment at early follow-up compared with mixed ICU survivor populations. Although cognitive performance improves over time for some ICU survivors, impairment is persistent in others. Studies have so far been unable to identify patients at higher risk of long term cognitive impairment; this is an active area of scientific investigation.

Introduction

Delirium, a neuropsychiatric syndrome characterized by acute, fluctuating disturbances of consciousness and cognition, is the most common manifestation of critical illness related brain dysfunction, occurring in up to 80% of the sickest patients admitted to an intensive care unit (ICU).[1-5] Patients who need ICU admission are at risk for delirium because of the severity of their illness and exposures in the ICU (for example, sedation and immobilization), a danger that may be exacerbated by cerebral metabolic insufficiency, peripheral inflammation and/or neuroinflammation, and neurotransmitter imbalances, as well as neuroanatomical substrates and failure of network connectivity.[6 7]

Delirium is a major public health problem, as it is associated with persistent morbidity including long term impairment in cognitive performance. Although the exact mechanism of experienced long term morbidities in ICU survivors is unknown, delirium is thought to accelerate cognitive decline in those with and without pre-existing impairment in cognitive function.[8-11] A recent meta-analysis of 24 studies (including 3562/6987 patients who experienced delirium) showed a significant association between delirium and long term cognitive impairment (estimated effect size (Hedges *g*) for 23 studies was 0.47 (95% confidence interval 0.35 to 0.59); P<0.001).[12] Other long term consequences associated with delirium include restrictions in motor function,[9 13] ongoing need for care in long term care institutions,[14 15] a higher likelihood of discharge to destinations other than home,[16] and greater long term disability.[17]

The most recent evidence based guidelines and consensus statements recommend the prioritization of a multicomponent non-drug approach to the management of delirium,[18-21] with a focus on prevention and early recognition. Embedded within recent evidence based clinical practice guidelines are recommendations to implement care bundles that include use of a validated instrument for daily assessment of all ICU patients for delirium.[20-24] Despite evidence of benefit, rates of compliance with care bundles remain low.[25] This shortcoming may be of particular importance given the recent covid-19 pandemic, during which standard of care has been strained by resource limitations (box 1). Recent reports from regions of the world hardest hit by covid-19 suggest that a flexible approach to management algorithms may be needed (box 2).

This review focuses on critical illness related delirium and long term cognitive impairment. It is aimed at clinicians caring for patients during and

Box 1: Acute neurologic manifestations in patients infected with covid-19

Early studies indicate that 20-30% of patients with covid-19 will present with or develop delirium during their hospital admission, with rates of 60-70% in cases of severe illness.[26] In a prospective cohort (n=140) of critically ill patients from two ICUs in Strasbourg, France, delirium was diagnosed in 80% of patients at least once during their ICU stay; hyperactive delirium was more common (87%) than hypoactive delirium (13%).[27] Experienced agitation required prolonged use of neuroleptic and sedative agents, which was associated with a statistically significant increase in the duration of mechanical ventilation (mean ratio 1.49; 95% confidence interval 1.01 to 2.20; P=0.045).[27] In a retrospective cohort (n=56), the use of low molecular weight heparin (enoxaparin 1 mg/kg/d) was associated with less frequent delirium events (P=0.004) and was accompanied by lower C reactive protein concentrations (P=0.006).[28] Heparin has been implicated in binding to SARS-CoV-2 spike proteins as well as down-regulating interleukin-6.[29] Interleukin-6 has been shown to be elevated in covid-19 patients.[30] Prevention of thrombosis and its subsequent inflammatory process may reduce the occurrence of delirium in covid-19 patients.28 Further studies are ongoing.

In addition to direct structural changes being associated with delirium and other neurologic changes in patients with covid-19, patients with severe disease may receive deeper sedation, fewer breathing trials, and more limited mobility sessions than other critically ill patients. A worldwide two day prevalence study of ABCDEF* bundle practices across 212 ICUs in 38 countries found implementation rates to be low: pain assessment (45%), paired spontaneous awakening trial and spontaneous breathing trial (28%), sedation assessment (52%), delirium assessment (38%), early mobility and exercise (16% if patient being mechanically ventilated), and family engagement and empowerment (16%).[31] In the face of staggering numbers of critically ill patients with covid-19 met with an imbalance of staffing and resources to meet the demand,[32] patients are unlikely to receive the usual quality of care. Prioritizing minimization of sedation, daily breathing trials, early mobility, and other evidence based practices is time intensive and coordination intensive. The impact of unprecedented strain on ICU capacity during different peaks of the pandemic has yet to be determined; however, many critically ill patients may not have been receiving the same standard of clinical care as before the pandemic (for example, prolonged sedation), and as a result their outcomes, such as rates of delirium and death, may be worse.[33] Critically ill patients in isolation as a result of their disease are particularly vulnerable as covid-19 related concerns create further challenges to receipt of usual care. Most recently, a multicenter cohort study including 2088 patients (88% mechanically ventilated) from 69 ICUs across 14 countries reported a prevalence rate of a patient ever being delirious, over the 21 day data collection period, of 55%.[34] Requirement for mechanical ventilation; use of restraints; opioid, benzodiazepine, and vasopressin infusions; and antipsychotic administration were all associated with an increased risk of delirium the following day (all P≤0.04), whereas family visitation was associated with a decreased risk of delirium (P<0.0001).[34]

*Assess, prevent, and manage pain, Both spontaneous awakening trials and spontaneous breathing trials, Choice of analgesia or sedation, Delirium: assess, prevent, and manage, Early mobility and exercise, and Family engagement and empowerment.

after ICU admission. We describe the epidemiology, criteria and tools for identification, and approaches to management of delirium in a critically ill patient population. We also describe the epidemiology, risk factors, and interventions for long term cognitive impairment in ICU survivors.

Sources and selection criteria

We did a PubMed search of articles published from 1 January 2010 to 1 September 2020, using the following search terms in combination with "delirium": "delirious", "acute confusion" or "inattention", "CAM-ICU" or "ICDSC", "management", "ICU", "acutely ill", or "critically ill". We included only peer reviewed articles written in English and involving adults. We screened 6590 titles for relevance, selected 426 for more detailed review on the basis of title and abstract, and finally included 123 articles. We gave precedence to large key studies that have informed international guidelines. We also reviewed a wider range of recent studies for which conclusions and evidence are mixed. We excluded case reports and small case series of non-covid-19 ICU patients. We did, however, include articles of historical importance, including pivotal trials outside of the searched decade. In addition, we searched the reference lists of high quality articles and reviews, and we included selected randomized controlled trials (RCTs), observational studies, systematic reviews, and meta-analyses from these sources. In reviewing the covid-19 literature, we included lower quality of evidence, including case series and case reports, but maintained the requirement for peer review. The search for covid-19 specific literature was last updated on 31 December 2020. All studies were organized in EndNote X9 (fig 1).

Epidemiology

Delirium is a syndrome characterized by an acute change or fluctuation in baseline mental status, inattention, and either disorganized thinking or altered level of consciousness. The cardinal features of delirium are disturbed level of consciousness, with reduced ability to focus, sustain, or shift attention, and either a change in cognition or the development of a perceptual disturbance (that is, hallucinations).[41] The classic three motoric presentations of delirium include hyperactive delirium (2%), characterized by agitation, aggression, disorientation, and hallucinations; hypoactive delirium (44%), characterized by lethargy, motor slowness, and social withdrawal; and mixed delirium (55%), characterized by fluctuations between hypoactive and hyperactive subtypes [42-44] (table 1).

The prevalence of delirium in an ICU patient population ranges from 32% to 87%.[45-49] Prevalence seems to vary considerably depending on whether the population studied received mechanical ventilation and other risk factors. For instance, the prevalence of delirium in a study of ventilated burn victims was 77%,[46] compared with 20% in a study of patients who were never intubated.[49] Different clinical phenotypes (phenotypes defined by clinical risk factors) of delirium were first used in an observational cohort of 97 patients receiving mechanical ventilation and showing differential responses to daily interruption of continuous sedation.[50] Delirium that was rapidly reversible with interruption of sedation was associated with shorter duration of mechanical ventilation, length of stay in ICU, and length of stay in hospital than was persistent delirium,[50] although the percentage of patients with rapidly reversible delirium was small (12%). Patients with persistent delirium were sicker, older, more septic, and likely more encephalopathic.[50] This study was the first to show the existence of different

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Box 2: Long term cognitive outcomes of survivors of covid-19 related critical illness

Few data are available on long term outcomes and recovery after severe covid-19 infection. A meta-analysis of 28 studies (n=2820) assimilated data on long term outcomes after coronavirus infection (SARS and MERS), reporting high rates of post-traumatic stress (39%), depression (33%), and anxiety (30%) at six months.[35] A prospective cohort study of covid-19 survivors (n=143), 19 of whom needed ICU admission, found high rates of persistent symptoms of fatigue, dyspnea, joint pain, and chest pain for two months after hospital discharge.[36] Cognitive impairment was not studied in these investigations. However, in a prospective cohort study comparing outcomes between patients with covid-19 who had survived an admission to the ward and those who needed ICU admission, after a mean of 110 days following hospital discharge, 34% of patients complained of memory loss and no difference was found between groups in terms of perceived symptoms.[37] In a single center case series, 28 patients were seen six weeks after hospital discharge, and 57% had mild cognitive impairment on completing the Montreal Cognitive Assessment.[38] In one case report, a 39 year old patient transferred for inpatient physical rehabilitation for profound ICU acquired weakness was later determined to have moderate to severe cognitive impairment (processing speed, waking memory, visuospatial processing, and executive function).[39] As a result, a multimodal cognitive rehabilitation strategy was incorporated into his physical rehabilitation, demonstrating the diverse rehabilitation challenges considering likely occult and subtle cognitive changes in covid-19 survivors.[39] Reduced access to essential rehabilitation services exacerbates delirium and is likely to impede cognitive recovery after critical illness. Many outbreaks of SARS-CoV-2 infection have occurred in skilled facilities. Patients and their caregivers may be reluctant to accept placement at a post-acute care facility given the possible risks; if they are willing, limits or delay to access may be present owing to closures, downsizing, or processes in place for quarantine. As a result, a greater proportion of patients may be discharged home, placing additional responsibility on informal caregivers and outpatient services. In a recent prospective cohort study of covid-19 survivors (n=1648; 405 received treatment in the ICU), 78% of patients were discharged home and 13% were discharged to a skilled nursing or rehabilitation facility.[40]

phenotypes with distinct outcomes. More recently, in a large multicenter, prospective cohort of 1040 ICU patients with acute respiratory failure, shock, or both, patients developed multiple clinical phenotypes of delirium including sedative associated, hypoxic, septic, metabolic, and unclassified delirium (that is, delirium in the absence of all other clinical risk factor phenotypes).[51] During their ICU stay, more than half of patients experienced hypoxic, septic, or sedative associated delirium, whereas metabolic and unclassified phenotypes were less common.[51] The percentage of patients experiencing either hypoxic or sedative associated delirium decreased over the course of ICU stay. Longer durations of sedative associated delirium, the most commonly experienced phenotype, predicted worse long term cognitive performance at both three and 12 months. Similarly, longer durations of hypoxic delirium (difference in score comparing three days versus zero days: −3.76, 95% confidence interval −7.16 to −0.37), septic delirium (−3.67, −7.13 to −0.22), and unclassified delirium (−4.70, −7.16 to −2.25) also predicted worse cognitive function at 12 months, whereas metabolic delirium did not.[51] These findings would suggest that clinicians should consider different clinical phenotypes of delirium as distinct indictors of acute brain injury and, in so doing, attempt to identify and mitigate relevant risk factors in an attempt to reduced long term sequelae (fig 2).

Effect of delirium on outcomes in ICU patients

In a recent meta-analysis, the risk ratio for death in patients with delirium was 2.2 (95% confidence interval 1.8 to 2.7; P<0.001).[52] Patients with delirium have increased mortality at six months, compared with patients who were never delirious (approximately 20-25% increase in risk)[49 53]; one prospective cohort study showed that the number days of delirium in the ICU was associated with time to death at one year after admission to ICU (hazard ratio 1.1, 1.0 to 1.2).[54] These findings are at odds with those of a recent, larger prospective cohort of more than 1000 ICU survivors that found no association between days delirious in the ICU and mortality at one year, after adjustment for sex, type of admission, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, and the cumulative Sequential Organ Failure Assessment (SOFA) score throughout the ICU stay.[55] In a prospective cohort of similar size, again no association was seen between delirium and mortality after adjustment for time varying confounders, suggesting that the evolution of disease severity before the onset of delirium was responsible for increased risk of death in ICU.[56] An increased absolute risk of mortality of 2.0% (95% confidence interval 1.2% to 2.8%), however, was seen in post hoc analyses, when delirium persisted for at least two days.[56] Patients with delirium had longer length of stay (standard mean difference 1.4 (0.99 to 1.8) days; P<0.001) than did those without delirium. Additionally, mean duration of mechanical ventilation was approximately two days longer than in patients without delirium (standard mean difference 1.8 (0.31 to 3.3) days; P<0.001).[52] Delirium carries an annual cost of $4bn to $16bn (£2.83-11.33bn; €3.28-13.13bn) in the US alone.[57]

Assessment of delirium in the ICU

The Confusion Assessment Method for the ICU (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) are the most commonly used tools for assessing delirium. On the basis of validation studies, they are recommended in most clinical practice guidelines, although other delirium assessment tools have been developed for use in the ICU (table 2). The CAM-ICU has been validated to assess delirium in ICU patients who may be non-verbal owing to mechanical ventilation and who can be assessed while sedated (unless they are comatose—that is, do not respond in any way to verbal stimulus).[48] Using a structured format that can be applied during a two to five minute examination, this tool evaluates four features of delirium—namely, acute onset or fluctuating course of mental status change, inattention, disorganized thinking, and altered level of consciousness. When administered by bedside nurses with no formal psychiatric training, the CAM-ICU showed high accuracy (sensitivity of 93-100%;

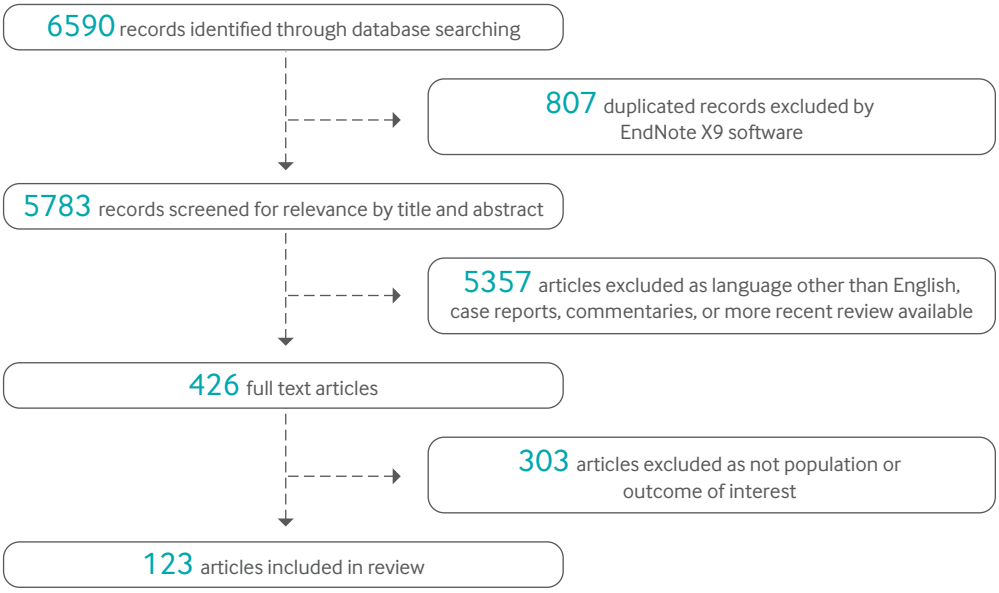

Fig 1 | Flow diagram of included articles

specificity 98-100%) and inter-rater reliability (κ=0.96) in a single center study.[48] The eight domain ICDSC, by contrast, assesses patients for eight signs and symptoms of delirium throughout a nursing shift, with a score of four or greater being positive for delirium. Interestingly, in a validation study of the ICDSC in medical-surgical ICU patients, the checklist showed a higher sensitivity (99%) than the CAM-ICU but a lower specificity (64%).[66] The items of the ICDSC (consciousness levels, inattentiveness, disorientation, hallucination, psychomotor agitation or retardation, inappropriate speech or mood, sleep-wake disturbance, symptom fluctuation) can be evaluated during daily routine nursing assessments.

Management of delirium

Risk factor reduction

The initial management of delirium should involve a detailed review of possible risk factors that may have triggered the episode of delirium. A systematic review of 33 studies identified 11 risk factors for delirium in the ICU, supported by medium to strong evidence.[67] Risk factors for delirium can be broadly categorized into three categories: features of the acute illness, patient or host related factors, and environmental or iatrogenic factors [68 69] (fig 3). Acute illness or precipitating variables include coma, severity of illness (for example, measured by the APACHE II or SOFA score), emergency surgery, polytrauma, and mechanical ventilation; characteristics of patients that are related to a higher risk of developing delirium include higher age and chronic pathology (for example, dementia, hypertension); most environmental or iatrogenic variables such as medication administration were inconclusive based on the available evidence at the time.[67 70] Of the 11 more definitive risk factors identified in the systematic review,[67] the potentially modifiable ones included minimizing the duration of sedative associated coma,[46 71-76] reducing days of mechanical ventilation,[74 76-80] and promoting the use of dexmedetomidine.[81-84] More recently, a systematic review of 20 studies found that neither age nor sex was associated with a delirium subtype.[85] Heterogeneity in study design and inconsistent reporting of subtype specific risk factors, however, limited data synthesis.[85]

Non-drug therapies for delirium in the ICU

In an RCT (n=104), early physical and occupational therapy during spontaneous awakening trials in mechanically ventilated medical patients reduced the duration of delirium (median 2.0 (interquartile range 0.0-6.0) days versus 4.0 (2.0-8.0) days; P=0.02 in the intervention and usual care groups, respectively).[86] Similarly, early mobilization of surgical patients led to improved functional status and shortened duration of ICU stay.[87] In this multicenter RCT in 200 patients, early mobilization reduced duration of delirium (group difference 3.0 (95% confidence interval 0.5 to 5.5) days: p=0.016).[87] Furthermore, the benefit of early mobilization was consistent

Table 1 | Motor presentations of delirium

Subsyndromal delirium	Incomplete presentation of delirium syndrome
Hyperactive delirium	Characterized by motor agitation, restlessness, and aggressiveness
Hypoactive delirium	Characterized by motor retardation, apathy, and slowing of speech
Mixed hyperactive and hypoactive delirium	Characterized by mix of motor features
Catatonic retardation or catatonic excitement	Extreme forms of hypoactive and hyperactive delirium, respectively

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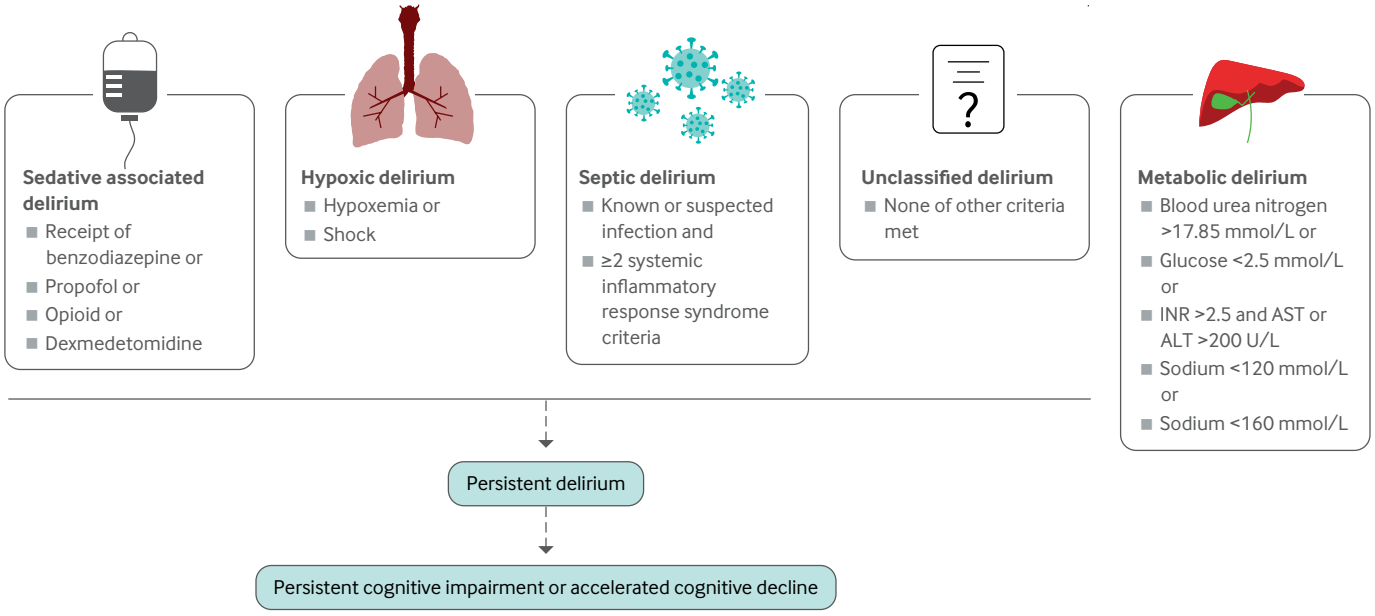

Fig 2 | Delirium phenotypes and risk of persistent cognitive impairment. ALT=alanine transaminase; AST=aspartate aminotransferase; INR=international normalized ratio

across Glasgow Coma Scale (GCS) levels without evidence of effect modification in a post hoc analysis for the primary outcome of functional independence at hospital discharge (P=0.53 for interaction).[88] Early mobilization is a component of evidence based care bundles for critically ill patients, promoting awake, spontaneously breathing, and mobile patients. Compliance with such bundles of care is associated with reduced risk of delirium on the next day (adjusted odds ratio 0.60, 0.49 to 0.72) and other clinically important outcomes.[22]

Drug therapies for delirium in the ICU

Although beneficial, non-drug management is not always effective in preventing or treating delirium. As a result, several studies have investigated the effects of pharmacologic agents, particularly antipsychotic drugs, in the management of delirium in the ICU.

Antipsychotic agents

The largest trial of antipsychotic treatment to date, the Modifying the Impact of Neuropsychological Dysfunction-USA (MIND-USA) study, was a multisite RCT comparing haloperidol, ziprasidone, and placebo in 566 patients with delirium, which found no significant difference in number of days alive without delirium or coma during the 14 day intervention period.[89] The median number of days alive without delirium or coma was 8.5 (95% confidence interval 5.6 to 9.9) in the placebo group, 7.9 (4.4 to 9.6) in the haloperidol group, and 8.7 (5.9 to 10.0) in the ziprasidone group (P=0.26 for overall effect across trial groups).[89] Furthermore, no significant between group differences were seen in the secondary endpoints (30 day and 90 day survival, time to freedom from mechanical ventilation, and time to ICU and hospital discharge).[89] These findings are consistent with a systematic review of 16 RCTs and 10 observational studies, which found no difference in delirium outcomes (for example, incidence, duration, or severity of delirium, sedation status, length of stay, cognitive function, or death) in patients treated with haloperidol, second generation antipsychotic drugs, or placebo.[90] Three multicenter RCTs have found that dexmedetomidine, compared with propofol or benzodiazepines, significantly reduces duration of delirium in mechanically ventilated patients.[83 84 91] In a placebo controlled trial to assess the effectiveness of dexmedetomidine in treating agitated delirium, delirium resolved a median of 16 (95% confidence interval 3.0 to 28.0) hours earlier (P=0.01; van Elteren site adjusted P=0.04) and time ventilator-free during the first seven days after randomization was reduced by a median of 17 (4.0 to 33.2) hours compared with placebo (P=0.01).[92]

Acetaminophen

Recently, in an RCT of 120 cardiac patients aged 60 years and older (only 16% were women) following on-pump coronary artery bypass graft (CABG) or CABG with valvular surgery, treatment with postoperative intravenous acetaminophen combined with intravenous propofol or dexmedetomidine had an 18% (95% confidence interval 5% to 32%) lower rate of in-hospital delirium than did placebo combined with propofol or dexmedetomidine.[93] By contrast, patients receiving dexmedetomidine rather than propofol had no significant difference in delirium rates (17% *v* 21%; difference −4%, −18% to 10%; hazard ratio 0.8, 0.4 to 1.9; P=0.54).[93] As this trial included only CABG patients, further study is needed to examine the effects of intravenous acetaminophen in a general ICU patient population, as well as broader investigation of underlying physiologic

Table 2 | Alternative instruments that have been used to assess delirium in critically ill patients; only 3 of 7 have been validated

Instrument	Features assessed	Time period	Scoring	Assessor	Comparator	No	Results
Delirium Detection Score[58]	Agitation, anxiety, hallucination, orientation, seizures, tremor, paroxysmal sweating, altered sleep-wake rhythm	Longer moment in time assessment	0-56	Clinical physicians and nurses	Sedation-Agitation Scale and defined clinical assessment	1073	69% sensitivity and 75% specificity if score ≥8
Neelon and Champagne Confusion Scale (NEECHAM)[59]	Attention, command, orientation, appearance, motor, verbal, vital function, oxygen saturation, urinary continence	Short moment in time assessment	0-30	Clinical nurses	Psychiatric intern assessment with DSM-IV criteria	105	97% sensitivity and 83% specificity if score ≥24
Nursing Delirium Screening Scale[60]	Disorientation, inappropriate behavior, inappropriate communication, hallucination, psychomotor retardation	Assessment over nursing shift or moment in time assessment	0-10	Research physicians and nurses	Psychiatric intern assessment with DSM-IV criteria	156	82% sensitivity and 83% specificity if score ≥2
Cognitive Test for Delirium[61]	Orientation, attention span, memory, comprehension and conceptual reasoning, vigilance	Longer moment in time assessment	0-30	Psychologist technician	Psychiatric expert assessment with DSM-IIIR criteria	103	100% sensitivity and 95% specificity if score ≤18*
Abbreviated Cognitive Test for Delirium[62]	Visual attention span, recognition memory	Short moment in time assessment	0-24	Psychologist technician	Psychiatric expert assessment with DSM-IIIR criteria	100	95% sensitivity and 99% specificity if score ≤10*
Family Confusion Assessment Method (FAM-CAM)[63]	Fluctuation, inattention, disorganized thinking or altered consciousness, disorientation, perceptual disturbances, inappropriate behaviors, disorientation, drowsiness in daytime	Assessment by caregiver	Positive or negative	Trained research associate	CAM-ICU-7	17	--†
Sour Seven Questionnaire[63]	Altered level of awareness, reduced attentiveness, fluctuation, disordered thinking, disorganized behavior, impaired eating/drinking, difficulty in mobility	Assessment by caregiver	0-18	Trained research associate	CAM	17	--‡

CAM=Confusion Assessment Method; DSM=Diagnostic and Statistical Manual of Mental Disorders; ICU=intensive care unit.
*17 caregivers and critically ill patients; descriptive study (feasibility); not powered to test validity or reliability of tool.
†52 paired dyads of caregivers and elderly patients; CAM as comparator; 88% sensitivity and 98% specificity.[64]
‡80 participants; seniors over age of 65 years; 92% sensitivity and 100% specificity.[65]

mechanisms (for example, immune mediated versus avoidance of hyperthermia).

Valproate

Recently, valproate has been administered to critically ill patients to treat agitation and delirium, but few published reports are available to support this practice.[94-97] Valproate has both intravenous and enteral formulations, has a low drug acquisition cost, and has not been associated with respiratory depression, hemodynamic derangements, or delirium. In a recent retrospective cohort study, 53 patients received an average of 1500 mg/day of valproate for agitation started at a median day 7 of an ICU stay and continued for a median of 7 days.[98] Whereas agitation and delirium were increasing in frequency over time before initiation of valproate, administration was associated with reduced agitation (61% on day 3 of valproate versus 96% on day 1; P<0.0001) and delirium (49% *v* 68%; P=0.012).[98] The use of opioids (95% *v* 61%; P=0.02) and dexmedetomidine (47% *v* 24%; P=0.004) was also reduced. Side effects were common, however, with hyperammonemia reported in 19% and thrombocytopenia in 13% of patients receiving valproate.[98] Two other retrospective reviews of prescription of valproate for agitation and delirium found similar results. In a retrospective descriptive analysis of a medical-surgical ICU patient population, median starting dose was 6.2 mg/day with median levels reaching 34.9 (interquartile range 22.3-78.1) µg/mL; median duration of therapy was 8 days, and a trend was seen toward reduced rates of agitation and delirium (48% *v* 17% and 85% *v* 63%, respectively).[99] In the largest retrospective cohort of 80 patients, 35 of whom received valproate alone and 45 of whom received valproate in combination with antipsychotics, resolution of delirium occurred in 55% of patients (69% in valproic acid alone group and 44% in valproic acid plus antipsychotics group; P=0.03).[100] Furthermore, delirium incidence decreased from initiation of valproate to day 3 of therapy from 93% to 68% (P<0.01), with no change in agitation (64% *v* 63%; P=0.28). Investigation in placebo controlled randomized trials is needed, however, to determine the value of valproate alone or as an adjunct in the management of ICU delirium.[101]

Diagnostic tools for delirium

Biomarkers

Biomarkers are an emerging tool that may further our understanding of the pathophysiology of delirium and possibly lead to earlier diagnosis and better risk stratification. Several biomarkers have been associated with delirium during critical illness. The S100B protein is an indicator of glial activation and/or death and thus is a non-specific marker of brain injury. This marker has also been validated as an indicator of blood-brain barrier injury.[102] Plasma S100B concentration has been found to be elevated in patients with delirium.[103-105] In a population with septic shock in which the incidence of delirium was approximately 50%, the odds ratio for developing delirium was 18 (95% confidence interval 2 to 196) with a S100B protein concentration of 0.15 µg/L or greater. Other research exploring general systemic inflammatory biomarkers as predictors of delirium include a pilot study of patients enrolled in the Maximizing Efficacy of Targeted Sedation

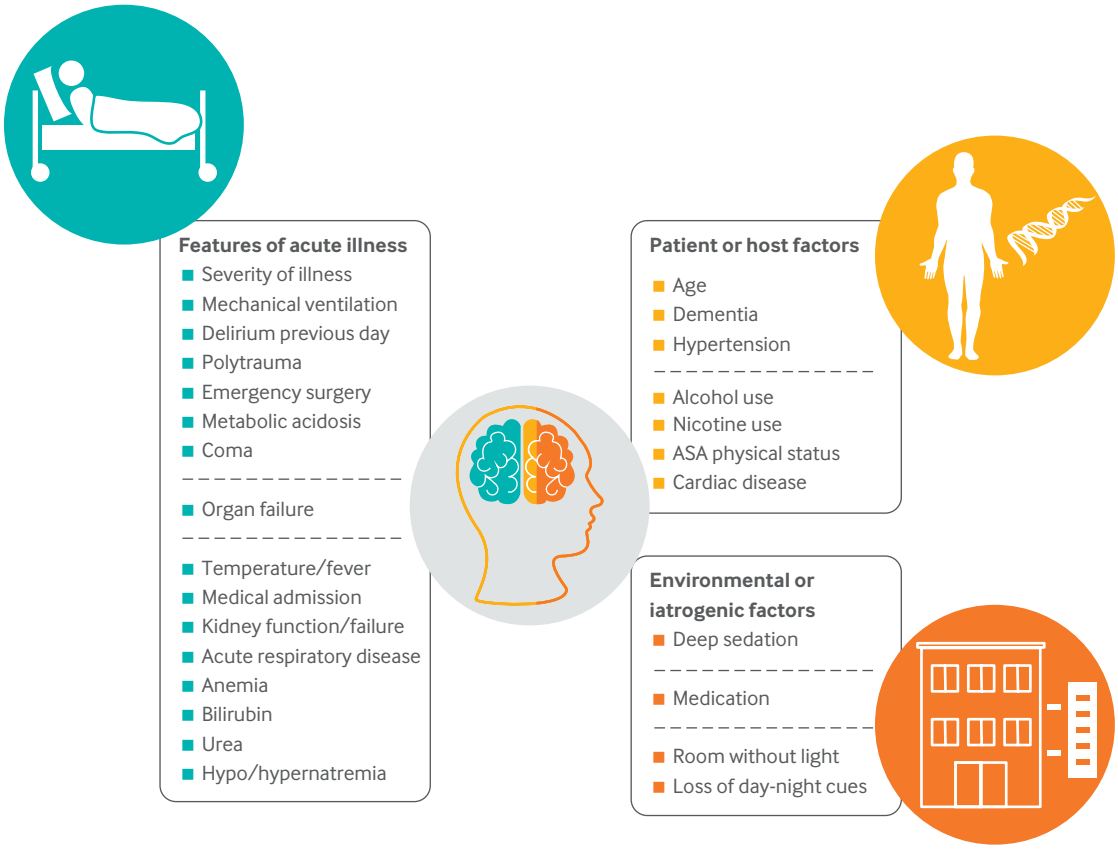

Fig 3 | Predisposing risk factors and precipitating factors for delirium. ASA=American Society of Anesthesiologists

and Reducing Neurological Dysfunction (MENDS) trial evaluating 87 critically ill patients, most of whom had sepsis on admission to the ICU.[106] This study found that higher baseline concentrations of procalcitonin or C reactive protein were associated with more days with delirium.[106]

Additional serum biomarkers shown to be elevated in patients with delirium include brain derived neurotrophic factor, neuron specific enolase, interleukins, and cortisol.[107 108] For example, a retrospective analysis of the large sepsis cohort, the Molecular Epidemiology of Severe Sepsis in the ICU (MESSI) study,[109] examined neuron specific enolase concentrations in the initial blood drawn at presentation to the emergency department for patients directly admitted to the ICU and in blood drawn during or just after decompensation for patients transferred to the ICU from the medical ward. Each doubling of the concentration was associated with a 5.2% (95% confidence interval 3.2% to 7.2%) increase in the risk of delirium; a concentration >12.5 µg/L was independently associated with a 29.3% (8.8% to 49.8%; P=0.005) increase in the risk of delirium.[109] Interestingly, in the Bringing to light the Risk factors And Incidence of Neuropsychological dysfunction in ICU survivors (BRAIN-ICU) study, in which 70% of 134 patients experienced delirium after admission for acute respiratory failure and/or shock, those with increased concentrations of plasminogen activator inhibitor-1, E-selectin, and S100B experienced fewer delirium-free and coma-free days and more delirium days than those without increased concentrations, after adjustment for potential confounders.[110] In a nested prospective cohort of 138 patients from the Awakening and Breathing Controlled RCT, most of whom were over 65 years of age, elevated matrix metalloproteinase-9, protein C, and soluble tumor necrosis factor receptor-1 within two days of enrollment increased the probability of transitioning to delirium during ICU stay.[111] Very few studies have used a time series design. In a cohort of patients at high risk of developing delirium (n=50; predicted risk of delirium >40% using the PRE-DELIRIC model), no differences in the concentrations of any biomarkers immediately before or after the onset of delirium were seen.[112] As the concentrations of biomarkers and the risk of transitioning to delirium may be fluid over time, serial measurements of biomarkers may further elucidate the interplay between inflammation and neuronal injury.

Neuroimaging

In addition to biomarkers, neuroimaging is an emerging diagnostic tool for delirium. Modalities such as functional magnetic resonance imaging (MRI), diffusion tensor imaging, arterial spin labeling, and positron emission tomography have revealed nonspecific or diffuse changes over time, including cortical atrophy, ventricular enlargement,

and white matter hyperdensities.[113 114] Research is preliminary, with three studies currently registered on clinicaltrials.gov: two examining delirium as a complication in the postoperative course, using a range of imaging modalities (for example, functional MRI, carbon dioxide stress testing; NCT02126215 and NCT03110185) and one study investigating structural and diffusion tensor imaging sequences at one year after discharge from the ICU and their relation with cognitive performance (NCT03562689).

Electroencephalography

Lastly, an emerging tool for the diagnosis of delirium is electroencephalography. Delirium is associated with slowing of background activity on electroencephalography, specifically an increased relative delta power (1-4 Hz).[115-118] Electroencephalograph based monitoring and quantification has recently shown potential for detecting delirium in routine daily practice. A single center observational study of 54 patients (26 adults with delirium, age and sex matched with 28 non-delirious

Table 3 | Studies of delirium and long term outcomes in patients with critical illness

Date	Characteristic	Study cohort	Primary outcome	Results
Girard et al, 2010[10]	Prospective cohort	126 medical ICU patients; mechanically ventilated	Cognitive outcome at 3 and 12 months	Duration of delirium independently associated with long term cognitive outcomes
Gunther et al, 2012[136]	Prospective cohort	47 patients from medical and surgical ICUs with respiratory failure or shock	3-Tesla brain MRI at discharge and 3 and 12 months follow-up	Delirium duration associated with white matter disruption at both discharge and 3 months; white matter disruption associated with worse cognitive scores at 12 months
Morandi et al, 2012[114]	Prospective cohort	47 patients from medical and surgical ICUs with respiratory failure or shock	3-Tesla brain MRI at discharge and 3 and 12 months follow-up	Longer duration of delirium associated with smaller brain volumes up to 3 months after discharge; smaller brain volumes associated with long term cognitive impairment up to 12 months
Van den Boogaard et al, 2012[8]	Prospective cohort	1292 patients; 272 with delirium and 1020 without delirium	Short Form-36v1, checklist individual strength-fatigue, and cognitive failure questionnaire at 18 months	Intensive care survivors with delirium had similar adjusted health related quality of life; duration of delirium associated with long term cognitive impairment
Pandharipande et al, 2013[11]	Prospective cohort	821 patients with respiratory failure or shock in medical or surgical ICU	Cognitive outcome at 3 and 12 months	Days of delirium in hospital associated with worse global cognition and executive function at 3 and 12 months
Brummel et al, 2014[17]	Prospective cohort nested within RCT of paired sedation and ventilator weaning strategy	126 survivors of critical illness	Katz activities of daily living, Functional Activities Questionnaire, Medical Outcomes Study 36-item Short Form, and Awareness Questionnaire	Days delirious independently associated with increased odds of disability in activities of daily living and worse motor-sensory function at 1 year
Jackson et al, 2015[139]	Prospective cohort	47 survivors of medical, surgical, or cardiac ICUs	Functional MRI at hospital discharge and 3 months post-discharge	Delirium not associated with distinct or abnormal brain activation patterns
Sakuramoto et al, 2015[146]	Prospective cohort	79 survivors of critical illness	MMSE at the time of hospital discharge	Patients experiencing delirium (63%) in ICU had higher rates of cognitive impairment at time of hospital discharge (28% *v* 3%; P=0.03); averaged ICDSC score over course of ICU stay positively associated with cognitive impairment (OR 1.6, 95% CI 1.02 to 2.54; P=0.041)
Wolters et al, 2017[140]	Prospective cohort	567 one year survivors from medical-surgical ICU	Cognitive failures questionnaire at 1 year	Days delirious independently associated with greater self-reported cognitive problems
Girard et al, 2018[51]	Prospective cohort	586 patients managed in medical or surgical ICU with respiratory failure, septic or cardiogenic shock, or both	Repeatable Battery for the Assessment of Neuropsychological Status, MMSE, and Trails Making Test B at 3 and 12 months	Sedative associated delirium, septic delirium, hypoxic delirium, and unclassified delirium were each associated with long term cognitive impairment, whereas metabolic delirium was not
Bruck et al, 2018[141]	Prospective cohort	125 ICU survivors	Cognitive failures questionnaire at 3 months	Neither severe sepsis nor ICU delirium was associated with self-rated cognitive function 3 months after ICU stay
Mitchell et al, 2018[142]	Prospective cohort	148 medical or surgical ICU survivors	Repeatable Battery for the Assessment of Neuropsychological Status and Trails Making Tests at 3 and 6 months	ICU delirium associated with impaired information processing speed and executive function at 6 months follow-up
Schulte, et al, 2019[144]	Retrospective cohort; Mayo Clinic Study of Aging and ICU	372 of 3673 participants who had ICU admission	Trails Making Test B, Digit Symbol Substitution Test, Boston Naming Test and Category Fluency, Wechsler Memory Scale-Revised Logical Memory II, Wechsler Memory Scale-Revised Visual Reproduction-II, Auditory Verbal Learning Test, Wechsler Adult Intelligence Scale-Revised Picture Completion test, Wechsler Adult Intelligence Scale-Revised Block Design test	ICU admission associated with greater long term cognitive decline compared with patients without ICU admission; findings were more pronounced in those who developed delirium while in ICU
Zhang et al, 2019[143]	RCT; low dose dexmedetomidine *v* placebo	700 elderly patients admitted to non-cardiac ICU	Telephone interview at 3 year follow-up; modified Telephone Interview for Cognitive Status	Low dose dexmedetomidine infusion did not significantly change 3 year overall survival but increased survival up to 2 years and improved cognitive function and quality of life in 3 year survivors
Bulic et al, 2020[145]	Prospective cohort	103 participants; 36% developed delirium	MMSE, Telephone Interview for Cognitive Status	Delirium in ICU independently associated with short term but not long term cognitive function, and with long term PTSD symptoms

ICDSC=Intensive Care Delirium Screening Checklist; ICU=intensive care unit; MMSE=Mini Mental State Examination; MRI=magnetic resonance imaging; OR=odds ratio; PTSD=post-traumatic stress disorder; RCT=randomized controlled trial.

patients after cardiothoracic surgery), found that electrode derivation of relative delta power in frontal and parietal leads was able to distinguish delirium from a non-delirious state (a cut-off value of 0.37 had a sensitivity of 100% and specificity of 96%).[117] More recently, a prospective multicenter study of 159 older (>60 years) patients who had major surgery requiring ICU care for more than 48 hours showed that delirious patients (84/276 assessments) had a 50% increase in relative delta power compared with non-delirious patients (area under the receiver operating characteristic curve of relative delta power was 0.75, 95% confidence interval 0.69 to 0.81).[119] Interestingly, delta power correlated with severity of delirium, showing a dose dependence that suggested that understanding slow waves may lead to important insights into the pathology of delirium. Specifically, understanding the biologic inter-relations of slow waves and connectivity of upper brainstem networks will be critical in understanding the pathogenesis of delirium. Although these data are preliminary and the participants were not sedated, validation studies conducted in unselected ICU patient populations and a rigorous evaluation of residual effects of sedatives would be highly valuable to the field. A prospective multicenter stepped wedge cluster randomized trial in four ICUs in Germany is under way to compare standard screening methods and delta power (DeltaScan) on delirium detection rates and length of stay in the ICU (NCT03735940). Electroencephalography based testing has the potential to be an objective and informative measure if it is able to detect delirium on a continuous scale, without the limits of language or sensory barriers (such as hearing impairment).

Long term cognitive impairment

Epidemiology

For many people, an acute hospital admission, especially one that includes an ICU stay, results in new or worsening cognitive decline.[11 120-124] In a multicenter cohort of 821 critically ill patients with respiratory failure or shock, one in four ICU survivors, across all adult age groups, had cognitive impairment one year after discharge, equating in severity to that of having mild Alzheimer's disease or moderate traumatic brain injury.[11] In a recent systematic review of 46 studies, aggregated frequency of cognitive impairment after critical illness was 35% and 45% at three and six months' follow-up, respectively.[125] Interestingly, survivors of acute respiratory distress syndrome had a higher prevalence of cognitive impairment than did a mixed ICU survivor population (approximately 80% compared with 50% prevalence at three month follow-up).[125] Cognitive impairment seems to improve on average, however, from three to six months' follow-up,[125 126] and any existing differences between survivor populations do not persist beyond three months.[125] Regardless of improvements that might be seen in early recovery, a substantial percentage of patients have persistent long term cognitive impairment, as high as 42% and 46% at one and two years after ICU discharge.[11 126-129] Post-intensive care syndrome describes the disability that remains in ICU survivorship; it comprises impairment in cognition, psychological health, and physical function in the ICU survivor and the consequent psychological health of family members of the survivor.[130]

Pre-existing cognitive impairment

Although patients can develop de novo cognitive impairment after critical illness,[131 132] hospital admissions may also adversely affect pre-existing cognitive deficits, perhaps owing to the effects of decreased cognitive reserve and accelerated processes of cognitive impairment. Recently, in a multicenter prospective cohort study of both planned and unplanned admissions (n=2467), the rate of cognitive impairment in a mixed patient population at baseline was determined to be 6% by patient or substitute decision makercompleted questionnaire.[133] These results are comparable to those of a study using data from the Health and Retirement Study, a nationally representative survey of US residents (1998-2006), in which 6.1% (95% confidence interval 4.2% to 8.0%) of eventual survivors of sepsis (n=1194) had moderate/severe cognitive impairment just before ICU admission, with the prevalence increasing to 16.7% (13.8% to 19.7%) at the first survey after severe sepsis (P<0.001 by χ^2).[132] Reported incidence of pre-existing cognitive impairment was higher (35%; n=136/387) in patients admitted to or transferred to the ICU in a population based study (Mayo Clinic Study of Aging), than in older patients admitted to hospital who did not need to be admitted to ICU (18%; n=391/1733).[134] After adjustment for important covariates, mild cognitive impairment remained a significant predictor of ICU admission (hazard ratio 1.50, 1.15 to 1.96).[134] Clinical factors associated with cognitive impairment included higher age, male sex, previous stroke, and poor self-reported health.[134] Pre-existing cognitive impairment, in addition to being a predictor of ICU admission and cognitive decline, also seems to influence disability. In a prospective cohort of 754 ICU survivors aged 70 years or older undergoing routine cognitive screening, the presence of pre-existing mild or moderate cognitive impairment predicted increased disability at six months (adjusted relative risks 1.19 (1.04 to 1.36) and 1.16 (1.02 to 1.32), respectively).[135]

Delirium as a risk factor for cognitive impairment

The most consistent risk factor for subsequent long term cognitive impairment identified during critical illness is delirium [10 11 51 114 136-146] (table 3). After adjustment for age, education, pre-existing cognitive function, severity of illness, and exposure to sedative drugs, increasing duration of delirium was an independent predictor of worse long term cognitive impairment in a large, multicenter study of survivors of critical illness.[10] In a separate prospective cohort of medical-surgical ICU survivors,

multiple days of delirium in the ICU was associated with increased self-reported cognitive problems at one year follow-up.[140] In another prospective cohort, the average ICDSC score during the ICU stay, a representation of severity of delirium, was positively associated with cognitive impairment at the time of hospital discharge (odds ratio 1.6, 1.02 to 2.54; P=0.041).[146]

Few studies have examined the pathophysiology of cognitive impairment after critical illness, but the link between delirium and long term cognitive impairment is hypothesized to be mediated directly or indirectly through a systemic inflammatory response inducing the activation of brain parenchymal cells and expression of pro-inflammatory cytokines and inflammatory mediators within the central nervous system.[147 148] This acute inflammatory response to critical illness may prime microglia, activating them from a resting state. Activated microglia may then perpetuate a state of chronic neuroinflammation and neurotoxicity that, in part, explains long term cognitive impairment.[149] Certain phenotypes of delirium, specifically hypoxic and septic delirium, have been associated with greater risk of long term cognitive impairment.[51] Longer duration of sedative associated delirium was also predictive of worse Repeatable Battery for Assessment of Neuropsychological Status (RBANS) global score at 12 months' follow-up.[10 11 114 136 140] Interestingly, elevated C reactive protein concentrations, a general marker of inflammation, did not modify the relation between days of delirium and long term cognition.[140] Whether sedative use is associated with the inflammatory response is unclear; a pilot trial is under way to investigate the effect of dexmedetomidine on brain derived neurotrophic factor, neuron specific enolase, and S100B in polytrauma.[150] Most recently, in a secondary analysis of two prospective multicenter cohorts (n=548; 88% received mechanical ventilation), neither inflammatory mediators nor coagulation parameters were associated with long term cognitive performance at three or 12 months' follow-up.[151]

Effect of sedation

The direct relation between sedative agents and cognitive outcome in survivors of critical illness has not be well studied. In a meta-analysis of 10 RCTs and one retrospective cohort study (n=1216), the use of lighter sedation was associated with a reduced risk of long term cognitive impairment (odds ratio 0.75, 0.63 to 0.90).[152] Only two of the included studies considered the specific hypothesis that higher doses of sedative and/or analgesic agents may be associated with cognitive impairment after hospital discharge.[11 129] At 12 months' follow-up, the intervention (received lower benzodiazepine exposure but higher propofol exposure) and usual care groups from the Awakening and Breathing Controlled Trial showed similar cognitive outcomes.[129] Comparable results were found in a multicenter prospective cohort in which delirium was an independent factor for worse cognitive function, but no significant association was found between sedative and analgesic medication and long term cognitive impairment.[11] Nevertheless, critically ill patients who develop multiple days of delirium in the setting of sedation are at higher risk for long term cognitive impairment than those who are delirious for a shorter duration (or not at all) while sedated,[51] suggesting a complex interaction between sedation, host susceptibility, and long term cognitive outcomes. Thus, RCTs are needed to determine whether interventions that limit sedative exposure and thereby reduce delirium mitigate long term cognitive impairment in survivors of critical illness (fig 4).

Predicting long term cognitive impairment

Studies have so far been unable to identify patients at higher risk of long term cognitive impairment after critical illness using brief cognitive screening tools in the hospital. For example, in a prospective cohort study, performance on neither the Mini Mental State Examination nor MiniCog at the time of hospital discharge predicted cognitive impairment at six months' follow-up.[154] Performance on more sensitive tests of cognitive impairment may have predictive value, but these have not been used in prediction focused investigations to date. A recent systematic review highlighted the absence of prediction models for cognitive impairment after surviving critical illness, whereas two studies have predicted physical function and one study predicted mental health disorders.[155] The lack of predictive ability restricts the ability of clinicians and researchers to adequately risk stratify patients to their individual rehabilitation needs.

Therapies to improve cognitive recovery

A limited number of studies have examined interventions designed to hasten recovery and/or prevent decrements in cognitive function after critical illness.[156] Most studies have focused on intervening during ICU admission to reduce cognitive impairment. Treatments have included strategies for optimizing enteral nutrition, fluids, sedation, weaning, mobilization, cognitive activities, statins, and sleep quality.[84 129 138 157-160] The only outpatient intervention examined to date was examined in a pilot study of 21 medical and surgical ICU survivors. The Returning to Everyday Tasks Using Rehabilitation Networks (RETURN) study randomized people to either 12 weeks of in-home combined cognitive and physical rehabilitation or usual care (characterized by sporadic rehabilitation).[161] Despite nearly equivalent scores on a measure of executive functioning at baseline, patients in the intervention group showed significantly better executive functioning at the end of the intervention and reported fewer disabilities in instrumental activities of daily living.[161] Large scale, well designed trials with specific aims and focused research collaboratives with the ability to combine clinical, basic science, and epidemiologic approaches are needed (fig 5).

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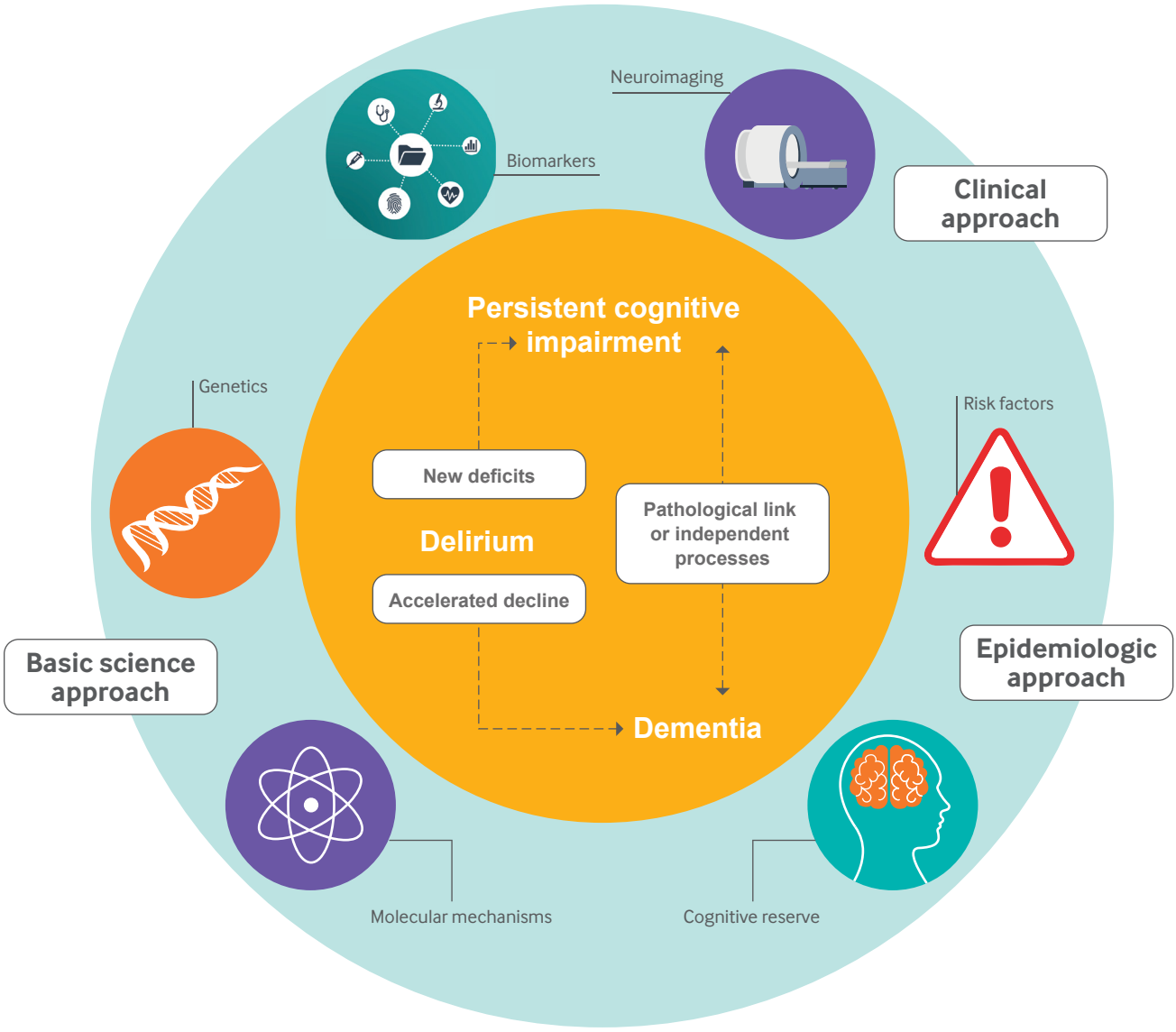

Fig 4 | Conceptual framework for exploring inter-relation between delirium and long term cognitive impairment and between delirium and acceleration of dementia. Source: Inouye and Ferrucci. *J Gerontol A Biol Sci Med Sci* 200[6153]

Ongoing trials

A search of clinicaltrials.gov and controlled-trials.com uncovered only two ongoing trials. One is a feasibility trial studying cognitive benefits of prevention and rehabilitation (clinicaltrials.gov NCT03972384). This US based feasibility study is investigating the recruitment, retention, and engagement of a program, Post-Intensive Care Unit Problem Solving (PIC-UPS), during which participants will work for 10 sessions on skills they select as treatment goals. The first session consists of an assessment and selection of goals to be met. In the subsequent sessions, held over 12 weeks and conducted at the participant's home, skills are practiced to reach those goals, assisted by the study team who advise on learning and performing strategies. Some examples of tasks that have been included are gardening, yoga breathing, handwriting, managing family finances, managing medication, or starting an exercise regimen. Participants in the control group will complete several surveys on enrollment and randomization. Follow-up data collection will be conducted in the home for all participants by a blinded data collector three months after enrollment. The primary outcome will be cognitive performance at three months after discharge from hospital. Secondly, the Improving Recovery and Outcomes Every Day after the ICU (IMPROVE) study (clinicaltrials.gov NCT03095417), is a four arm RCT comprising cognitive training and physical exercise, cognitive control and physical exercise, cognitive training and physical exercise control, and cognitive and physical exercise control.[162] Cognitive training facilitated by online modules in patients' homes and physical exercise will also be administered using internet enabled videoconferencing in small groups.

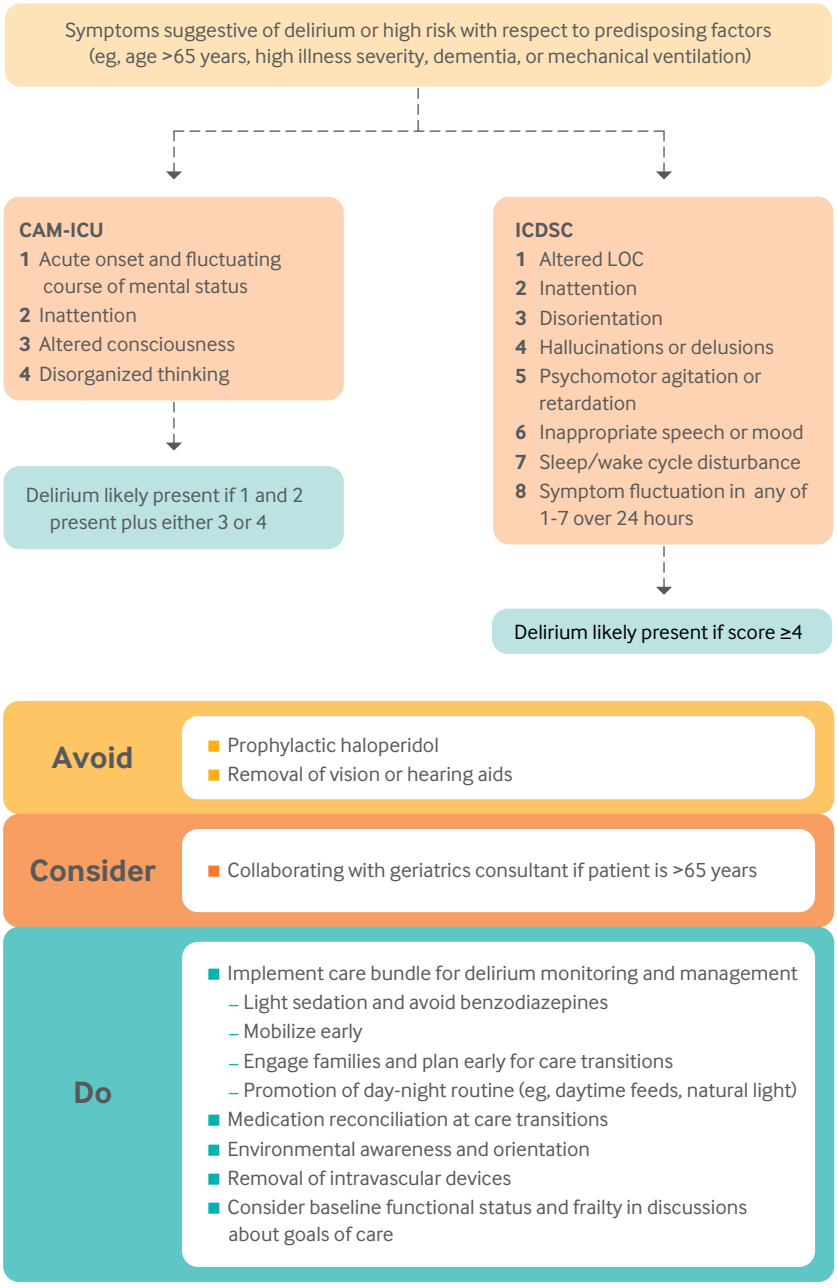

Fig 5 | Populations at high risk, validated screening tools, and prevention/treatment strategies for delirium. CAM-ICU=Confusion Assessment Method for the ICU; ICDSC=Intensive Care Delirium Screening Checklist; LOC=level of consciousness

The primary outcome is cognitive impairment at six months compared with baseline and three months after discharge from ICU.

Guidelines

International guidelines exist for the prevention and management of delirium (table 4). We report the similarities and differences between six international guidelines from the US, UK, Denmark, Germany, Japan, and Panamerica-Iberia: Society of Critical Care Medicine (SCCM),[20] National Institute for Health and Care Excellence and Scottish Intercollegiate Guidelines Network (NICE/SIGN),[19] Danish Society of Anesthesiology and Intensive Care Medicine and the Danish Society of Intensive Care Medicine (DASAIM/DSIT),[163] German Society of Anaesthesiology and Intensive Care Medicine and German Interdisciplinary Association for Intensive Care and Emergency Medicine (GSAICM/GIAICEM),[164] Japanese Society of Intensive Care Medicine (JSICM),[165] and Panamerican-Iberian Federation of Societies of Critical and Intensive Care Medicine (FEPIMCTI).[18] If multiple iterations for a specific society exist, we chose the most current to discuss. A recent systematic review formally appraised eight clinical practice guidelines by using the AGREE II methodology,[166] including

two versions of each of the GSAICM/GIAICEM, SCCM PADIS (formally PAD), and FEPIMCTI guidelines; the JSICM guidelines were not included. Overall, five of the eight guidelines exceeded the overall quality threshold of 60% in four of six domains.[21 166]

A total of 73 recommendations have been made with respect to assessment and management of delirium.[18 19 20 163-165] All guidelines reported on risk factors for delirium; only the SCCM PADIS guidelines comment on transfusion and benzodiazepine use being modifiable. The SCCM PADIS, DASAIM/DSIT, GSAICM/GIAICEM, and JSICM guidelines recommend regular assessment with a validated delirium screening tool, whereas the NICE/SIGN guideline specifically recommends the CAM-ICU or ICDSC. The FEPIMCTI guideline recommends the CAM-ICU, with a caution about its risk of false negatives. With regard to drug treatment, most guidelines do not recommend any agent for the prevention of delirium but recommended minimizing the amount of sedation. All guidelines recommended non-drug multicomponent interventions as a delirium management strategy.

Implementation challenges

Many studies have reported improved patient centered outcomes with implementation of evidence based bundles aimed at reducing ICU acquired delirium. For example, the use of the Assess, prevent, and manage pain, Both spontaneous awakening trials and spontaneous breathing trials, Choice of analgesia or sedation, Delirium: assess, prevent, and manage, Early mobility and exercise, and Family engagement and empowerment (ABCDEF) bundle in before-after and observational studies has been associated with reduced rates of delirium, shorter duration of mechanical ventilation, and improved survival.[23 167-172] A prospective cohort study of 1855 patients admitted to two medical ICUs showed that implementation of bundle components reduced duration of mechanical ventilation, length of stay in ICU and hospital, and total ICU and hospital costs.[173] Also, in this study, duration of mechanical ventilation and length of stay in ICU and hospital were reduced, as was use of midazolam infusion, with implementation of PAD guidelines.[174]

Many multifaceted implementation programs have involved the implementation of processes of care and clinical outcomes targeted at screening for delirium, limited use of benzodiazepines, light sedation targets, and early mobilization.[22 24 168 175] As an example, one program resulted in a reduction in both mean duration of delirium (from 5.6 to 3.3 days; difference −2.2 days; P<0.001) and coma days (risk ratio 0.5; P<0.001).[175] This program was informed by a previous study by the same group on attitudes,

Table 4 | Summary of international guidelines for delirium in intensive care unit (ICU) patients

Guideline	Organization, country	Title	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity and presentation	Applicability	Editorial independence
SIGN, 2019[19]	Healthcare Improvement Scotland and Scottish Intercollegiate Guidelines Network, UK	Risk reduction and management of delirium (SIGN 157)	+	+	+	+	+	+
Devlin et al, 2018[20]	Society of Critical Care Medicine, USA	Clinical Practice Guideline for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, Sleep Disruption in Adult Patients in the ICU	+	+	+	+	+/−	+
Fonsmark et al, 2015[163]	Danish Society of Anesthesiology and Intensive Care Medicine (DASAIM) and Danish Society of Intensive Care Medicine (DSIT), Denmark	Danish national sedation strategy. Targeted therapy of discomfort associated with critical illness	+	+/− (no patient engagement)	−	+	−	−
Baron et al, 2015[164]	German Society of Anaesthesiology and Intensive Care Medicine and German Interdisciplinary Association for Intensive Care and Emergency Medicine, Germany	Evidence and consensus-based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015)	+	+/− (no patient engagement)	+	+	+/−	+
Committee for the development of Japanese guidelines for the management of Pain, Agitation, and Delirium in intensive care unit, 2014[165]	Japanese Society of Intensive Care Medicine, Japan	Japanese guidelines for the management of Pain, Agitation, and Delirium in intensive care unit (J-PAD)	+	+/− (no patient engagement)	+	+	+/−	+
Celis-Rodriquez et al, 2020[18]	Panamerican and Iberian Federation of Societies of Critical and Intensive Care Medicine	Clinical practice guidelines for evidence-based management of sedoanalgesia in critically ill adult patients	+	+/− (no patient engagement)	+	+	+/−	+

knowledge, and practice concerns about bundle implementation.[176] Important barriers identified before the intervention included knowledge deficit, belief that delirium is not preventable, low satisfaction with physician described delirium management, poor collaboration between nursing staff and physicians, and perception that guideline implementation is cumbersome.[176] Given such significant barriers, widespread deployment of such programs could prove difficult, despite the magnitude of potential benefit. More work is needed to better delineate the most effective formats for messaging to frontline workers.

Several publications have reported significant care gaps with regard to guideline implementation, with routine assessment of delirium being the most consistently reported shortfall. For example, over 1101 patient days, a quality improvement initiative found that 39% of delirium assessments were performed compared with 78% agitation assessments.[177] Similarly, in a single center, an audit of practices showed that delirium assessments were performed approximately 30% of the time, with a greater number of assessments being performed during day shifts.[178] A multisite initiative of 69 adult and eight pediatric ICUs reported on challenges in incorporating the ABCDEF bundle into everyday practice as part of a 20 month nationwide multicenter quality improvement intervention.[169] Routine collection of detailed implementation data is likely essential for program evaluation and generalizability.[179] In a systematic review and meta-analysis, 12 multilevel causal factors affecting implementation outcomes were categorized and subdivided into patient, provider, and organizational factors.[179] Interestingly, organizational factors were rarely reported (for example, hospital type, daily screening frequency, and assessment method used).[179] Organizational factors such as educational strategies, staff knowledge, motivation, and screening compliance may influence the reported incidence of delirium. A standardized framework for reporting such factors would facilitate further insights into different processes of care and their subsequent impact.

Conclusions

Delirium is the most common manifestation of acute brain dysfunction in critically ill patients. It is associated with both poor short term outcomes and adverse long term sequelae related to critical illness. Current strategies for prevention, diagnosis, and treatment are subject to ongoing investigation. In addition to appreciating the acute process of delirium, it is important to recognize that the syndrome, together with other physiologic insults sustained in the ICU, is associated with long term cognitive impairment. The pathophysiology underlying this relation remains a field of active investigation, and uncovering such mechanisms may lead to targeted interventions that improve cognition and quality of life. Advancement of the field will depend on focused research collaboratives with the ability to combine clinical, basic science, and epidemiologic approaches.

RESEARCH QUESTIONS

- Can tools to identify and risk stratify delirium in critically ill patients (eg, electroencephalography) be developed and validated?
  - Can objective tools to measure delirium on a continuous scale, not limited by language or sensory barriers, be developed?
- How can we better understand the attributable risk of delirium in terms of intensive care unit related outcomes?
  - What is the pathophysiology of delirium, and what is its mechanistic relation with long term cognitive impairment?
  - How can we integrate biomarkers of delirium into predictive models of long term cognitive impairment?
  - What is the bidirectional relation between sleep/circadian rhythm and delirium?
- What are the effects of sleep optimization, physical rehabilitation, and cognitive training on delirium and long term cognitive impairment?
  - Can valid intermediate endpoints for testing interventions that may decrease the risk of long term cognitive impairment be identified?
  - Can phenotype driven trials of drug therapies for delirium be designed?
  - Can hybrid trials be conducted to ensure implementation of best practices?
- What is the impact of social networks and family engagement on delirium and long term cognitive impairment?
  - How can socioeconomic inequalities be reduced to improve long term cognitive follow-up and outcomes?
  - How does socially isolated hospital admission during covid-19 affect the risk of delirium and the trajectory of cognitive recovery after critical illness?

PATIENT INVOLVEMENT

A patient and his caregiver reviewed the manuscript and provided useful comments about its content, the presentation of the article, and the use of language. The patient is a middle aged man who experienced delirium during a prolonged stay in intensive care and who remains on medical leave from his job. His wife, who is his primary caregiver, witnessed first-hand her husband's delirium in the intensive care unit, an experience that was very vivid and frightening for her.

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