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REVIEW

The intensive care delirium research agenda: a multinational, interprofessional perspective

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Abstract

Delirium, a prevalent organ dysfunction in critically ill patients, is independently associated with increased morbidity. This last decade has witnessed an exponential growth in delirium research in hospitalized patients, including those critically ill, and this research has highlighted that delirium needs to be better understood mechanistically to help foster research that will ultimately lead to its prevention and treatment. In this invited, evidence-based paper, a multinational and interprofessional group of clinicians and researchers from within the fields of critical care medicine, psychiatry, pediatrics, anesthesiology, geriatrics, surgery, neurology, nursing, pharmacy, and the neurosciences sought to address five questions: (1) What is the current standard of care in managing ICU delirium? (2) What have been the major recent advances in delirium research and care? (3) What are the common delirium beliefs that have been challenged by recent trials? (4) What are the remaining areas of uncertainty in delirium research? (5) What are some of the top study areas/trials to be done in the next 10 years? Herein, we briefly review the epidemiology of delirium, the current best practices for management of critically ill patients at risk for delirium or experiencing delirium, identify recent advances in our understanding of delirium as well as gaps in knowledge, and discuss research opportunities and barriers to implementation, with the goal of promoting an integrated research agenda.

Keywords: Delirium, Research agenda, Cognitive impairment

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Brief introduction: epidemiology of delirium

Definition

Delirium is a manifestation of acute brain dysfunction defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1] as a disturbance in attention and awareness that develops over a short period of time, fluctuates, and is accompanied by a change in cognition. These disturbances are not explained *completely* by an established or evolving neurocognitive disorder/injury

(though it can exist superimposed on a primary cognitive disorder/brain injury), and there is evidence that the disturbance is caused by a direct physiologic consequence of a medical condition, an intoxicating substance, medication use, or from multiple etiologies (Fig. 1).

Prevalence

Rates of delirium range from 20% to 40% among critically ill patients, with the higher rates of 60–80% observed in mechanically ventilated (MV) medical or surgical patients [2–4]. A substantial proportion of ICU patients have hypoactive delirium [5], and hypoactive delirium may portend worse outcomes than hyperactive delirium [6].

Delirium and outcomes

Delirium is a strong independent predictor of longer time on MV and in ICU, cost, and mortality, with every day with delirium being independently associated with an increased hazard of death of 10% [2]. The attributable mortality to delirium (whether delirium causes higher mortality) is difficult to ascertain and still under investigation. Moreover, delirium is a strong predictor of cognitive decline that persists for months to years after ICU, and is associated with patients not returning to their prior quality of life or employment [7–9].

There is much heterogeneity in delirium etiologies and thus different possible phenotypes (sepsis-associated delirium, sedation-associated delirium, etc.), yet very little evidence exists to support differences in outcomes based on etiological phenotypes. Lumping all delirium together, irrespective of etiology, has helped our understanding of the prevalence, risk factors, and outcomes associated with delirium, and to raise awareness of delirium and simplify implementation of monitoring and management programs. The field will advance further when data allow us to characterize delirium etiology on the basis of pathophysiology and prognosis, to better tailor therapeutic options.

Delirium risk factors

Delirium risk factors can be divided into vulnerability factors (e.g., age, comorbidities) and hospital-related precipitating factors (e.g., acute illness and management related) [10]. Patients with increased vulnerability may be predisposed to delirium with the smallest of precipitating factors,

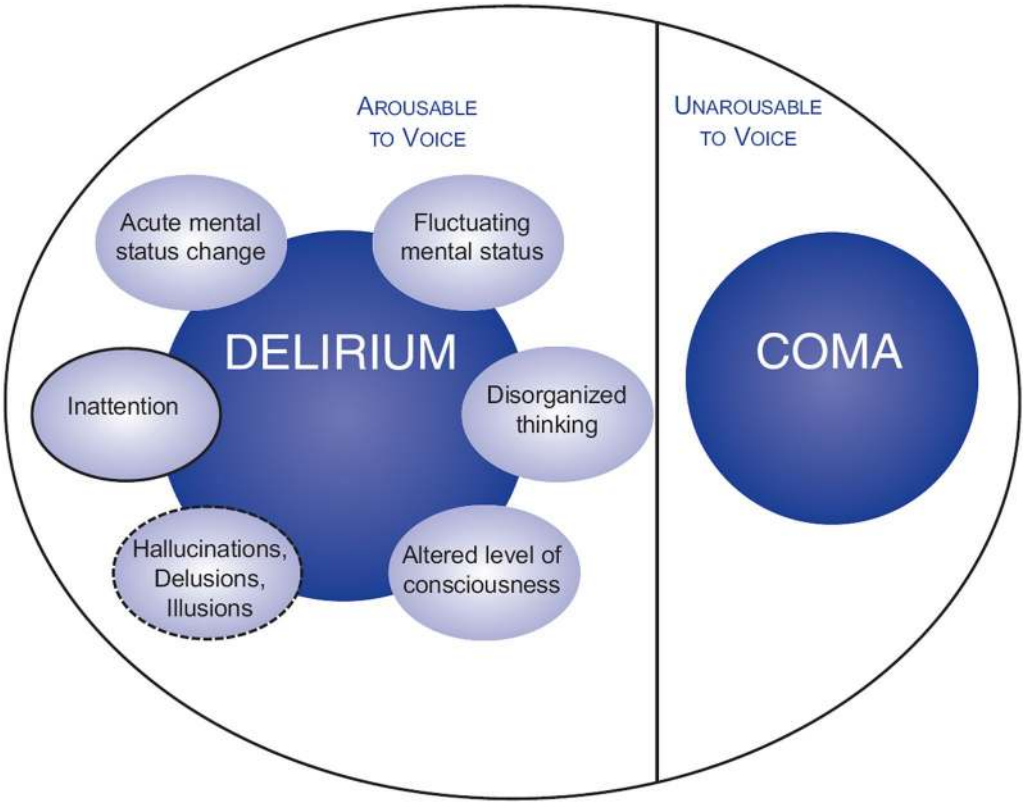

Fig. 1 Acute brain dysfunction (delirium and coma)

and vice versa. Of many known delirium risk factors, psychoactive medication (particularly benzodiazepines) use [11], drug-induced coma, sleep alterations [12], metabolic disturbances, and sepsis are common, potentially modifiable factors that clinicians should address when formulating delirium prevention and treatment strategies.

What is the current standard of care for managing delirium?

The lack of feasible biomarkers or radiological findings hampers the promulgation of delirium as a major organ dysfunction when such markers exist for cardiac, renal, and respiratory dysfunction, yet delirium cannot be ignored given its associated outcomes.

Assessment tools

Delirium will frequently go unrecognized if clinicians do not screen patients with validated delirium monitoring instruments. Based on their psychometric properties, the Society of Critical Care Medicine (SCCM) Pain Agitation and Delirium (PAD) [13] guideline recommends the use of sedation scales to assess arousal level followed by the validated Confusion Assessment Method-ICU (CAM-ICU) [14] or the Intensive Care Delirium Screening Checklist (ICDSC) [15] to assess for delirium. All four domains of the CAM-ICU, anchored on the presence of inattention, are evaluated in a focused patient assessment usually taking less than 2 min to complete. The eight-domain ICDSC, in contrast, assesses four symptoms of delirium in a focused patient assessment (including inattention) and four domains over the current and prior nursing shift, with four or more positive symptoms consistent with delirium. The importance of monitoring for delirium using one of these validated tools far outweighs their nuanced differences; choice of instrument should be based on clinician preference.

Prevention and management of delirium

Multicomponent, evidence-based bundles aimed at reducing ICU-acquired delirium have been proposed in the literature. For example, use of the ABCDEF bundle (Table 1) has been associated with a reduction in delirium and ventilation time, with a recent large implementation study showing additional survival benefits [16, 17]. These are before/after and observational studies and thus their benefits need to be interpreted with caution. The *E*arly implementation of *C*omfort and *A*nalgesia using minimal *S*edation and *H*umane care (eCASH) [18] bundle is a relatively new concept that is yet to be evaluated in clinical practice (Fig. 2).

With regards to pharmacological approaches, the SCCM guidelines [13] suggest the use of short-acting agents (e.g., propofol and dexmedetomidine) over benzodiazepines in MV patients, and that dexmedetomidine may be associated with improved delirium outcomes [19–23]. Access to early mobility and physical rehabilitation may shorten the duration of mechanical ventilation and reduce the risk and/or accelerate the resolution of delirium [24, 25].

While prevention remains the best strategy to combat delirium, effective treatment of delirium is critical to accelerate its resolution. The search for, and management of, delirium risk factors, such as sepsis, pain, hypoperfusion, high fever, deliriogenic medications, and electrolyte imbalance is imperative and is the cornerstone for management in patients, and particularly those with hypoactive delirium. Furthermore, it is important to rule out fearful hallucinations/delusions in any patient with hypoactive delirium. Very limited data support any role for conventional antipsychotic therapy such as haloperidol, or atypical antipsychotics such as olanzapine, quetiapine, and ziprasidone, for either delirium prevention or treatment in critically ill adults [26–28]. In MV and non-intubated patients, dexmedetomidine has been associated with improved hyperactive delirium resolution [20, 29].

Table 1 The ABCDEF bundle targeting patient symptoms

ABCDEF bundle elements	Symptoms being addressed	Examples of monitoring tools to use
*A*ssessment, prevention, and management of pain	Pain	Numeric Pain Rating Scale (NRS) Behavioral Pain Scale (BPS) Critical Care Pain Observation Tool (CPOT)
*B*oth spontaneous awakening and breathing trials *C*hoice of sedatives and analgesia	Agitation or sedation	Richmond Agitation-Sedation Scale (RASS) Sedation-Agitation Scale (SAS)
*D*elirium assessment, prevention, and management	Delirium Weakness	Confusion Assessment Method for the ICU (CAM-ICU)
*E*arly mobility/exercise		Intensive Care Delirium Screening Checklist (ICDSC)
*F*amily engagement and empowerment		Pediatric or Preschool Confusion Assessment Method for the ICU (pCAM-ICU; psCAM-ICU)
		Cornell Assessment for Pediatric Delirium (CAPD)

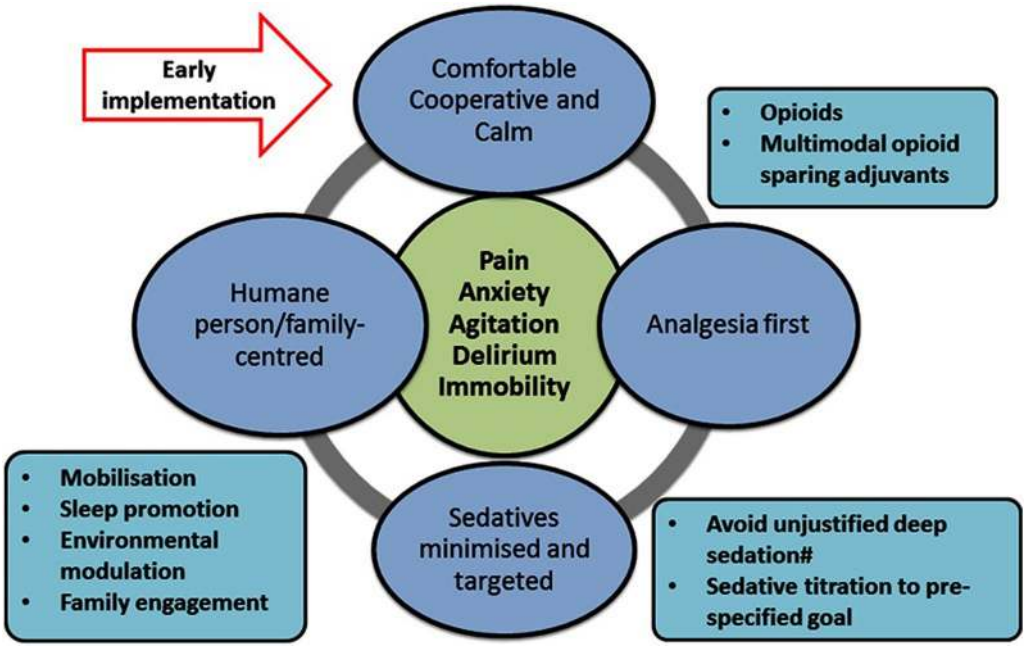

Fig. 2 The *E*arly implementation of *C*omfort and *A*nalgesia using minimal *S*edation and *H*umane care (eCASH) approach

What are the major recent advances in delirium research and care?

The development of animal models to study acute brain dysfunction, the increasing ability to screen for delirium, and the creation of delirium networks have played an important role in advancing delirium research and advocacy.

Experimental models in acute brain dysfunction

The induction of peritonitis by caecal ligation and puncture in rodents is the most used animal model to study acute and long-term brain dysfunctions that are close to those observed in septic patients. This induced brain dysfunction includes behavioral changes such as suppressed spontaneous activity and altered escape reflex that can be scored [30]. However any true cognitive dysfunction is embedded within, and perhaps masked by, severe sickness behavior (an adapted physiological response elicited by the limbic, neuroendocrine, and autonomic systems); most cognitive studies in sepsis therefore refer to dysfunction after peak illness has passed. There are now several validated tests for assessing psychological and cognitive functions that may remain impaired after sepsis in animal models, enabling objective assessment of functioning of particular brain structures or networks. There is also evidence of long-term affective and cognitive changes in studied animal models [31, 32].

Measures such as glucose metabolism (fluorodeoxyglucose by positron emission tomography), electroencephalography, and brain magnetic resonance imaging or spectroscopy are perhaps more informative during peak illness and it is necessary to establish criteria for these in animal models of acute brain dysfunction [33, 34]. An alternative approach has been to examine milder inflammation, induced by lipopolysaccharide, on a background of existing brain vulnerability in models of neurodegeneration and aging. These studies have produced acute onset, fluctuating, and transient cognitive dysfunction in domains relevant to delirium [35].

Monitoring delirium in vulnerable populations

Delirium is grossly underdiagnosed and is surrounded by myths, such as delirium cannot be assessed in children or in the very old with concomitant cognitive impairment/dementia, or in patients with neurological injury. These myths have recently been challenged.

Children

Approximately 40% of children and 50% of infants and toddlers experience delirium in the ICU [36, 37]. The Pediatric CAM-ICU (pCAM-ICU) with 99% specificity and 83% sensitivity [36], and the preschool CAM-ICU (psCAM-ICU) with 91% specificity and 75% sensitivity [37], are validated for use in children from 18 years down to 6 months, accounting for developmental milestones. Similarly, the Cornell Assessment for Pediatric Delirium (CAPD) [38], with specificity of 79% and sensitivity of 94%, is a validated tool for delirium utilizing observed behaviors in infants and children.

Neurologically injured patients

There are emerging data surrounding delirium monitoring and its prognostic value in critically ill patients with primary neurological injury, with both the CAM-ICU and ICDSC utilized [39–41]. The general construct one needs to consider is that delirium—a "micro-diffuse" injury occurring as a result of cellular and neurotransmitter abnormalities—can occur on top of the "macro-focal" primary neurological injury, such as stroke or a traumatic brain injury. New baseline neurological function needs to be assessed and documented and any change or fluctuation of neurological function needs to be considered in the context of the primary brain injury or evolvement of the same. Delirium should be considered in the differential diagnosis, given data that delirium superimposed on a primary neurological injury may portend worse outcomes [39–41].

Cognitively impaired patients

Critically ill patients with mild cognitive impairment are at risk for delirium and similarly delirium can occur in patients with dementia—delirium superimposed on dementia (DSD) [42, 43]. In the ICU, delirium evaluation in the context of dementia requires an accurate evaluation of the level of arousal. Acknowledging the current limitations of tools to assess DSD, it is still imperative to screen for DSD, using standard tools such as the CAM-ICU and ICDSC [43].

Creation of delirium networks and advocacy initiatives

Specialty societies such as the American Geriatric Society and SCCM have provided guidelines to assist their representative constituents to address delirium [13, 44]. Three major international interdisciplinary delirium societies—the Europe Delirium Association, the American Delirium Society, and Australasian Delirium Association—provide a platform for research collaboration and knowledge translation and have recently formed a global representative group called iDelirium to provide a unified voice for advancing care and to increase public health efforts to address delirium worldwide.

The ICU Liberation Collaborative is an initiative that has hospitals working with teams of leading national experts to implement evidence-based bundles of care (e.g., the ABCDEF bundle), enhance teamwork, and create partnerships with other institutions across the USA.

Finally, the Network for Investigation of Delirium across the US (NIDUS) has recently been funded by the National Institute of Aging to foster collaboration and accelerate scientific discovery in delirium.

What are the common beliefs that have been challenged by recent trials?

ICU delirium research has increased substantially in the last 15 years from about 10 articles per year in the early 2000s to an estimated 300 articles per year in 2013–2016.

Is delirium an epiphenomenon or is it causally linked to important outcomes such as mortality and long-term cognitive impairment?

Delirium is associated with a two- to threefold increased risk of death [2]. A more recent study, adjusting for disease severity until delirium onset, determined that delirium was not "causally" related to mortality [45]. These findings do not undermine the deleterious effects associated with delirium but rather raise awareness of the difference between "associations" and "causality". Criteria for causality require strength of association, consistency, temporality, biological gradient, plausibility, and an experiment that shows an intervention reducing delirium would result in a decrease in the outcome. Present research does not support all the causality criteria for mortality or for cognitive impairment associated with delirium. Delirium, for example, is independently and consistently associated with cognitive impairment, there is a biological gradient [7], and it is plausible since transient systemic inflammation (manifesting as delirium) may lead to long-lasting neuroinflammation [46]. By contrast, delirium does not always precede cognitive impairment and there is no randomized clinical trial (RCT) yet that shows that treatment of delirium improves long-term cognitive dysfunction.

What is rapidly reversible sedation-associated delirium?

The level of consciousness, an important component of delirium assessment, is affected by sedation and may confound delirium assessment [47]. Delirium rates may be 10–15% higher when assessed while patients are receiving sedation [47]. This raises the issue of whether sedation-associated delirium has different prognostic effects? A recent evaluation of 102 MV patients receiving continuous sedation showed that of patients who were delirious while on sedation, only 12% rapidly reversed their delirium status within 2 h of sedation interruption [48]. This small subset of patients who had rapidly reversible sedation-associated delirium had outcomes similar to patients who never had delirium, while patients in whom delirium persisted for longer than 2 h after stopping sedation had worse clinical outcomes [48]. This study suggests that clinicians should focus delirium screening efforts, whenever possible, when patients are least sedated, but should not ignore positive delirium assessments when patients are arousable on sedation because in the majority of patients

delirium persists even after discontinuation of sedation [48].

What is the role of antipsychotic medications in delirium?

Antipsychotics are given to more than 10% of ICU patients, often to reduce agitation. Small randomized studies have evaluated the role of antipsychotics to reduce delirium in MV adults [26–28]. Of these, only one study of 36 patients, comparing quetiapine to placebo, showed a reduction in delirium [26]. Important limitations exist for each study.

In the absence of dangerous agitation, there is little reason to administer antipsychotics, given these medications have side effects. Other potential causes of delirium such as pain or substance withdrawal should be considered. Antipsychotic medication should not be used for hypoactive delirium and rarely beyond ICU discharge [49]. While antipsychotic medications have been proposed for distressing symptoms such as hallucinations and delusions [50], no data supporting their use in ICU patients is available.

Is there a role for dexmedetomidine in hyperactive delirium?

Dexmedetomidine has been shown to reduce postoperative delirium [19], and when compared to a benzodiazepine infusion reduce delirium prevalence [22] and days without coma or delirium [23]. It should be noted though that in some studies, delirium was not the primary outcome [22]. Dexmedetomidine has also been shown to help in agitated delirium in non-intubated patients [29].

Recently the DahLIA trial [20] specifically assessed the role of dexmedetomidine in patients whose critical illness had resolved, but agitation precluded weaning from mechanical ventilation. Seventy-four patients were randomized to dexmedetomidine or placebo; patients treated with dexmedetomidine had increased ventilator-free hours at 7 days (median 144.8 vs 127.5 h) and faster resolution of their delirium symptoms (median 23.3 vs 40.0 h).

Do corticosteroids or statin medications have a role in delirium?

Two large studies [10, 51] have suggested that systemic corticosteroids increase the probability of delirium in the ICU. A subsequent single-center observational study of medical-surgical ICU patients [52] contradicted these finding. A recent single-center substudy [53] within the Dexamethasone for Cardiac Surgery (DECS) trial [54] showed no difference in delirium outcomes in the ICU patients randomized to dexamethasone or placebo. One very recent controlled study found that hydrocortisone use in patients with sepsis reduced the incidence of delirium by half [55]. Taken together these studies [52, 53, 55] suggest that corticosteroids with primarily glucocorticoid effects are neither a major risk factor for delirium nor do they reduce its incidence or duration but that corticosteroids with primarily mineralocorticoid activity may in fact reduce delirium incidence.

In observational studies in critically ill patients, ICU statin use has been associated with reduced delirium [56], especially early during sepsis [56]; discontinuation of a previously used statin was associated with increased delirium in that study [56]. The recent MoDUS RCT [57] of early treatment with simvastatin versus placebo in critically ill patients, showed no difference in delirium or coma outcomes. Similarly, recent Statin AKI Cardiac Surgery RCT of high-dose perioperative atorvastatin treatment showed no difference in delirium outcomes in patients randomized to a statin and an ancillary study in ARDS patients also demonstrated no difference in delirium in patients randomized to statins vs placebo [58].

Should patients be treated with cholinesterase inhibitors to decrease the duration of delirium?

Impaired cholinergic neurotransmission is proposed as a pathophysiologic mechanism for delirium, making cholinesterase inhibitors an attractive treatment choice to increase acetylcholine levels. A recent RCT [59] randomized critically ill patients with delirium to either rivastigmine or placebo as an adjunct to haloperidol, but the trial had to be halted prematurely because mortality in the rivastigmine group (22%) was higher than in the placebo group (8%) and median duration of delirium was longer in the rivastigmine group (5 vs 3 days). Given these safety concerns, the SCCM PAD guidelines strongly recommend against the use of cholinesterase inhibitors to either treat or prevent delirium [13].

Should benzodiazepines always be prescribed in patients at risk for or with symptoms of alcohol withdrawal?

Alcohol use disorder (AUD) is the most serious substance abuse problem in the USA and worldwide, with reported rates of 20–50% in hospitalized patients. Many alcohol-dependent patients will develop uncomplicated alcohol withdrawal symptoms (AWS), but only 20% will require pharmacological intervention; benzodiazepines have frequently been the mainstay of therapy [60]. The use of objective tools now allows targeting of only those patients at risk for complicated AWS with prophylactic management strategies [61]. Benzodiazepine-sparing protocols consisting of alpha-2 agonists (i.e., dexmedetomidine, guanfacine, clonidine) that address the adrenergic storm associated with AWS and/or various anticonvulsant agents (e.g., gabapentin, carbamazepine, valproic acid) acting primarily as

glutamate modulators to safely and effectively manage AWS have been recently proposed, and will need to be evaluated in larger studies.

What are remaining areas of uncertainties/work to be done?

Harmonization of outcomes/development of core outcomes

For studies to be maximally informative, and to allow cross comparisons between studies evaluating similar interventions in similar populations, outcomes should be selected, defined, and measured consistently. For these reasons, core outcome sets (COS) have been proposed and these outcome sets include those outcomes perceived, through a rigorous consensus process involving key stakeholders, including patients, as fundamental to measure in all trials related to a specific and defined area of interest (may be based on a disease, condition, or intervention) [62]. The COS should be small enough to minimize participant burden, limit research costs, and encourage researcher adoption, but large enough to capture outcomes deemed important to future decision-makers.

Improved statistical methods in delirium research

Evaluating the efficacy of interventions for reducing delirium in the ICU is challenging given that (1) delirium status changes over time, (2) delirium cannot be assessed when patients are comatose, (3) delirium assessment often does not continue after ICU discharge, preventing assessment of its full duration, and (4) mortality is a competing event for delirium assessment. Sometimes a composite outcome of delirium status and mortality is used—delirium-free days. However, use of delirium-free days does not fully address the competing risk of coma, leading to use of delirium/coma-free days in some studies [23]. More recently, joint models [63] have been proposed to address these challenges via linking two survival models: one for the recurrent daily delirium status and one for a terminating event (e.g., ICU discharge or death). This approach (as used in recent critical care delirium research [58]) yields a hazard ratio (HR) for delirium in the intervention vs control group, with HR <1 interpreted as a lower daily hazard of delirium—implying a shorter mean duration of delirium among days at risk for delirium (i.e., days in which a patient is alive, in the ICU, and in a non-comatose state).

Standardization of terminology: delirium vs encephalopathy, role of consciousness in delirium diagnosis, arousal level and delirium (untestable patients?)

While the DSM-5 definition [1] of delirium is used widely in clinical and research settings, it does not represent a consensus definition in all fields of medicine. In classic neurologic texts, delirium falls under the broader rubric of acute confusional states and, while including primarily hyperactive delirium subtypes, it excludes hypoactive delirium. The term "encephalopathy" is often employed to describe a range of mental states, including hypoactive delirium when a primary etiology is identified. Given that delirium is often multifactorial, this convention may be reductionist, resulting in overlooking reversible causes. The lack of consensus definition exists even within psychiatry as evidenced by the evolving DSM delirium criteria. For example, the DSM-IV-TR criteria required that a disturbance in consciousness must be present, while in the most recent DSM-5 [1], this criteria was changed to a disturbance in attention and awareness. A particular example is the debate whether delirium can be diagnosed in states with severely reduced arousal, which the DSM-5 specifically excludes [1]. Level of arousal exists along a continuum and there is no clear evidence that patients with severely disturbed arousal are different from patients with milder disturbance. Thus if non-comatose, but non-communicative patients unable to demonstrate inattention are excluded from delirium evaluations, these cases of delirium may be missed and this will have negative implications on patient safety and outcomes in clinical and research endeavors.

Sleep and delirium

A disturbed sleep–wake rhythm occurs commonly during delirium, but it is unclear whether this is a cause of delirium, an early sign of delirium, or both [64]. A before–after study of a multifaceted sleep-promoting intervention found 50% lower odds of delirium and coma, though self-reported sleep ratings did not improve [12]. It is therefore unclear whether the reduced delirium resulted from improved sleep [12].

Melatonin plays an important role in the sleep–wake cycle. In 67 patients, hospitalized because of serious medical problems, an RCT comparing the oral melatonin receptor agonist ramelteon to placebo reported a lower incidence of delirium in the ramelteon group [65].

Alpha-2 agonists, such as dexmedetomidine, may promote sleep [66], and recent studies point to beneficial effects in ICU patients [67]. The bidirectional relationship between sleep and delirium still needs to be better understood.

Electroencephalography in delirium

It is assumed, but not studied extensively, that different etiological subtypes of delirium (e.g., toxic-metabolic, infectious, postoperative) share the same electroencephalographic (EEG) features. The EEG during delirium shows diffuse slowing of background activity and increased spectral variability with often periodic discharges such as triphasic waves and polymorphic delta activity [68]. In some delirious patients, the EEG may

show electrographic seizures and periodic epileptiform discharges. Non-convulsive status epilepticus (NCSE) is a form of status epilepticus where there may be minimal seizure activity clinically, but there is evidence of its presence on EEG. Many patients with NCSE present with delirium, and it should be considered in the differential diagnosis in high risk patients [68]. Various approaches are being explored to develop more sensitive delirium monitoring with objective tools. A promising approach seems to be a brief EEG registration with a limited number of electrodes and automated processing [69].

Family-centered perspective in delirium and humanizing intensive care

Non-pharmacological interventions, including early mobilization, are examples of highly humanistic approaches that involve communication and reassurance, and are effective in preventing delirium [24, 70]. Despite qualitative descriptions of patients' ICU experiences being significantly enhanced by the presence of family members [71], no RCTs have evaluated the potential role of families in altering the course of ICU delirium or post-critical illness trajectories. Similarly the impact of delirium on patient, caregivers [72], and family experiences need to be better studied.

Role of implementation science in rapidly translating delirium research into practice

The current translational cycle of evidence-based medical research discoveries into widely implemented clinical therapeutics and healthcare services is inefficient and expensive [73, 74]. Implementation science is an action-oriented science that aims to develop tools, processes, and strategies to rapidly implement evidence-based, sustainable, and scalable healthcare solutions into the local healthcare environment [73]. Implementation scientists view the healthcare system as a complex adaptive network that includes a large number of semiautonomous agents interacting in dynamic and nonlinear ways. This complex interaction leads to constant emerging behaviors with limited centralized control [75]. Principles and tools of implementation science should be used to create a local coalition of brain research centers, advocacy groups, and clinical services. Brain-care service line should be created across the hospital and ambulatory services, with standardized data collection (preferably leveraging information technology), to serve the clinical operation, quality, and safety mission first, then research, and should lead to delirium-specific decision support tools. Finally, delirium scientists need to start innovating in a limited resource environment by including future payments of their solutions into their development requirement; thinking about the value of their solutions within a population health management payment model.

What are some of the top study areas/trials to be done in the next 10 years?

1. Development and validation of objective tools for delirium screening/diagnosis in critically ill patients, e.g., electroencephalogram, computer-based apps
2. Understanding the pathophysiology of delirium and its relationship mechanistically to long-term cognitive decline
3. Development of new models to improve delirium phenotyping
4. Understanding the attributable risk of delirium on outcomes; going beyond associations to causal inferences
5. Elucidating the biomarkers of delirium and incorporation into predictive models
6. Large RCTs that are needed in ICU patients:

    (a) Safety and efficacy of antipsychotic medications on delirium and long-term outcomes
    (b) Safety and efficacy of sleep optimization (non-pharmacological or pharmacological) on delirium and long-term outcomes
    (c) Safety and efficacy of cognitive and physical training on delirium and long-term outcomes
    (d) Safety and efficacy of alternate sedation paradigms (dexmedetomidine, clonidine, propofol, general anesthetics) on delirium and long-term outcomes
    (e) The role of humanization of ICU care, specifically family engagement and other non-pharmacological interventions (e.g., restraints), on delirium and patient and family long-term outcomes

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Compliance with ethical standards

Conflicts of interest

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References

1. Association AP (2013) Diagnostic and statistical manual of mental disorders: DSM-5. American Psychiatric Association, Washington, DC
2. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS (2004) Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 291:1753–1762
3. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, Dittus R, Ely EW (2008) Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. J Trauma 65:34–41
4. McPherson JA, Wagner CE, Boehm LM, Hall JD, Johnson DC, Miller LR, Burns KM, Thompson JL, Shintani AK, Ely EW, Pandharipande PP (2013) Delirium in the cardiovascular ICU: exploring modifiable risk factors. Crit Care Med 41:405–413
5. Peterson JF, Pun BT, Dittus RS, Thomason JW, Jackson JC, Shintani AK, Ely EW (2006) Delirium and its motoric subtypes: a study of 614 critically ill patients. J Am Geriatr Soc 54:479–484
6. Meagher DJ, Leonard M, Donnelly S, Conroy M, Adamis D, Trzepacz PT (2011) A longitudinal study of motor subtypes in delirium: relationship with other phenomenology, etiology, medication exposure and prognosis. J Psychosom Res 71:395–403
7. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Moons KG, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW (2013) Long-term cognitive impairment after critical illness. N Engl J Med 369:1306–1316
8. Norman BC, Jackson JC, Graves JA, Girard TD, Pandharipande PP, Brummel NE, Wang L, Thompson JL, Chandrasekhar R, Ely EW (2016) Employment outcomes after critical illness: an analysis of the bringing to light the risk factors and incidence of neuropsychological dysfunction in ICU survivors cohort. Crit Care Med 44:2003–2009
9. Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, Pun BT, Vasilevskis EE, Morandi A, Shintani AK, Hopkins RO, Bernard GR, Dittus RS, Ely EW, Bringing to light the Risk factors And Incidence of Neuropsychological dysfunction in ICU (BRAIN-ICU) study investigators (2014) Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med 2:369–379
10. Wassenaar A, van den Boogaard M, van Achterberg T, Slooter AJ, Kuiper MA, Hoogendoorn ME, Simons KS, Maseda E, Pinto N, Jones C, Luetz A, Schandl A, Verbrugghe W, Aitken LM, van Haren FM, Donders AR, Schoonhoven L, Pickkers P (2015) Multinational development and validation of an early prediction model for delirium in ICU patients. Intensive Care Med 41:1048–1056
11. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW (2006) Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 104:21–26
12. Kamdar BB, King LM, Collop NA, Sakamuri S, Colantuoni E, Neufeld KJ, Bienvenu OJ, Rowden AM, Touradji P, Brower RG, Needham DM (2013) The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. Crit Care Med 41:800–809
13. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R, American College of Critical Care Medicine (2013) Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 41:263–306
14. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R (2001) Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 286:2703–2710
15. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y (2001) Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 27:859–864
16. Balas MC, Vasilevskis EE, Olsen KM, Schmid KK, Shostrom V, Cohen MZ, Peitz G, Gannon DE, Sisson J, Sullivan J, Stothert JC, Lazure J, Nuss SL, Jawa RS, Freihaut F, Ely EW, Burke WJ (2014) Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med 42:1024–1036
17. Barnes-Daly MA, Phillips G, Ely EW (2016) Improving hospital survival and reducing brain dysfunction at seven California Community Hospitals: implementing PAD guidelines via the ABCDEF bundle in 6064 patients. Crit Care Med 45:171–178
18. Vincent JL, Shehabi Y, Walsh TS, Pandharipande PP, Ball JA, Spronk P, Longrois D, Strom T, Conti G, Funk GC, Badenes R, Mantz J, Spies C, Takala J (2016) Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med 42:962–971
19. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, Zhu X, Zhu SN, Maze M, Ma D (2016) Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 388:1893–1902
20. Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, Davies A, Delaney A, Ghosh A, van Haren F, Harley N, Knight D, McGuiness S, Mulder J, O'Donoghue S, Simpson N, Young P, Dah LIAI, Australian, New Zealand Intensive Care Society Clinical Trials Group (2016) Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA 315:1460–1468
21. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J, Dexmedetomidine for Long-Term Sedation Investigators (2012) Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 307:1151–1160

22. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG, SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group (2009) Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 301:489–499
23. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW (2007) Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 298:2644–2653
24. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP (2009) Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 373:1874–1882
25. Schaller SJ, Anstey M, Blobner M, Edrich T, Grabitz SD, Gradwohl-Matis I, Heim M, Houle T, Kurth T, Latronico N, Lee J, Meyer MJ, Peponis T, Talmor D, Velmahos GC, Waak K, Walz JM, Zafonte R, Eikermann M (2016) Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet 388:1377–1388
26. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, Robbins T, Garpestad E (2010) Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med 38:419–427
27. Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, Pun BT, Thompson JL, Shintani AK, Meltzer HY, Bernard GR, Dittus RS, Ely EW, MIND Trial Investigators (2010) Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med 38:428–437
28. Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, Jackson J, Perkins GD, McAuley DF (2013) Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. lancet Respir Med 1:515–523
29. Carrasco G, Baeza N, Cabre L, Portillo E, Gimeno G, Manzanedo D, Calizaya M (2016) Dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in nonintubated ICU patients: a nonrandomized controlled trial. Crit Care Med 44:1295–1306
30. Reis PA, Comim CM, Hermani F, Silva B, Barichello T, Portella AC, Gomes FC, Sab IM, Frutuoso VS, Oliveira MF, Bozza PT, Bozza FA, Dal-Pizzol F, Zimmerman GA, Quevedo J, Castro-Faria-Neto HC (2010) Cognitive dysfunction is sustained after rescue therapy in experimental cerebral malaria, and is reduced by additive antioxidant therapy. PLoS Pathog 6:e1000963
31. Weberpals M, Hermes M, Hermann S, Kummer MP, Terwel D, Semmler A, Berger M, Schafers M, Heneka MT (2009) NOS2 gene deficiency protects from sepsis-induced long-term cognitive deficits. J Neurosci 29:14177–14184
32. Anderson ST, Commins S, Moynagh PN, Coogan AN (2015) Lipopolysaccharide-induced sepsis induces long-lasting affective changes in the mouse. Brain Behav Immun 43:98–109
33. Bozza FA, Garteiser P, Oliveira MF, Doblas S, Cranford R, Saunders D, Jones I, Towner RA, Castro-Faria-Neto HC (2010) Sepsis-associated encephalopathy: a magnetic resonance imaging and spectroscopy study. J Cereb Blood Flow Metab 30:440–448
34. Semmler A, Hermann S, Mormann F, Weberpals M, Paxian SA, Okulla T, Schafers M, Kummer MP, Klockgether T, Heneka MT (2008) Sepsis causes neuroinflammation and concomitant decrease of cerebral metabolism. J Neuroinflamm 5:38
35. Davis DH, Skelly DT, Murray C, Hennessy E, Bowen J, Norton S, Brayne C, Rahkonen T, Sulkava R, Sanderson DJ, Rawlins JN, Bannerman DM, MacLullich AM, Cunningham C (2015) Worsening cognitive impairment and neurodegenerative pathology progressively increase risk for delirium. Am J Geriatr Psychiatry 23:403–415
36. Smith HA, Boyd J, Fuchs DC, Melvin K, Berry P, Shintani A, Eden SK, Terrell MK, Boswell T, Wolfram K, Sopfe J, Barr FE, Pandharipande PP, Ely EW (2011) Diagnosing delirium in critically ill children: validity and reliability of the pediatric confusion assessment method for the intensive care unit. Crit Care Med 39:150–157
37. Smith HA, Gangopadhyay M, Goben CM, Jacobowski NL, Chestnut MH, Savage S, Rutherford MT, Denton D, Thompson JL, Chandrasekhar R, Acton M, Newman J, Noori HP, Terrell MK, Williams SR, Griffith K, Cooper TJ, Ely EW, Fuchs DC, Pandharipande PP (2016) The preschool confusion assessment method for the ICU: valid and reliable delirium monitoring for critically ill infants and children. Crit Care Med 44:592–600
38. Traube C, Silver G, Kearney J, Patel A, Atkinson TM, Yoon MJ, Halpert S, Augenstein J, Sickles LE, Li C, Greenwald B (2014) Cornell assessment of pediatric delirium: a valid, rapid, observational tool for screening delirium in the PICU. Crit Care Med 42:656–663
39. Mitasova A, Kostalova M, Bednarik J, Michalcakova R, Kasparek T, Balabanova P, Dusek L, Vohanka S, Ely EW (2012) Poststroke delirium incidence and outcomes: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 40:484–490
40. Naidech AM, Beaumont JL, Rosenberg NF, Maas MB, Kosteva AR, Ault ML, Cella D, Ely EW (2013) Intracerebral hemorrhage and delirium symptoms. Length of stay, function, and quality of life in a 114-patient cohort. Am J Respir Crit Care Med 188:1331–1337
41. Frenette AJ, Bebawi ER, Deslauriers LC, Tessier AA, Perreault MM, Delisle MS, Bertrand JC, Desjardins M, Rico P, Khwaja K, Burry LD, Bernard F, Williamson DR (2016) Validation and comparison of CAM-ICU and ICDSC in mild and moderate traumatic brain injury patients. Intensive Care Med 42:122–123
42. Fick DM, Agostini JV, Inouye SK (2002) Delirium superimposed on dementia: a systematic review. J Am Geriatr Soc 50:1723–1732
43. Morandi A, Han JH, Meagher D, Vasilevskis E, Cerejeira J, Hasemann W, MacLullich AM, Annoni G, Trabucchi M, Bellelli G (2016) Detecting delirium superimposed on dementia: evaluation of the diagnostic performance of the Richmond agitation and sedation scale. J Am Med Dir Assoc 17:828–833
44. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults (2014) AGS clinical practice guideline for postoperative delirium in older adults. In: Clinical practice guideline for postoperative delirium in older adults. American Geriatrics Society, New York
45. Klein Klouwenberg PMC, Zaal IJ, Spitoni C, Ong DSY, van der Kooi AW, Bonten MJM, Slooter AJC, Cremer OL (2014) The attributable mortality of delirium in critically ill patients: prospective cohort study. BMJ 349:g6652
46. van Gool WA, van de Beek D, Eikelenboom P (2010) Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet 375:773–775
47. Haenggi M, Blum S, Brechbuehl R, Brunello A, Jakob S, Takala J (2013) Effect of sedation level on the prevalence of delirium when assessed with CAM-ICU and ICDSC. Intensive Care Med 39:2171–2179
48. Patel SB, Poston JT, Pohlman A, Hall JB, Kress JP (2014) Rapidly reversible, sedation-related delirium versus persistent delirium in the Intensive Care Unit. Am J Respir Crit Care Med 189:658–665
49. Morandi A, Vasilevskis E, Pandharipande PP, Girard TD, Solberg LM, Neal EB, Koestner T, Torres RE, Thompson JL, Shintani AK, Han JH, Schnelle JF, Fick DM, Ely EW, Kripalani S (2013) Inappropriate medication prescriptions in elderly adults surviving an intensive care unit hospitalization. J Am Geriatr Soc 61:1128–1134
50. Inouye SK, Westendorp RG, Saczynski JS (2014) Delirium in elderly people. Lancet 383:911–922
51. Schreiber MP, Colantuoni E, Bienvenu OJ, Neufeld KJ, Chen KF, Shanholtz C, Mendez-Tellez PA, Needham DM (2014) Corticosteroids and transition to delirium in patients with acute lung injury. Crit Care Med 42:1480–1486
52. Wolters AE, Veldhuijzen DS, Zaal IJ, Peelen LM, van Dijk D, Devlin JW, Slooter AJ (2015) Systemic corticosteroids and transition to delirium in critically ill patients. Crit Care Med 43:e585–e588
53. Sauer AM, Slooter AJ, Veldhuijzen DS, van Eijk MM, Devlin JW, van Dijk D (2014) Intraoperative dexamethasone and delirium after cardiac surgery: a randomized clinical trial. Anesth Analg 119:1046–1052
54. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D, Dexamethasone for Cardiac Surgery Study Group (2012) Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA 308:1761–1767
55. Keh D, Trips E, Marx G et al (2016) Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS randomized clinical trial. JAMA 316:1775–1785
56. Morandi A, Hughes CG, Thompson JL, Pandharipande PP, Shintani AK, Vasilevskis EE, Han JH, Jackson JC, Laskowitz DT, Bernard GR, Ely EW, Girard TD (2014) Statins and delirium during critical illness: a multicenter, prospective cohort study. Crit Care Med 42:1899–1909

57. Page VJ, Ely EW, Casarin A, Zhao XB, McDowell C, Murphy L, McAuley DF (2017) Evaluating early administration of the hydroxymethylglutaryl-CoA reductase inhibitor simvastatin in the prevention and treatment of delirium in critically ill ventilated patients: a randomised, placebo controlled trial (MoDUS). Lancet Respir Med **(in press)**
58. Needham DM, Colantuoni E, Dinglas VD, Hough CL, Wozniak AW, Jackson JC, Morris PE, Mendez-Tellez PA, Ely EW, Hopkins RO (2016) Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial. Lancet Respir Med 4:203–212
59. van Eijk MM, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, Spronk PE, van Gool WA, van der Mast RC, Kesecioglu J, Slooter AJ (2010) Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet 376:1829–1837
60. Moss M, Burnham EL (2006) Alcohol abuse in the critically ill patient. Lancet 368:2231–2242
61. Maldonado JR, Sher Y, Das S, Hills-Evans K, Frenklach A, Lolak S, Talley R, Neri E (2015) Prospective validation study of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) in medically ill inpatients: a new scale for the prediction of complicated alcohol withdrawal syndrome. Alcohol Alcohol 50:509–518
62. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S (2010) What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set. Arthritis Care Res (Hoboken) 62:640–646
63. Rondeau V, Mathoulin-Pelissier S, Jacqmin-Gadda H, Brouste V, Soubeyran P (2007) Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. Biostatistics 8:708–721
64. Trompeo AC, Vidi Y, Locane MD, Braghiroli A, Mascia L, Bosma K, Ranieri VM (2011) Sleep disturbances in the critically ill patients: role of delirium and sedative agents. Minerva Anestesiol 77:604–612
65. Hatta K, Kishi Y, Wada K, Takeuchi T, Odawara T, Usui C, Nakamura H (2014) Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. JAMA Psychiatry 71:397–403
66. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M (2003) The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 98:428–436
67. Wu XH, Cui F, Zhang C, Meng ZT, Wang DX, Ma J, Wang GF, Zhu SN, Ma D (2016) Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial. Anesthesiology 125:979–991
68. Kaplan PW (2004) The EEG in metabolic encephalopathy and coma. J Clin Neurophysiol 21:307–318
69. van der Kooi AW, Zaal IJ, Klijn FA, Koek HL, Meijer RC, Leijten FS, Slooter AJ (2015) Delirium detection using EEG: what and how to measure. Chest 147:94–101
70. Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM Jr (1999) A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 340:669–676
71. Svenningsen H, Tonnesen E (2011) Delirium incidents in three Danish intensive care units. Nurs Crit Care 16:186–192
72. Belanger L, Ducharme F (2011) Patients' and nurses' experiences of delirium: a review of qualitative studies. Nurs Crit Care 16:303–315
73. Azar J, Adams N, Boustani M (2015) The Indiana University Center for healthcare innovation and implementation science: bridging healthcare research and delivery to build a learning healthcare system. Z Evid Fortbild Qual Gesundhwes 109:138–143
74. Boustani MA, Frame A, Munger S, Healey P, Westlund J, Farlow M, Hake A, Austrom MG, Shepard P, Bubp C, Azar J, Nazir A, Adams N, Campbell NL, Chehresa A, Dexter P (2012) Connecting research discovery with care delivery in dementia: the development of the Indianapolis Discovery Network for Dementia. Clin Interv Aging 7:509–516
75. Boustani M, Baker MS, Campbell N, Munger S, Hui SL, Castelluccio P, Farber M, Guzman O, Ademuyiwa A, Miller D, Callahan C (2010) Impact and recognition of cognitive impairment among hospitalized elders. J Hosp Med 5:69–75