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Epidemiology and risk factors for delirium across hospital settings

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Abstract

Delirium is one of the most common causes of acute end-organ dysfunction across hospital settings, occurring in as high as 80% of critically ill patients that require intensive care unit (ICU) care. The implications of this acute form of brain injury are profound. Across many hospital settings (emergency department, general medical ward, postoperative and ICU), a patient who experiences delirium is more likely to experience increased short- and long-term mortality, decreases in long-term cognitive function, increases in hospital length of stay and increased complications of hospital care. With the development of reliable setting-specific delirium-screening instruments, researchers have been able to highlight the predisposing and potentially modifiable risk factors that place patients at highest risk. Among the large number of risk factors discovered, administration of potent sedative medications, most notably benzodiazepines, is most consistently and strongly associated with an increased burden of delirium. Alternatively, in both the hospital and ICU, delirium can be prevented with the application of protocols that include early mobility/exercise. Future studies must work to understand the epidemiology across settings and focus upon modifiable risk factors that can be integrated into existing delirium prevention and treatment protocols.

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Keywords

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Introduction

Delirium is an acute organic brain syndrome characterised by inattention, cognitive impairment and alteration of consciousness. Delirium can be further characterised as hypoactive, hyperactive or mixed.¹ It is important to remember that delirium is the end product of a sequence of insults and injury that lead to a common measurable manifestation of end-organ brain injury. Implicit in the syndromal characterisation is the underlying notion that delirium does not have a single aetiology but rather has multiple different and potentially interacting aetiologies.^{2–4}

As the underlying mechanism of delirium may be variable, it is therefore not surprising that the epidemiology and associated risk factors vary from one setting to another. Importantly, the predisposing and precipitating factors that place a patient at high risk in one setting (e.g., postoperative) may be non-existent in others (e.g., intensive care unit (ICU)). Another difference to consider is that delirium measurement tools vary across settings, and even among the same setting, each of which exhibit variable test characteristics that impact measures of prevalence, incidence and risk-factor associations.^{5,6} Despite differences in underlying sources of injury, epidemiology and measurement, there are important shared factors that resonate regardless of the setting.

The goal of this review is to consider the unique and shared knowledge that has been acquired about the epidemiology and risk factors of delirium across inpatient settings. We will consider the emergency department (ED), general medical ward, postoperative setting and the ICU. Each area is relevant to the practising anaesthesiologist as well as hospital-based clinicians (e.g., ED physicians, hospitalists and intensivists).

Epidemiology of delirium in the hospital setting

Delirium is common in hospitalised general medical patients. Upon admission, approximately 11–25% of hospitalised elder patients will have delirium (prevalent delirium).^{7–12} An additional 29–31% of hospitalised older patients admitted without delirium will develop delirium (incident delirium).^{10,13} This distinction may be important in general medical patients because prevalent versus incident delirium may have differing effects on patient outcomes.¹⁴

Risk factors of delirium in the general medical ward setting

Risk factors for delirium across any setting, including the medical ward, can be categorised into patient vulnerability (or predisposing) factors and potentially modifiable (or precipitating) factors.^{15,16} Note that classification of factors serves as a framework to understand their modifiability and is not a firm dividing line. Some factors (e.g., acute physiology) may be a presenting condition, but may also be a consequence of the care provided in the hospital.

Numerous patient vulnerability factors have been identified in this setting,^{17,18} but dementia is the most consistently observed vulnerability factor for delirium.^{15,19–23} In addition, as the severity of dementia worsens, the risk of delirium increases.²⁴ Low education attainment is also associated with delirium and may be related to cognitive reserve.²⁵ Other vulnerability factors reported in the hospital literature include advanced age,^{22,26,27} high co-morbidity

burden,²³ visual impairment,¹⁵ depression,²³ history of alcohol abuse,²³ malnutrition^{16,28} and home opioid or benzodiazepine use.⁸

Several potentially modifiable factors of delirium have been identified in the hospital literature. Patients with higher severity of illness are more likely to experience delirium.^{8,15,22} Infections, such as a urinary tract infection or pneumonia, are probably some of the most common precipitants of delirium and may be present in 34–64% of the hospitalised patients with delirium.^{20–22,26,29–31} Other delirium precipitants in the hospital literature include dehydration,⁹ electrolyte abnormalities,^{8,32} acute kidney injury or liver failure,^{8,32} ethanol or benzodiazepine withdrawal,^{33–35} central nervous system insults^{20,21,29} and seizures.³¹ Congestive heart failure^{22,31} and acute myocardial infarction^{31,36} have also been implicated as delirium precipitants. Multiple delirium precipitants may co-exist at one time in many delirious patients,⁸ and conversely in some patients, no obvious aetiological agent can be found.³⁷

Importantly, delirium can be precipitated by iatrogenic events and, therefore, may be avoidable if appropriate action is taken. For example, physical restraints, bladder catheters or polypharmacy are associated with precipitating delirium.¹⁶ Opioid, benzodiazepine and medication with anticholinergic properties are commonly thought of as delirium precipitants. However, the number of high-quality trials establishing these relationships in general medical patients are sparse.³⁸ In addition, much of the data regarding psychoactive medications and delirium are from studies conducted in the postoperative and ICU setting. In 426 hospitalised medical patients, Agostini et al. observed a trend towards increased risk (relative risk = 2.1, 95% confidence interval: 0.9–4.7) of developing delirium when diphenhydramine was used.³⁹ In stroke patients, Caerio observed that patients who used home medications with anticholinergic properties were susceptible to developing delirium in the hospital.⁴⁰ Finally, Schor et al. found that older patients who used narcotics were 2.5 times more likely to develop delirium during the hospitalisation.²⁶

Epidemiology of delirium in the ED

The ED plays a vital role in the health care of the ageing population and serves as the gateway for the majority of hospital admissions. In the United States, the ED sees approximately 120 million patients annually, 15% of whom will be 65.⁴¹ Despite these statistics, the epidemiology of delirium in the ED is not as well established.

Although significant overlap exists between hospital and ED patient populations, special care must be taken when attempting to generalise the results of studies across settings. Unlike the hospital setting, the ED population comprises a substantial number of patients who are discharged directly home. In addition, many inpatient studies enrol patients within 24–48 h of hospitalisation, potentially causing misclassification bias. The patient's delirium status at enrolment may reflect the patient's delirium status previously in the ED.^{10,11,23,42,43} For example, because delirium can resolve in 24 h in 20–51% of patients, those classified as non-delirious in the hospital may have been delirious in the ED.^{44–46}

Delirium occurs frequently in older ED patients, affecting 8–10% of patients.^{47–53} However, most of the ED delirium prevalence studies have limitations. For example, most ED studies assess for delirium at one point in time, and the proportion of patients that go on to experience incident delirium is unknown. Incident delirium likely happens with regularity in the ED since psychoactive medications (e.g., benzodiazepines and opioids) are frequently given. Studies need to be performed to determine delirium incidence in the ED.

Despite comprising over half the older ED patient population,⁵⁴ the epidemiology of delirium in older patients who are discharged from the ED is unclear. Han et al. observed

that 19% of older ED patients who are discharged from the ED still had delirium.⁵⁵ Similarly, Naughton et al.⁵⁰ observed that 13% of discharged older ED patients were delirious. The short-term and long-term consequences of discharging delirious patients are unknown and needs further study, especially in light of one study that observed delirium at discharge was associated with increased 6-month mortality.⁵³

Risk factors for delirium in the ED

There are limited data regarding risk factors in older ED patients. Similar to findings in the hospital setting, Han et al. observed that older ED patients with dementia, functional impairment and hearing impairment were more likely to present to the ED with delirium.⁴⁹ Kennedy et al. found that age as well as a past history of dementia, cerebrovascular disease or seizure disorder increased the odds of delirium in the ED.⁵⁶ Both studies demonstrate the notion of the vulnerable brain being at increased risk for the development of acute brain dysfunction. The latter study also observed that older ED patients who had a respiratory rate >20 breaths per minute or had a diagnosis of urinary tract infection or intracranial haemorrhage were more likely to have delirium.⁵⁶ It is still unclear which, if any, process measures in the ED place patients at increased risk for the development of delirium in the ED or following admission.

Epidemiology of postoperative delirium

Similar to other patient cohorts, delirium in the postoperative setting has been associated with significant increases in hospital stay, functional decline, prolonged cognitive dysfunction and mortality.^{57,58} While the incidence of postoperative delirium (POD) is common, similar to other settings, there is a wide discrepancy in the literature regarding rates. This is partly attributed to the lack of a clearly defined distinction between emergence, post-anaesthesia care unit and POD, as well as differing criteria for delirium diagnosis.^{1,59} In addition, prior studies examining POD have focussed on hyperactive delirium, likely under-diagnosing hypoactive sub-types when not using validated delirium-monitoring instruments. Despite these limitations, the incidence and risk factors of POD reported in the literature appear to be strongly influenced by the severity of the surgical insult, co-morbidities and sedative and/or analgesic drug exposure.

Risk factors for POD

Among the unique vulnerability risk factors of the postoperative setting is the relationship of delirium to the type of operation. For example, the incidence of POD appears to increase with the risk of the surgery, such that otolaryngological (12%), general surgery (13%), aortic (up to 29%), major abdominal (up to 50%) and cardiac (up to 51%) surgeries have, respectively, increased reported incidence.^{57,60–65} In addition, open versus endovascular surgery, emergency versus elective surgery, increased blood transfusion and increased surgical duration all have increased surgical burden and increased risk of POD.^{60–62,65–68} Specific to cardiac surgery, balloon pump support, valve surgery and prolonged cardiopulmonary bypass also increase the risk of POD,^{65,69–71} whereas conflicting evidence exists as to whether off-pump coronary bypass is protective or carries the same risk of POD as on-pump coronary bypass.^{72,73}

Across multiple types of surgical interventions, numerous patient vulnerability characteristics have been reported as risk factors for POD. Increasing age, pre-existing cognitive impairment, increased cardiovascular co-morbidities (including diabetes) and severity of illness (e.g., American Society of Anesthesiologists classification 3) have been consistently shown to be associated with POD in a variety of postoperative patients.^{57,60,61,63,65,67–70,74} Male sex, smoking, obstructive sleep apnoea, alcohol excess,

atrial fibrillation, renal dysfunction, obesity, heart failure and postoperative ICU admission have also been reported as risk factors.^{60,69,72,75,76} Meanwhile, younger age and higher education have been found to be protective,^{72,77} and the data on preoperative statin administration prior to cardiac surgery are mixed with regard to the development of POD.^{78,79}

Among the potentially modifiable factors, multiple prospective cohort studies have examined the effects of perioperative psychoactive medications on POD. Two studies examining emergence delirium found a significant increase if benzodiazepines were administered as a preoperative medication.^{80,81} Benzodiazepines have also been associated with POD in both cardiac and non-cardiac surgery patient populations.^{82,83} Alternative sedatives to benzodiazepines have shown promise. For example, in a randomised study of postoperative cardiac surgery patients, the incidence of delirium was significantly decreased in patients sedated with dexmedetomidine versus propofol or midazolam,⁸⁴ and another randomised controlled study found that dexmedetomidine reduced the duration but not the incidence of delirium after cardiac surgery as compared to morphine-based therapy.⁸⁵ These studies speak primarily towards either reducing the incidence of delirium or decreasing the duration of delirium by using dexmedetomidine at the onset of sedation requirement in the postoperative patient.

While data on the risk of perioperative benzodiazepines have been fairly consistent, studies have not shown a clear association of analgesics on POD, and have looked at variable opiate types, routes and patient populations. For example, opioids administered either intravenously or via an epidural route have been associated with the development of POD in some cohorts.^{63,83,86} Yet, these same cohorts implicate different opiates (tramadol, meperidine and fentanyl) as risk factors, while showing either no or even protective effects for alternative opiates. Other studies have shown that fast-track management with opioid sparing decreased POD after elective hip and knee arthroplasty⁸⁷ and less POD when a femoral nerve block was provided in addition to patient-controlled opioid analgesia.⁸⁸ Other studies found no association between postoperative opioid use and incident delirium⁷⁶ or protective effects of opioid therapy for pain control.^{86,89} Additional studies are needed to understand the optimal pain management strategies and their relation to delirium and longer-term cognitive and psychiatric outcomes.

Similar to analgesic therapy, the risk of general anaesthesia on POD is not clear. Sedation during spinal anaesthesia for hip surgery targeted towards lighter sedation decreased the incidence of POD in elderly patients,⁹⁰ and a Cochrane Database review suggested that regional anaesthesia (and subsequent higher levels of consciousness compared to general anaesthesia) may decrease postoperative confusion in hip surgery patients.⁹¹ However, a recent meta-analysis did not find an increased risk of general versus regional anaesthesia for POD,⁹² and a recent large prospective cohort study of elderly patients undergoing hip surgery did not find an independent association between benzodiazepines, opioids, anticholinergics or general anaesthetics (vs. regional) and POD.⁹³ With regard to specific general anaesthetic agents, no difference in POD or long-term cognitive dysfunction (3 months) was found between desflurane and propofol, but patients anaesthetized with propofol had a higher incidence of early cognitive dysfunction (days 3–7).⁹⁴ In a small prospective study of cardiac surgery patients, sevoflurane was associated with worse early (day 3 and 6) neurocognitive function and higher S100 beta protein (a marker of brain injury) than either isoflurane or desflurane.⁹⁵

Epidemiology of delirium in the ICU

Similar to other settings, there is widely reported prevalence and incidence of delirium in the ICU. The prevalence of delirium in ICU cohort studies has been reported as low as 20–30%,^{96,97} and as high as 70–80% or more.^{98–100} Incident delirium has similarly been described from 22 to 83%.^{59,101} The wide variation depends on study design factors (e.g., duration of patient follow-up), patient characteristics, delirium measurement instrument (e.g., Confusion Assessment Method for the ICU,^{59,102–105} Intensive Care delirium Screening Checklist,^{97,106,107}) and site-specific variability of practices known to impact delirium prevalence and incidence (e.g., sedation practice^{86,108,109}). In addition to these factors, the prevalence of coma may impact the prevalence of delirium, since delirium cannot be assessed among comatose patients and therefore may lead to biased assessments of acute brain dysfunction.^{108,110}

Whether considering prevalence or incidence, the most common form of delirium is the hypoactive type,^{103,110} characterised by psychomotor slowing, apathy and decreased responsiveness. Alternatively, a purely hyperactive sub-type of delirium, characterised by psychomotor agitation, hallucinations and emotional lability, is very infrequent in the intensive care setting. When hyperactive delirium does occur, it is usually not the only sub-type experienced but rather may fluctuate with hypoactive delirium, and be considered a mixed sub-type.^{103,111} The unique risk factors for, and clinical implications of, these sub-types are still yet defined and worthy of future study.

Risk factors for ICU delirium

Multiple studies have investigated factors that may be associated with prevalent delirium, incident delirium or prolongation of delirium. Over 100 different risk factors have been investigated for a potential association with delirium incidence in the ICU. The studies are heterogeneous, differing by study location, design, population inclusions/exclusions and the outcome assessment (e.g., delirium prevalence, incidence, delirium duration or the number of delirium coma-free days).^{96,98,100,106,109,112–115} Therefore, it is not surprising that heterogeneity exists in the number, type and consistency with which individual risk factors have been reported to be associated with delirium.

Despite the heterogeneity, there are predisposing risk factors that are of broad importance in the ICU setting. Similar to other settings, cognitive impairment is one of the more commonly cited predictors that appear to indicate a vulnerable population.^{109,112} Age is an additional factor,^{114,116} although this factor has not been consistently reported across studies.^{96,112,113} Both of these factors have tremendous implications in light of increasing rates of mechanical ventilator and ICU use among the elderly^{117–119} coupled with the rapidly changing and ageing demographics of many developed nations.

Among precipitating risk factors, acute physiologic derangements (e.g., Acute Physiology and Chronic Health Evaluation II score)^{98,112,114} appear to increase risk. Among the most modifiable precipitants, exposure to benzodiazepines appear to be the most strongly associated with delirium.^{98,99,114,120,121} Pandharipande et al.^{86,114} and Pisani et al.⁹⁹ have demonstrated in separate observational studies the harms associated with benzodiazepines (both lorazepam and midazolam) and shown a dose-dependent increase in risk, with almost near certainty of delirium with lorazepam doses above 20 mg day⁻¹.¹¹⁴ In addition, two randomised controlled trials demonstrated that when compared to midazolam¹²¹ or lorazepam,¹²⁰ sedation management with dexmedetomidine results in reduced number of delirium or delirium coma-free days, respectively. These data highlight the importance of sedation choice and avoidance of benzodiazepines in the prevention of delirium in the ICU. Opioid administration has similarly been associated with increases with

delirium,^{98,106,112,114} but has not been consistent across all studies¹¹⁴ and settings, including trauma.⁸⁶ Among the most protective modifiable factors appear to be the receipt of early mobility.^{122,123} Schweickert et al. demonstrated that patients randomised to early physical therapy when compared to usual care experienced on average 2 fewer days of delirium. Similar effects on delirium reduction were demonstrated by Needham et al. following implementation of an early mobility protocol.¹²³ Efforts to reduce sedation and improve mobility are well recognised and are being actively implemented in the **Awakening and Breathing Coordination, Choice of Sedation, Delirium Monitoring and Management and Early Mobility** ('ABCDE') bundle (Fig. 1).^{124–126}

Only recently have investigators explored the relationship between ICU delirium and genetics,¹¹³ biochemical factors^{98,127–129} and environmental factors in the development of delirium.¹¹² Among the biomarkers investigated, there are early indicators that inflammatory biomarkers (procalcitonin and C-reactive protein),^{127,130} as well as metabolites of tryptophan may be associated with incident delirium.^{98,116} Among the environmental factors, inadequate access to light and interactions with friends or family may increase risk.¹¹² Continued identification of novel risk factors and validation of previously reported risk factors will play a critical role in risk prediction and development of new prevention and treatment paradigms.

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Summary and practice points

Overall, no matter the setting, a complex inter-relationship between patient vulnerability and precipitating factors exists. A patient who is highly vulnerable (e.g., a patient with severe dementia, poor functional status and high co-morbidity burden) can develop delirium with a benign precipitant such as a simple urinary tract infection. Similarly, a patient who is less vulnerable (e.g., a patient with no dementia and is highly functional) requires a more noxious stimulus such as severe sepsis to become delirious (Fig. 2). This relationship is important to understand when trying to understand the impact of specific risk factors as they apply to specific patient populations and in different settings (e.g., hospital, emergency department, postoperative or ICU).

For a practising clinician, special attention should be placed on limiting the exposure to risk factors that can be modified. Among these, exposure, choice and dose of sedative and analgesic medications should be a top priority. When possible, practitioners should avoid the use of benzodiazepine medications, and when sedatives are required, select alternative medications (e.g., propofol or dexmedetomidine) that have not been shown to increase the risk for delirium. For the surgical patient, the risk of delirium may be attenuated by less invasive surgical techniques, decreased surgical duration, and the avoidance of reduction of blood transfusions as well as benzodiazepines. In addition, when possible, efforts should be made to promote early mobility in the ward and ICU setting, and implement standard delirium prevention protocols (e.g., Hospital Elder Life Program¹³¹ on the ward or ABCDE in the ICU) to prevent the onset of this serious form of acute brain injury.

Research agenda

- Further description of emergency department epidemiology is warranted, especially investigating the incidence of delirium in this setting, and the implications of incident delirium on patient outcomes.
- An agreed upon definition of emergence versus postoperative delirium is required, and large cohort studies utilizing validated delirium assessment tools are necessary to further identify risk factors and outcomes associated with delirium in the perioperative setting.
- Investigators must continue to test medical and environmental strategies toward preventing or reducing ICU delirium, and describe effective implementation strategies for proven treatments.

Fig. 1.

Adapted from Vasilevskis et al.¹²⁴ the ABCDE is an ICU-acquired delirium and weakness mitigation strategy for the critically ill patient. This strategy is a protocolized bundle performed daily on mechanically ventilated and/or sedated patients in the ICU. ABCDE = Awakening and Breathing Coordination, Choice of sedation, Delirium monitoring and management, and Early mobility/exercise. Adapted from: Vasilevskis EE et al. ICU-acquired delirium and weakness – Crossing the quality chasm. Reproduced with permission from the American College of Chest Physicians. *Chest*. 2010; 138(5): 1224–1233.

Fig. 2.

The interrelationship between patient vulnerability and precipitating factors in the development of delirium.¹⁶ Low-level vulnerability requires high-level noxious stimuli to develop delirium (black arrow). High-level vulnerability requires low-level noxious stimuli to develop delirium (gray arrow).