Chapter

Delirium Management, Treatment and Prevention Solid Organ Transplantation

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Abstract

Delirium following solid organ transplant is a very common complication. Post-operative delirium has been shown to be associated with longer length of stays, increased post-operative complications, increased readmission rates, higher costs, and increased mortality. Therefore, every healthcare provider who is involved in the care of transplant recipients should be well educated in the importance of early diagnosis of delirium, treatment of potential contributing factors, and optimizing management. Routine delirium screening to allow prompt diagnosis and workup is paramount to the care of post-operative transplant patients. Identifying high risk individuals for pre-operative rehabilitation to help decrease post-operative delirium rates, as well as focusing on functional and cognitive recovery following delirium are important preventative and rehabilitation efforts to optimize outcomes for transplant patients. This chapter will highlight a proactive approach to delirium prevention and management in the transplant population.

Keywords: delirium, outcomes, complications, altered mental status, solid organ transplant, cognitive impairment

1. Introduction

Delirium following transplantation is a wide reaching problem that has a significant effect on recovery time, functional outcomes, and has a profound economic impact on the healthcare system. Delirium is now being recognized as a major driver of poor health care related outcomes. Post-operative delirium has been shown to be associated with longer length of stays, increased post-operative complications, increased readmission rates, higher costs, longer periods of mechanical ventilation, prolonged cognitive impairment and increased mortality [1, 2]. With this in mind, early diagnosis of delirium, treatment of potential contributing factors, and optimized management is paramount to improve post-transplant outcomes. This chapter will highlight a proactive approach to delirium management and prevention in the abdominal transplant population.

1.1 Definition

Delirium is defined as a condition highlighted by an acute disturbance in attention, awareness and cognition that is not explained by a preexisting neurocognitive

disorder. Delirium is characterized by reduced capacity to direct, focus, sustain, or shift attention, as well as reduced orientation to the environment [1, 3]. These symptoms must present acutely and fluctuate throughout the day. Importantly, the diagnosis of delirium identifies the constellation of symptoms representing altered brain function, but does not identify the etiology (**Figure 1**).

Delirium can be classified into three subtypes based on psychomotor behavior: hyperactive, hypoactive and mixed type delirium. Delirium is under diagnosed due to inconsistent screening, but also because delirium has varying and inconsistent presentations especially in patients suffering from hypoactive delirium. Hypoactive delirium is characterized by slowed mentation, lethargy, and decreased movement, whereas hyperactive delirium is marked by agitated behavior, confusion and difficulty with re-orientation. Without consistent, evidence-based screening methods, hypoactive delirium is more likely to be overlooked compared to hyperactive delirium. In addition, the different forms of delirium carry different prognosis. In a study of patients admitted to the intensive care unit after elective operations, patients that suffered from hypoactive delirium had an increased six-month mortality compared to patients with other subtypes of delirium (32 vs. 8.7%, P = 0.04) [4]. Therefore, it is important understand the various forms of delirium and the clinical scenarios in which it can present to allow timely diagnosis and management.

1.2 Prevalence

The prevalence of delirium is highly variable based on the population being evaluated. It has been reported to occur in 16–89% of hospitalized patients, and up to 50% of post-operative patients [5, 6]. Delirium is the most common manifestation of acute brain dysfunction during critical illness. Reports note that delirium affects 50–75% of patients who receive medical ventilation in the intensive care unit [5]. The prevalence in the transplant population has been reported to range from 12 to 47% of patients [7]. Patients undergoing liver transplant have a higher prevalence of developing delirium than other abdominal transplant recipients occurring in

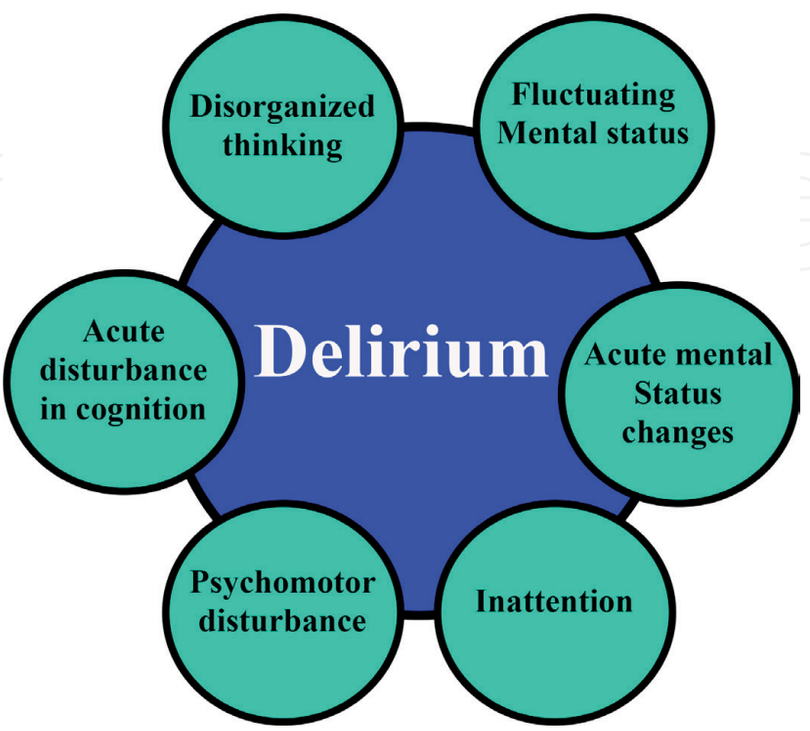

Figure 1.
Clinical symptomatology associated with delirium.

approximately 45% of the liver recipients [8]. In a recent report by Haugen et al. only 0.8% of kidneys transplant recipients developed delirium [9]. The difference in prevalence of delirium in abdominal transplant recipients needs to be considered when developing preventive strategies to provide targeted interventions on high-risk populations.

1.3 Pathophysiology

The pathophysiology associated with delirium development is multifactorial and is associated with complex interactions between systemic and cerebral physiology. The precise mechanisms are still being investigated, however many hypotheses exist for the underlying precipitating factor(s) that lead to delirium development. Examples of different hypotheses include inflammatory-mediated neuronal injury, altered cerebral perfusion, increased permeability of the blood brain barrier from endothelial dysfunction, and altered neurotransmitter balance [10]. In addition, the anatomic changes associated with advanced age including cerebral atrophy and changes in white matter density have been considered to contribute to the underlying mechanism of delirium, and also represent risk factors for delirium development [11].

Delirium pathophysiology is also believed to be associated with the systemic inflammatory cascade that occurs as a result of the stress response following an acute event, trauma or surgical intervention. The release of inflammatory mediators and cytokines (cortisol, c-reactive protein, interleukin-6, interleukin-8, etc.) following surgery likely play a significant role in the pathophysiologic link between surgery and delirium development [10]. Microglial cells have an intimate involvement in mediating the cerebral inflammatory response that occurs as a result of the systemic inflammatory response following surgery. The microglial cells up regulate the production of pro-inflammatory cytokines, which lead to disturbances in cognitive function and alterations in cerebral activity. In addition, over-activation of microglial cells can lead to neuronal apoptosis [10]. Thus, understanding the cellular and molecular pathways associated with microglial physiology may provide opportunities for intervention and targeted therapy for delirium treatment.

Endothelial cells serve as integral components of a competent blood brain barrier; however, in the setting of stress, surgery, inflammation, etc., endothelial function is altered leading to a reduction in the integrity of the highly selective blood brain barrier. This increases the risk of cerebral dysfunction and delirium development. Hughes et al. assessed biomarkers associated with the integrity of the blood brain barrier and endothelial dysfunction, and found that elevations in S1008, E-selectin and plasminogen activator-1 were associated with delirium in critical illness [12]. Endothelial dysfunction also up-regulates the coagulation pathways leading to microvascular thrombi formation, which consequently alters cerebral blood flow further leading to cerebral dysfunction.

Delirium is also linked to neurotransmitter dysfunction and deregulation. Acetylcholine is an important modulator of the systemic inflammatory response by decreasing the number of inflammatory cytokines. Critical illness and surgical stress create a physiologic environment that leads to depletion of acetylcholine stores and availability. A lack of acetylcholine receptor activation on the surface of microglial cells causes a lack of inhibition and leads to hyperactivation of microglial cells [10]. The acetylcholine association with delirium explains the pathophysiology involved with the increased risk of delirium in patients receiving anti-cholinergic medications. These medications exacerbate the depleted stores of acetylcholine that is associated with stress and post-surgical states. Hence, an important component of post-operative delirium prevention is to avoid the use of anti-cholinergic medications.

Additional neurotransmitter imbalances associated with the development of delirium include dopamine, serotonin, and norepinephrine [1, 10]. Elevated levels of dopamine and norepinephrine are associated with hyperactive delirium [13]. Increased norepinephrine levels contribute to agitation, impaired attention and cerebral dysfunction. Increased serotonin levels are also linked to cerebral dysfunction and increased risk of delirium. Gamma-aminobutyric acid (GABA) is the primary neurotransmitter associated with inhibitory pathways in the brain. Dysregulation of GABA is associated with delirium. The administration of drugs that are mechanistically involved in activation or inhibition of the GABA receptor or altering levels of other important neurotransmitters are associated with delirium, and efforts should be made to minimize patient exposure to these medications, such as benzodiazepines [13].

Overall, the pathophysiology linked to delirium is complex and incompletely understood. Importantly, delirium is the clinical manifestation that results from the interaction of multiple different dysfunctional systemic and cerebral physiologic pathways. As the understanding of the pathophysiology that leads to delirium improves, targeted pharmacologic agents can be developed and tested in clinical scenarios.

2. Diagnosis

2.1 Risk factors

Delirium is a very common complication following transplantation. It is important to have an appreciation for the risk factors linked to delirium development in order to optimize preventive measures and allow for early diagnosis. Advancing age and baseline cognitive impairment are the most commonly described risk factors for developing delirium [14, 15]. Certain medical conditions can also predispose patients to delirium. Sleep apnea, heart failure, diabetes and frailty have been shown to increase the risk of developing delirium [16]. Patients with lower cognitive and functional reserve likely have a reduced ability to maintain normal brain function in the setting of an acute stress event, such as surgery, sepsis or trauma. It is important to identify these risk factors that are present pre-operatively to help reduce the prevalence of delirium after transplant.

If cognitive dysfunction can predispose patients to delirium, an important question to answer when discussing delirium in transplant recipients is if surgery and/or anesthesia is an independent risk factor for post-operative cognitive defects (i.e. an unmodifiable risk factor for transplant recipients). A multicenter, prospective cohort study involving patients with surgical and nonsurgical critical illness was performed to evaluate if surgery and anesthesia was a risk factor for delirium. This study reported that surgery/anesthesia was not a risk factor for impairment of long-term global cognitive function or executive function after major non-cardiac surgery. In addition, increasing the level of exposure as measured by number of surgeries and duration of anesthesia was not associated with worse global cognitive or executive function. Cognitive impairment was highly prevalent at 3 and 12 months after hospital discharge in patients who suffered delirium. However, delirious patients who were exposed to general anesthesia and surgery suffered cognitive impairment at rates similar to those who did not undergo a surgical procedure. Post-operative cognitive impairment was associated with pre-existing cognitive deficits and level of education [3]. Based on these data, surgery and anesthesia does not appear to be an independent risk factor for delirium development and emphasizes the need for patient- and disease-focused risk stratification as transplant patients have many disease-specific risk factors that increase the incidence of delirium.

Risk factors for delirium in patients undergoing liver transplantation include a history of alcohol abuse, pre-operative hepatic encephalopathy, pre-operative renal replacement therapy, intra-operative red blood cell transfusion volume and increasing Acute Physiologic and Chronic Health Evaluation II (APACHE II) scores upon intensive care unit admission. A study by Wang et al. showed that risk factors associated with delirium in liver transplant patients in the intensive care unit included history of alcohol abuse (Odds ratio: 6.40), preoperative hepatic encephalopathy (Odds ratio: 4.45), APACHE II score > 16 (Odds ratio: 1.73), and duration of endotracheal intubation for >5 days (Odds ratio: 1.81) [17]. Lescot et al. performed an observational study of liver transplant patients admitted to the intensive care unit after deceased donor transplant. Neither age nor etiology of cirrhosis was significantly associated with delirium [18]. Furthermore, delirium was not significantly associated with Model for End Stage Liver Disease score or Child-Pugh score. The median number of intraoperative transfused packed red blood cell units in patients with delirium was more than double that of in patients without delirium ($P = 0.001$). The risk of developing delirium was greater in patients with pre-transplant encephalopathy ($P = 0.02$) and in patients who underwent renal replacement therapy during the pretransplantation period ($P < 0.01$). In the logistic regression model, number of red blood cell transfusions, renal replacement therapy, and elevated APACHE scores were associated with increased risk of delirium. Interestingly, if a patient required renal replacement therapy, they had 13-fold greater odds of becoming delirious [18].

Haugen et al. evaluated 893 kidney transplant recipients and examined risk factors for developing postoperative delirium [9]. Risk factors in patients with end stage renal disease undergoing kidney transplantation include age greater than 65 (Odds ratio: 2.65, $P = 0.004$), frail patients (Odds ratio: 2.05, $P = 0.04$), and increasing comorbidities (two or more on the Charlson Comorbidity Index) (Odds ratio: 1.93 $P = 0.05$). In regards to delirium in pancreas transplant recipients, there are currently no organ specific factors detailed in the literature; however, the known risk factors for delirium associated with patients undergoing kidney transplantation can be theoretically applied to pancreas transplant recipients as these patients share similar demographics and disease processes.

Post-operative factors that contribute to delirium include inadequate pain control, need for mechanical ventilation, sedation levels, benzodiazepine use, poor sleep hygiene, electrolyte disturbances, and infections. Medication used to treat common post-operative symptoms such as nausea including prochlorperazine or phenergan are associated with delirium. Benzodiazepines are also strongly associated with a higher risk of delirium and should only be used in very select circumstances at reduced doses in young patients with chronic home benzodiazepine use. Opioids increase delirium risk and should be used in moderation. Pain control should focus on multimodal treatment protocols with opioid sparing when applicable. Medications that alter the cholinergic neurotransmitter pathway, such as diphenhydramine, promethazine, tricyclic antidepressants or prochlorperazine are strongly associated with delirium development and should be avoided. In addition, immunosuppressive medications, such as calcineurin inhibitors and steroids, can be associated with mental status changes [19]. In transplant recipients at high risk for developing delirium or patients who have developed delirium, an important step in managing and optimizing these patients is to review the medication list to limit and discontinue any deliriogenic medication.

2.2 Screening

Early diagnosis of post-operative delirium is paramount for prompt management and minimization of risk for improved speed of recovery. There are several

validated screening tools for assessing for the presence of delirium. The gold standard for diagnosis of delirium is a formal evaluation performed by a psychiatrist using The Diagnostic and Statistical Manual of Mental Disorders criteria; however, the application and feasibility of a formal psychiatric evaluation is not clinically practical [1]. More commonly used methods of delirium screening utilize nursing expertise for frequent and consistent bedside screening. The Richmond Agitation Sedation Scale (RASS) is a widely used screening tool to evaluate and communicate patients' level of sedation and arousal [20]. With an appropriate level of consciousness, there are many validated tools for delirium screening. Importantly, a patient must be arousable to voice (i.e. RASS score of −1) to be able to screen for delirium. The most commonly used tool for screening is the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) [21]. The CAM-ICU (**Figure 2**) is an abbreviated version of the Confusion Assessment Method. The CAM-ICU tool screens for acute changes in mental status, inattention, disorganized thinking and altered level of consciousness in a condensed approach ideal for a fast paced clinical setting. The CAM-intensive care unit screening tool requires less than 2 min to complete and in addition to being rapidly applied, has been shown to be 93% sensitive and 98% specific for diagnosing delirium [21].

Other screening tools include the Nursing Delirium Symptom Checklist (NuDESC) [22], Confusion Assessment method (CAM) [23] and the Intensive Care Delirium Screening Checklist (ICDSC) [24]. The multiple, validated tools available speaks to the importance for using a tool of any type to achieve consistent screening. More important than which tool to use is having a program in place for regular, routine, and consistent screening. If delirium is not screened for using a validated screening tool, delirium may be missed up to 75% of the time [25–28], especially in the setting of hypoactive delirium. Given the fluctuating course of critically

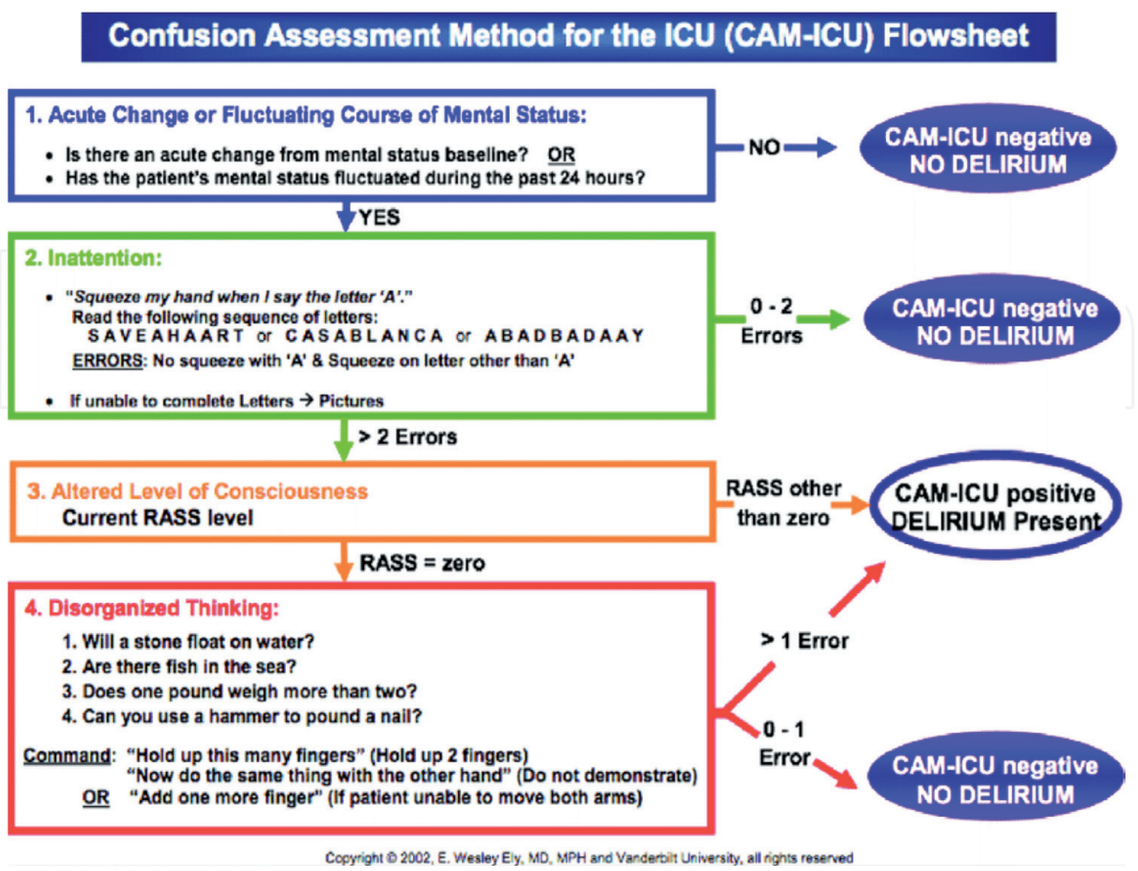

Figure 2.
Delirium screening tool and flowchart outlining the confusion assessment method for the intensive care unit [2].

ill patients and delirium, it is important that screening be performed in a serial, repeatable and consistent manner to achieve timely diagnosis and prevent under diagnosis. Routine implementation of validated screening tools allows for rapid and dependable evaluation and subsequent work up to identify potential underlying etiologies and ultimately directed delirium management.

2.3 Delirium work up

Following a positive screening evaluation for delirium, working through a differential diagnosis to identify treatable underlying causes is essential. In the transplant population in the setting of immunosuppression, infection is an extremely important diagnosis to consider and rule out in a timely manner. Immunosuppressed patients do not have a robust systemic inflammatory response as compared to non-immunosuppressed, post-operative patients, so infections present in a more discreet and subtle manner, often with mental status changes as the only clinical symptomatology. In a patient with new onset delirium, initial work up should include a comprehensive laboratory evaluation including a complete blood count, comprehensive metabolic panel, liver function tests, lipase and amylase. In the post-transplant recipient where renal dysfunction and electrolyte fluctuations are common, a basic metabolic panel should also be obtained to ensure that uremia or an underlying electrolyte disturbance is not present. Hormone dysregulation should also be considered as a cause of delirium with laboratory evaluation of thyroid function and the pituitary–adrenal axis. The patient's medication list should also be reviewed to ensure that medication toxicity is not contributing or exacerbating the mental status changes. However, in the immunosuppressed, post-operative transplant recipient with clinical decompensation highlighted by new onset mental status changes, sepsis needs to be at the top of the differential diagnosis.

Mental status changes are often the initial presenting symptom of an underlying infection or sepsis in the transplant population. Blood cultures, urine cultures, and a chest x-ray should be obtained to rule out bacteremia, urinary tract infection or pneumonia, respectively. In addition, based on the operative details and time since surgery, cross sectional axial imaging should be considered to rule out a deep space infection or other possible surgical complications. Importantly, early initiation of broad-spectrum antibiotics is strongly recommended if there is any concern that an underlying infection is contributing to the mental status changes.

If surgical drains are present, evaluating the character of the abdominal fluid is important to rule out intra-abdominal pathology. Organ specific evaluation of surgical drains is an important step in evaluating for potential infectious sources. In the setting of liver transplant, drains should be evaluated for elevated bilirubin to rule out a biloma and anastomotic biliary complication. In pancreas recipients, drain amylase and bilirubin should be obtained to evaluate for a pancreatic parenchyma leak and/or an enteric anastomotic leak. If clinically applicable in kidney transplant recipients, drain fluid should be checked for creatinine to evaluate for a possible urine leak. Drain fluid studies should be correlated with high resolution, axial imaging to further define the anatomic location of potential fluid collections to determine if percutaneous drainage or open drainage is needed.

Furthermore, the work up should include placing the patient on a pulse oximeter to obtain an oxygen saturation and obtain an arterial blood gas to ensure that hypoxia or hypercarbia is not causing or contributing to the mental status changes.

Myocardial infarctions and cerebral vascular events can also present with delirium. An electrocardiography, troponins and a possible echocardiography should be obtained if there is a concern for a cardiac event. If there is clinical suspicion for a stroke based on neurologic exam, a non-contrast and subsequently

contrasted cerebral, cross sectional imaging should be obtained. In addition, an electroencephalography should be performed if there is clinical concern for seizure activity or postictal metal status changes.

Mental status changes in the transplant recipient can be caused by multiple contributing factors, and a systematic and thoughtful work up is paramount for rapid initiation of treatment. However, the work up for delirium is often negative for any treatable, underlying medical condition. Once all potential medical conditions that can contribute to delirium are evaluated and eliminated as the diagnosis, the focus should shift to optimizing the environment for delirium resolution and cognitive recovery.

3. Prevention

3.1 Pre-operative prevention

Surgery can result in accelerated cognitive and functional decline, and this cognitive impairment after surgery has been associated with increased mortality and disability with deficits in activities of daily living occurring in up to 50% of patients even 12 months after major surgery [29–34]. Patients with a higher physical and cognitive reserve have a protective effect on reducing the risk of developing delirium [35, 36]. Therapeutic approaches for improving cognitive reserve may present opportunities for reducing cognitive impairment after acute stressors, particularly in situations with time available for prehabilitation. An area that is understudied in the transplant population is whether building patients' mental and physical reserve through a prescribed program of cognitive and physical exercise, as well as nutritional optimization can improve long term outcomes. Prehabilitation efforts before surgery thus far have focused on preemptive physical therapy to improve post-surgical functional outcomes. Multiple studies have demonstrated that physical training prior to surgery to build physical reserve can improve functional outcomes after major surgery [37–39]. No work, however, has been done to attenuate the cognitive decline by "exercising the brain" before the physiologic insult that is commonly seen in chronic disease and surgical intervention such as transplantation.

By targeting high-risk individuals, such as those who are frail, encephalopathic, uremic, have a history of alcohol abuse, are of advanced age, and have higher Model for End Stage Liver Disease scores, cognitive reserve could be improved. There are interventions focused on cognitive remediation/rehabilitation that are being studied, which potentially hold promise for improving long-term brain functioning in transplant recipients. Among them, Cognitive Retraining is a novel therapeutic approach. Conceptually, Cognitive Retraining applies well-understood techniques derived from brain plasticity research [40]. The learning theory facilitates improvement in information processing, attention control, aspects of memory, and executive functioning. Research has been performed evaluating the effectiveness of computer-based cognitive remediation on various aspects of neuropsychological functioning including memory, attention, processing speed, and others [41–43]. Based on prior experience with a wide variety of patient populations, there is a high likelihood of fostering improvement in patient outcomes in transplant recipients if applied to high risk individuals at risk for cognitive impairment and delirium during their postoperative recovery.

3.2 Intra-operative management

It is extremely important for anesthesia providers to practice delirium preventive strategies. There are operative factors that need to be considered that are associated

with increased delirium, which include the use of anticholinergic medications, electrolyte disturbances (specifically sodium fluctuations), and the amount of red blood cell transfusions. Efforts to decrease the prevalence of postoperative delirium should focus on limiting patient exposure to deliriogenic medications intra-operatively. The choice of anesthetic does not increase the risk of delirium as there is no conclusive evidence that propofol versus an inhaled based anesthetic changes the incidence of post-operative delirium [44, 45]. However, the level/depth of sedation provided during the operation is associated with delirium development, and therefore instruments such as intra-operative electroencephalography or brain activity monitors have been suggested to mitigate excessive levels of anesthesia helping with delirium prevention post-operatively. [46]. Close attention to electrolyte concentrations and fluctuations intraoperatively is also important. This is especially critical in patients with chronic hyponatremia, and in operations that involve large volume crystalloid resuscitation or excessive blood loss with associated blood product administration. Detailed pre-operative planning to minimize large fluctuations and optimize electrolyte disturbances should be performed with the surgical and anesthesia teams in high-risk individuals. Intra-operative management is an important part of the continuum of care for the transplant patient in delirium prevention.

3.3 Post-operative prevention

3.3.1 Pharmacologic prophylaxis

Studies evaluating whether pharmacologic prophylaxis reduced the incidence of delirium have shown mixed results. A large double blind, placebo controlled trial studied prophylactic dexmedetomidine infusion upon arrival to the intensive care unit. The intervention group demonstrated a significant reduction in the incidence of delirium in non-cardiac post-operative elderly patients compared to the control group [47]. Treatment with dexmedetomidine in elderly patients admitted to the intensive care unit after non-cardiac surgery reduced the incidence of delirium from 23 to 9%. Dexmedetomidine also reduced the amount of sedative drugs including narcotics administered. The authors suggested that the delirium reduction seen in the trial could be contributed to a possible neuroprotective effect of dexmedetomidine and/or a reduction in sedation medications. Wide spread clinical use of dexmedetomidine is limited by the fact that it must be used in in an intensive care setting being administered intravenously, as well as the possible cardiopulmonary side effect profile causing respiratory depression, hypotension and bradycardia. However, these results are encouraging for the use of dexmedetomidine in the prophylactic setting in patients at high risk for delirium.

There are no data on the use dexmedetomidine use in patients admitted to the intensive care unit following abdominal transplant, but this approach could be applicable to liver transplant patients who remain intubated at the time of intensive care unit admission to be used as sedation instead of fentanyl or propofol. Further work will need to be done to delineate a clinical benefit for routine use of dexmedetomidine in postoperative transplant patients.

A recent randomized controlled trial-The Haloperidol Effectiveness in ICU Delirium (HOPE-ICU) study-showed no difference in days alive and free of delirium between patients prophylactically treated with intravenous haloperidol (2.5 mg every 8 hours) or placebo [48]. At this time, the data are not conclusive to make a formal recommendation for routine pharmacologic prophylaxis for delirium prevention.

3.3.2 Non-pharmacologic prevention

Implementing non-pharmacologic based prevention bundles for delirium reduction have resulted in improved rates of delirium. The clinical care bundles focus on reducing exposure to and mitigating delirium risk factors such as appropriate pain management, timely Foley catheter removal, re-orientation strategies, and reducing hearing and vision deficits. Implementation of these protocols has reduced delirium rates and total days of delirium in multiple studies [49–51]. There is a growing emphasis on a multimodal approach to pain control to reduce exposure to deliriogenic narcotic pain medication. Multimodal pain control emphasizes opioid reduction with the use of a combination of acetaminophen, non-steroidal anti-inflammatory medications, ketamine, gabapentin and/or regional anesthetic techniques where appropriate. A multi-disciplinary approach with anesthesia, pain specialists and the surgical team should be implemented to optimize post-operative pain control with narcotic avoidance/reduction protocols.

Combining evidence-based interventions that reduce delirium rates have been shown to be effective and the combination of different strategies can have additive beneficial effects on delirium prevention. The Awakening and Breathing Coordination, Delirium Monitoring/Management, and Early Mobility (ABCDE) bundle is the most described bundle in the literature (**Figure 3**). Initially published in 2011 [52], this bundle has proven to be an effective strategy in delirium prevention. The ABCDE bundle is comprised of a number of interventions shown to improve outcomes in several well-designed clinical trials. The ABCDE bundle is an evidence-based, multicomponent management strategy aimed at reducing sedation exposure, duration of mechanical ventilation and hospital-acquired delirium and weakness. In comparison to standard practice including spontaneous breathing trials and spontaneous awakening trials (but no consistent delirium screening), the ABCDE bundle group experienced less delirium (48.7 vs. 62.3%, P = 0.02) and a lower percent of intensive care unit days spent delirious (33 vs. 50%, P = 0.002) [53]. The "AB" component of the bundle focuses on expedited mechanical ventilation liberation, and has been shown to decrease duration of medical ventilation, duration of coma and mortality [54, 55]. The "C" of the bundle is focused on avoiding over sedation and use of benzodiazepines, which has been shown in clinical trials to decrease delirium and duration of mechanical ventilation [56–58]. The "D" of the bundle refers to regular delirium screening and monitoring. The "E" of the bundle highlights the need for early mobility, which has been shown to decrease duration of delirium, intensive care unit length of stay and mortality [59]. A recent prospective, cohort study evaluated the effects of the ABCDE bundle on delirium rates. After the bundle was implemented, the prevalence of delirium decreased significantly from 38 to 23% (P = 0.01). The number of days with delirium was also reduced from 3.8 to 1.72 days (P = <0.001) [60]. These data support a focused, clinical care bundle approach to delirium prevention and prospective implementation in postoperative solid organ transplant recipients.

4. Treatment and management

4.1 Management

Most of the data exploring practice recommendations for delirium management is rooted in the critical care literature. Over the past two decades, significant shifts in practice paradigms have helped reduce the incidence of delirium in the intensive care unit. The major advancements in delirium management and prevention include

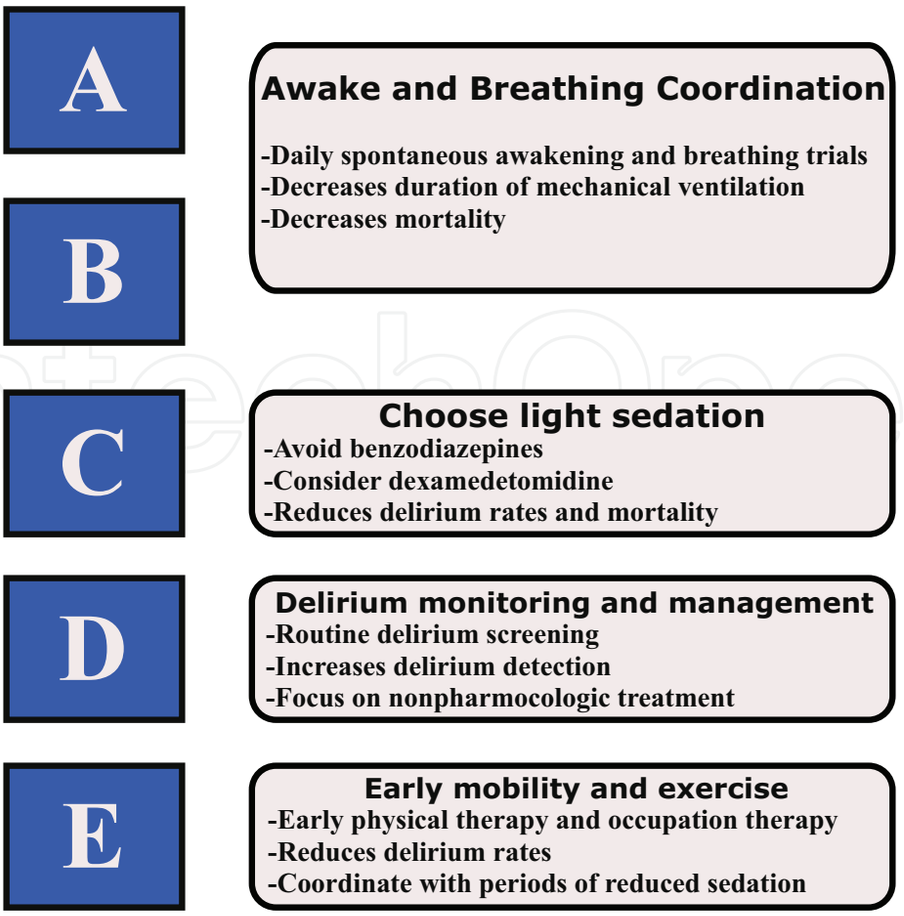

Figure 3.
Overview of the ABCDE delirium prevention bundle.

the level of sedation delivered while receiving mechanical ventilation. Daily awakening trials where sedation is interrupted to evaluate the ability to liberate from mechanical ventilation coupled with spontaneous breathing trials has been shown in randomized controlled studies to reduce mechanical ventilation days as well as delirium incidence [54, 61].

In addition, the choice of medication for sedation has shifted from benzodiazepines to propofol or dexmedetomidine infusions. This management shift was based on randomized controlled studies evaluating delirium outcomes and rates in patients receiving dexmedetomidine versus lorazepam infusions for sedation. Longer duration of lorazepam exposure was significantly associated with increased rates of delirium [57]. This study of 106 critically ill patients found that the patients receiving dexmedetomidine had more delirium free days compared to the lorazepam group (7 vs. 3, P = 0.01). Not only does duration of benzodiazepine exposure increase the incidence of delirium, it has been shown that delirium risk increases with amount of lorazepam administered [62].

An unintended consequence of routine intensive care unit care is sleep disruption and interference with sleep quality. Fragmented sleep has been associated with delirium. A focus on promoting and maintaining adequate sleep hygiene is an important delirium preventive measure. Efforts to minimize overnight disruptions and promote normal circadian rhythms have been associated with lower odds of developing delirium. Non-pharmacologic measures should be implemented to aid in sleep quality improvement and maintenance of sleep hygiene such as exposure to natural light, activity/mobility during the day, reduction of nighttime noise, removal of nocturnal stimulation, and reductions in night time nursing disruptions. A quality improvement project aimed at improving sleep by minimizing sleep

disruptions and promoting normal circadian rhythms using non-pharmacological sleep aids has been shown to decrease the incidence of delirium and improve daily delirium free status [63].

Early mobilization is also an important strategy for delirium prevention. A trial of early mobilization that randomized hemodynamically stable patients to daily sedation interruptions timed with physical and occupation therapy versus usual care without early mobilization therapy achieved a two-day reduction in delirium duration in the treatment arm (days with delirium: 2 vs. 4 days, P = 0.03) [59]. In addition, early mobilization in this study reduced the time in the intensive care unit with delirium (33% of patients in the intervention group were diagnosed with delirium vs. 57% of patients in the control group were diagnosed with delirium, P = 0.02), as well as time in the hospital with delirium (28% of patients in the intervention group were diagnosed with delirium vs. 41% of patients in the control group were diagnosed with delirium, P = 0.01). Therapy included passive range of motion, active range of motion, and activities of daily living training depending on the patients' level of sedation and ability. In another recent randomized controlled trial of surgical critically ill patients, early goal-directed mobilization reduced the incidence of delirium and increased the number of delirium free days in the intensive care unit when compared to usual care [64].

4.2 Pharmacologic treatment

Currently, there are no evidence-based guidelines regarding specific pharmacological agents for delirium treatment. The current first line agents used in the treatment of hyperactive delirium are antipsychotic medications including haloperidol, olanzapine and quetiapine. Of note, neither antipsychotics nor dexmedetomidine have FDA approval for the treatment of delirium. In an international survey of 1521 intensivists, 65% reported that they treat delirium in the intensive care unit with haloperidol and 53% reported that they treat delirium with atypical antipsychotic medications [65], but there is no evidence-based literature showing efficacy of these medications for delirium treatment and symptom resolution. Despite current practice patterns, there are few data to support their definitive use in treating delirium.

A recent study evaluating the treatment of delirium with haloperidol (2.5–5 mg every 8 h) versus olanzapine (5 mg daily) showed no difference in length of delirium in 73 critically ill patients [66]. Furthermore, in a randomized, double blind, placebo-controlled trial, patients with acute respiratory failure or shock and hypoactive or hyperactive delirium were assigned to receive intravenous boluses of haloperidol (maximum dose, 20 mg daily), ziprasidone (maximum dose, 40 mg daily), or placebo [67]. The primary end point was the number of days alive without delirium or coma during the 14-day intervention period. The use of haloperidol or ziprasidone, as compared with placebo, in patients with acute respiratory failure or shock and hypoactive or hyperactive delirium in the intensive care unit did not significantly alter the duration of delirium. This randomized, placebo-controlled trial of intravenous antipsychotic medications for the treatment of delirium in critically ill patients showed that pharmacologic treatment was no different than placebo [67].

Dexmedetomidine in delirium management has gained popularity over the past several years. A recent trial studied dexmedetomidine in mechanically ventilated patients who were unable to be weaned from mechanical ventilation due to hyperactive delirium. This study, Dexmedetomidine to Lessen ICU Agitation trial, randomized patients to receive 7 days of intravenous dexmedetomidine (up to 1.5 μg/kg/h) or placebo. Patients treated with dexmedetomidine had fewer days requiring ventilator

support and had faster resolution of delirium symptoms (23 vs. 40 h, P = 0.01) [68]. Dexmedetomidine must be administered as an infusion, which means the drug can only be given to patients having critical care needs. Alternative oral alpha-2 agonists exist, including clonidine or guanfacine, which could facilitate therapy in non- intensive care unit settings or during transition of care. However, these agents have not been rigorously studied in regards to delirium treatment and prevention as options for oral transition or alternatives to dexmedetomidine.

As strong evidence supporting the use of single pharmacological agents in delirium is lacking, preventive strategies and non-pharmacologic treatment bundles, such as the ABCDE bundle as discussed above, should be incorporated into delirium prevention and management algorithms.

4.3 Cognitive therapy following delirium

Cognitive and physical dysfunction is a common sequela for patients following a prolonged course of delirium. Recently, efforts have been made to minimize the long-term effects of delirium through exercises focused on orientation, memory, attention, and problem solving. A recent study implemented a graded cognitive therapy protocol with varying degrees of intensity guided by the patient's RASS assessment immediately preceding the session [69]. Examples of the cognitive therapy performed in this study included matrix puzzles, noun list recall, paragraph recall, letter-number sequence, and pattern recognition. The authors showed that following discharge from the intensive care unit, combined cognitive and physical therapy was associated with improved executive functioning at the time of hospital discharge [69]. These data suggest that once a patient is able to participate in therapy following delirium recovery, efforts should be made to incorporate cognitive rehabilitation as an integral part of the recovery process to maximize functional outcomes.

Extending beyond inpatient rehabilitation, research has been conducted into performing cognitive rehabilitation following hospital discharge in patients who suffered from delirium [70]. In this study the rehabilitation program was provided over a 12-week period after discharge in each patient's home and integrated both traditional "face-to-face" interventions as well as telephone and video-based interventions for cognitive, physical and functional rehabilitation. The cognitive training was based on the goal-management training (GMT) protocol, a focused and theoretically derived stepwise approach to the rehabilitation of executive function. The GMT sessions build on one another to increase the "dose" of rehabilitation delivered. These cognitive sessions resulted in improved scoring on tests evaluating executive functioning [70].

Based on studies in non-transplant populations, it would appear that transplant patients could similarly benefit from both inpatient and outpatient cognitive rehabilitation following delirium recovery in order to optimize long-term outcomes and maximize quality of life following transplantation.

As patients are recovering from delirium and transitioning to cognitive rehabilitation, it is important to focus on the completion of the treatment for any underlying condition, like sepsis, that lead to or contributed to delirium development to ensure optimal functional recovery.

5. Outcomes

Delirium in the postoperative setting significantly impacts outcomes. Delirium is a predictor of mortality in hospitalized patients [61], and mortality increases

with the duration of delirium [71]. The relative hazard of death is nearly four times greater if a patient has delirium for 3 days versus no delirium. Beyond mortality, delirium also impacts quality of life following recovery. Delirium has been shown to negatively impact long-term cognitive function [72]. A recent multicenter, prospective, cohort study of critically ill patients was evaluated to estimate the prevalence of long-term cognitive impairment after critical illness [2]. The study enrolled adults with respiratory failure or shock in the medical or surgical intensive care unit, evaluated them for in-hospital delirium, and assessed global cognitive and executive function 3 and 12 months after discharge with the use of the Repeatable Battery for the Assessment of Neuropsychological Status. The study showed that one out of four patients had cognitive impairment 12 months after critical illness that was similar in severity to that of patients with mild Alzheimer's disease. At 3 months, 40% of the patients had global cognition scores that were 1.5 standard deviations below the population means (similar to scores for patients with moderate traumatic brain injury), and 26% had scores 2 standard deviations below the population means (similar to scores for patients with mild Alzheimer's disease). Interestingly, the degree of cognitive impairment affected older and younger patients equally. A longer duration of delirium was independently associated with worse global cognition at 3 and 12 months ($P = 0.001$ and $P = 0.04$, respectively) and worse executive function at 3 and 12 months [2]. These data strongly support efforts to initiate cognitive rehabilitation programs for patients who suffer from delirium during the postoperative period to enhance functional outcomes.

In regards to transplant specific outcomes in patients who suffer from delirium, Lescot et al. examined postoperative outcomes for patients with and without delirium following liver transplant [18]. Patients who suffered from delirium after liver transplant had higher rates of sepsis during the intensive care unit stay (18 vs. 1.2%, $P \leq 0.001$), longer days requiring mechanical ventilation (2 vs. 1, $P \leq 0.001$), longer intensive care unit length of stay (9 vs. 4 days, $P \leq 0.001$), and longer hospital length of stay (37 vs. 20 days, $P \leq 0.001$). In addition, patients who developed delirium had increased mortality compared to those patients who did not suffer from delirium, both in the short-term as well as at 1 year following transplant (intensive care unit mortality: 10.7 vs. 2%, $P = 0.04$; in-hospital mortality: 25 vs. 6%; 1 year mortality: 32 vs. 12%, $P = 0.007$) [18]. A recent prospective cohort study to evaluate postoperative delirium after liver transplantation showed that 45% of recipients experience delirium with a median duration of 5 days [8]. Furthermore, postoperative delirium was associated with a four-fold increase in intensive care unit length of stay, a more than two-fold increase in hospital length of stay, and decreased survival probability at 1 year. The authors suggest that postoperative delirium should be considered a preventable clinical complication, and not just a predictive risk factor for worse outcomes in the liver transplant population [8]. Postoperative complications likely contribute to both increased rates of delirium and mortality, however, it is clear that delirium is associated with worse outcomes.

Haugen et al. recently evaluated 125,304 adult kidney transplant recipients between 1999 and 2015 as reported to the Organ Procurement and Transplantation Network and linked to Medicare claims by the US Renal Data System [9]. International Classification of Diseases 9 codes for delirium were identified from inpatient claims throughout the entire set of initial kidney transplant hospitalizations. Haugen and colleagues showed that delirium in kidney transplant recipients significantly associates with patient survival, with an approximately 40% mortality at 5 years for patients who developed delirium post transplant compared to 10% mortality for patients who did not suffer from delirium [9].

6. Summary

Delirium is a common clinical diagnosis in the solid organ transplant population. Delirium is under diagnosed, yet the recent appreciation of its impact on cognitive recovery indicates it is vital make efforts to mitigate its development and recognize it in a timely fashion to optimize transplant outcomes. Delirium has been shown to be associated with a longer length of stay, increased medical costs, increased morbidity/mortality and decreased cognitive function following hospital discharge. Non-pharmacologic preventive strategies, routine delirium screening, and performing a comprehensive evaluation for an underlying medical cause of delirium with prompt treatment are the cornerstones of delirium management. With a better understanding of the negative impact on both short and long term outcomes associated with delirium in the transplant population, a focused, multidisciplinary approach to delirium prevention and management strategies to decrease the prevalence and minimize duration of delirium is paramount in transplant recipients. Delirium should no longer be viewed as an unavoidable clinical complication in transplant patients. Instead, proactive measures for cognitive prehabilitation in high risk transplant candidates, together with the use of clinical prevention bundles and post-delirium rehabilitation programs are key components of maximizing patient survival and functional outcomes following solid organ transplantation.

Conflict of interest

The authors have no conflicts of interest to report.

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