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Transplantation-Associated Altered Mentation and Encephalopathy: A New Classification for Acute Neurocognitive Changes Associated with Hematopoietic Cell Transplantation from the ASTCT Committee on Practice Guidelines

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A B S T R A C T

Acute encephalopathy, manifesting clinically as delirium, is a common but often unrecognized complication of hematopoietic cell transplantation (HCT). Delirium can occur in patients of any age and is observed after autologous or allogeneic HCT. Although delirium has been studied primarily during initial HCT hospitalizations in recipients of myeloablative conditioning, recent investigations have identified delirium later post-transplantation and in recipients of reduced-intensity conditioning. Acute encephalopathy can be driven by infectious complications, medications, tissue damage, and/or organ dysfunction. Altered consciousness, either mild or profound, is often its only clinical manifestation. Identifying delirium is essential to overall HCT care, because patients who experience delirium have longer hospitalization and recovery times and are at risk for other poor post-HCT outcomes. Given the critical nature of this common complication and the ongoing expansion of HCT for more vulnerable populations, the American Society of Transplantation and Cellular Therapy (ASTCT) recommends intensifying research into post-HCT cognitive changes and establishing standardized definitions that encompass the full spectrum of altered consciousness for clinical care purposes and to provide benchmark endpoints for future research studies. To capture a range of acute neurocognitive changes specifically found in HCT patients (often referred to as acute encephalopathy), the ASTCT proposes a new diagnosis, transplantation-associated altered mentation

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and encephalopathy (TAME). The TAME diagnosis includes HCT patients who meet *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for delirium and those with acute neurocognitive changes who do not meet all the DSM-5 criteria for delirium (subsyndromal delirium). Early TAME is defined as occurring during conditioning or ≤100 days post-HCT, whereas late TAME occurs >100 days post-HCT in patients with additional HCT-related complications. This manuscript establishes clear diagnostic criteria and discusses factors that can potentially impact the development of TAME, as well as the workup and management of TAME.

INTRODUCTION

Delirium is a significant acute neurocognitive disorder characterized by an altered sensorium with deficits in attention, orientation, and memory that wax and wane. It commonly complicates critical illness, hospitalization, and surgical procedures and is seen in adults and children. It is a symptom of acute encephalopathy, which can be driven by a combination of environmental, medical, and physiologic factors. Delirium can manifest as stupor (hypoactive delirium), agitation and aggression (hyperactive delirium), or a combination of both states at various times (mixed delirium). It has been associated with poor outcomes in all patient populations studied; delirium increases the risk of posthospitalization all-cause mortality, institutionalization, and dementia; prolongs hospitalization; and is associated with an increased rate of readmission [1,2].

Hematopoietic cell transplantation (HCT) is a rigorous procedure typically associated with intensive chemotherapy and/or radiotherapy, profound cytopenias, immunosuppression, mucosal injury, and often prolonged hospitalization. Initial reports of HCT-associated delirium in the early 2000s showed rates of up to 73% in adults and children during the initial HCT course [3-8]. Even with resolution of delirium symptoms during hospitalization, delirium in HCT recipients has been associated with increased nonrelapse mortality [6], higher rates of 1-year mortality [5], worse post-transplantation neurocognitive functioning, higher rates of cancer and treatment distress, and decreased health-related quality of life during the first year post-transplantation [9,10]. As noted above, delirium rates during HCT are high when rigorously and prospectively investigated, emphasizing underrecognition. This observation, together with a now heterogeneous, older, and more vulnerable HCT patient population, mandates the need for a new clinical and research approach to HCT-associated delirium.

With the challenges and unique features of HCT patients in mind, the American Society of Transplantation and Cellular Therapy (ASTCT) Committee on Practice Guidelines sought to develop guidelines to establish new classifications for HCT-associated encephalopathy and delirium. We propose a new group of diagnoses, transplantation-associated altered mentation and encephalopathy (TAME) to capture delirium and the spectrum of acute neurocognitive changes that can occur ≤100 days post-transplantation (early TAME) and beyond (late TAME). The goal of establishing HCT-associated definitions is to promote clarification of the spectrum of acute neurocognitive changes experienced, highlight factors that increase the risk of cognitive changes, champion neurocognitive screening as a routine aspect of HCT care, and facilitate research into this common HCT complication. By establishing a standard catalog of TAME diagnoses, we can expand the study of risk factors and critical agents contributing to acute neurocognitive complications in patients undergoing HCT and identify treatments to reduce the risk or improve outcomes in this population.

This article provides practice recommendations for screening, diagnosing, preventing, and managing TAME. Key issues will be presented in a frequently asked questions (FAQs) format, with answers that attempt to provide the most practical guidance relevant to clinical care. Guideline development included literature review, primarily prospective and retrospective studies relevant to HCT, delirium etiology, and its impact on post-transplantation outcomes. Numerous studies in non-HCT patients and cancer patients were reviewed, and findings were used prudently to help guide our definitions and prevention and management recommendations. Data or recommendations for recipients of chimeric antigen receptor T cell therapy/TCR were considered beyond the scope of this study.

FREQUENTLY ASKED QUESTIONS

FAQ1: What criteria should we use to diagnose and categorize acute cognitive changes in HCT patients?

Diagnosing and categorizing altered mental states during HCT has been unclear, largely because hypoactive delirium is the most common form of delirium in hospitalized cancer patients [11] and the most challenging to identify because multiple pathologic and physiologic HCT-specific changes can manifest as acute neurocognitive changes, thereby confounding the clinical picture. For example, mucositis, cytopenias, thrombotic microangiopathy, calcineurin inhibitor-associated posterior reversible encephalopathy syndrome with or without seizures, viral encephalitis (eg, human herpesvirus-6 [HHV-6]), or other infections can all manifest as confusion, disorientation, and alterations in attention.

Therefore, we first propose clear criteria for diagnoses included under the pathophysiologic brain process "acute encephalopathy" and the spectrum of clinical manifestations, which includes coma, delirium, and subsyndromal delirium (Figure 1). Our definitions align with the 2020 consensus guidelines from 10 relevant international societies [12]. Specifically, for the definitions of delirium and subsyndromal delirium, we recommend using *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria A through C (Table 1) to evaluate acute neurocognitive changes in HCT patients, and delirium may be diagnosed when criteria A, B, and C are all present. Table 1 also provides clinical examples relevant to HCT and guidance on performing a bedside evaluation. We also recommend the term "subsyndromal delirium" for acute cognitive changes that are compatible with delirium but do not meet all 3 A, B, and C DSM-5 criteria. Using the DSM-5 criteria for delirium, changes in attention and awareness, rapidly evolving with fluctuating severity, plus additional cognitive changes all must be present and not associated with a known neurocognitive disorder or coma, and they also must occur in the context of a medical condition or treatment such as HCT.

We recommend the term "acute encephalopathy" to describe "a rapidly developing (≤4 weeks) pathobiological brain process which is expressed clinically as either subsyndromal delirium, delirium or coma and may have additional features, such as seizures or extrapyramidal signs. . .and is not recommended as a descriptor of the clinical features that can be observed at the bedside" [12]. We acknowledge that coma is a clinical manifestation of acute encephalopathy, but further discussion of coma is beyond the scope of this work. Delirium and subsyndromal delirium encompass clinical manifestations of acute encephalopathy. By acknowledging the pathophysiologic process (acute encephalopathy) plus patient experience (delirium or subsyndromal delirium), we hope to

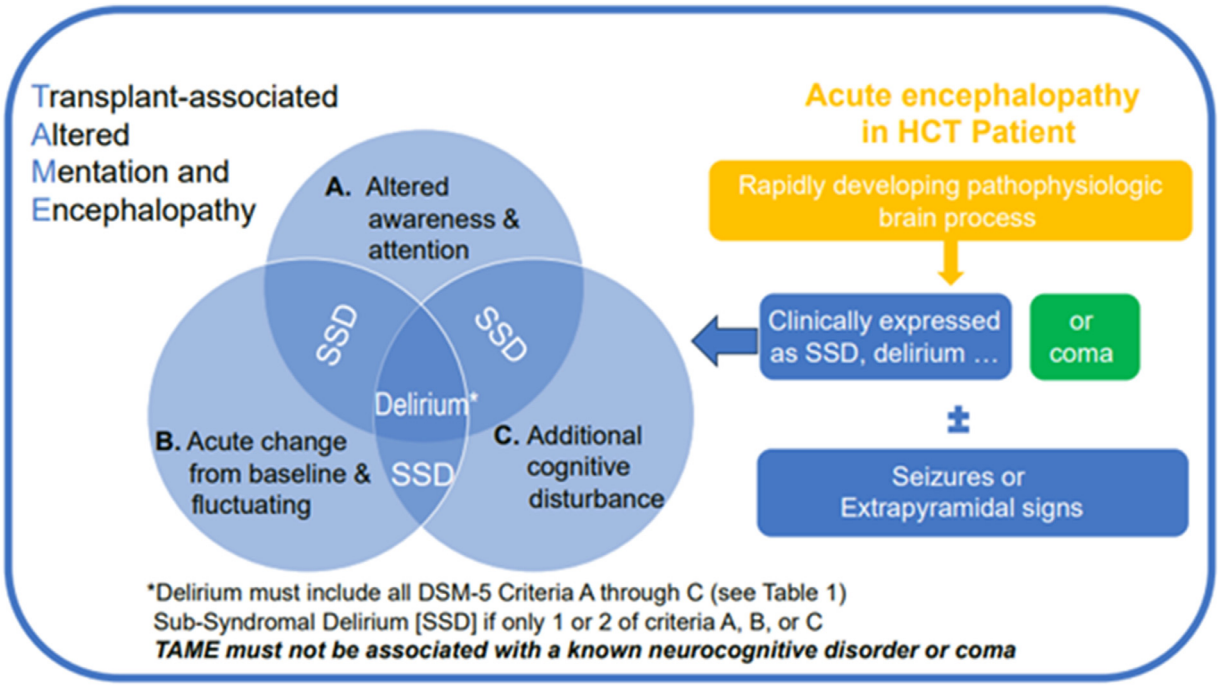

Figure 1. Acute encephalopathy and diagnostic criteria for TAME.

Table 1
DSM-5 Criteria for Diagnosing Delirium, Clinical Manifestations, and Evaluation Tools

DSM-5 Criteria	Patient Clinical Presentation	Evaluation Tools
Disturbance in attention and awareness	• Drowsy or stuporous • Not knowing they are in hospital • Difficulty remembering conversations or following directions	Tests of attention: ask patient to state days of the week or months of the year backwards. Tests of awareness: orientation questions
Disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the day	• New changes in attention and awareness that were not present earlier in the shift or the prior days • Moments of clarity, followed by other moments of significant cognitive changes	Evaluate patient and perform testing at different times of the day. Ask nursing staff whether they are seeing changes over the shift. Ask patient's family or caregivers whether this is an acute change in mental status.
An additional disturbance in cognition is present (memory deficit, disorientation, language, visuospatial ability, or perception)	• Difficult time writing, using their phone, or remembering passwords • Not recognizing caretaker • Asking same questions repeatedly • Hallucinations • Rambling or incoherent speech not attributed to other findings (like mucositis)	Ask patient to repeat back 3 words, then recall those words after a 3- to 5-minute pause. Ask patient to draw a clock or copy a 3-dimensional figure Ask patient to describe their surroundings or current medical condition

enhance future research and interventional studies by documenting a formal diagnosis of acute encephalopathy and its clinical expression.

FAQ2: How do we diagnose early and late TAME?

Moving forward, we propose that patients with various HCT-related neurocognitive deficits or syndromes (Table 2) guided by DSM-5 criteria should be diagnosed with TAME (see FAQ1 and Figure 1).

TAME is separated into "early" and "late" forms based on post-transplantation timing to acknowledge that neurocognitive changes related to HCT also may occur after the initial

Table 2
Diagnosis of Early and Late TAME

TAME	Criteria	Diagnoses Inclusive in TAME
Early TAME	• Meets at least 2 of the 3 DSM-5 criteria for delirium and • <100 days from HCT	• Metabolic encephalopathy • Toxic encephalopathy • Sepsis • TA-TMA • Steroid-induced cognitive changes • CNI-related neurotoxicity • PRES • CRS during mismatched HCT • Stroke • Medication-induced • CNS relapse
Late TAME	• Meets at least 2 of the 3 DSM-5 criteria for delirium and • >100 days from HCT and • An HCT-related complication	• Metabolic encephalopathy • Toxic encephalopathy • Infectious encephalitis • Sepsis • TA-TMA • Steroid-induced cognitive changes • CNI-related neurotoxicity • CNS relapse • PRES • Stroke • Medication-induced • CNS GVHD

TA-TMA indicates transplantation-associated thrombotic microangiopathy; CNI, calcineurin inhibitor; PRES, posterior reversible encephalopathy syndrome; CRS, cytokine release syndrome; CNS, central nervous system.

transplantation hospitalization and/or conditioning regimen-related complications have resolved. Moreover, the presence of a transplantation-related complication is required for a diagnosis of late TAME. To clarify, a patient on glucocorticoid therapy for graft-versus-host disease (GVHD) and hospitalized at 150 days post-transplantation with fever and delirium could be diagnosed with late TAME. Alternatively, a patient in remission who developed delirium related to pain medications after knee replacement surgery at 1-year post-transplantation, off all immune suppression, would not meet our diagnosis of TAME. The incidence and implication of acute neurocognitive changes that occur later (>100 days) in the post-HCT course have not been well studied. Creating this new definition will facilitate further studies of this HCT-related complication.

We recommend using early or late TAME to broadly categorize the presence of acute neurocognitive changes in HCT patients from conditioning to ≤100 days post-transplantation (early) or beyond (late). However, we also recommend documenting more discrete diagnoses as appropriate, for example, delirium or subsyndromal delirium, toxic or metabolic encephalopathy, HHV-6 infection, and thrombotic microangiopathy.

FAQ3: When should hospitalized HCT patients be evaluated for neurocognitive deficits?

We recommend integrating daily attention and orientation assessments (see FAQ4) for all HCT recipients from admission forward, with a particular focus during post-transplantation days 7 to 20. This is because the highest rates of delirium during the initial HCT hospitalization were seen at 10 to 18 days post-transplantation, when conditioning symptom burden, infection risk and cytopenic complications are peaking [6,13,14]. During this period, sedative medications, reduced mobility, and sleep alterations are common, all of which can increase the risk of developing neurocognitive changes. Hospitalizations are common within the first 100 days for complications including fever, infection, and GVHD, and remaining vigilant for early TAME is important.

When considering a diagnosis of late TAME, patients hospitalized for complications after day +100 post-transplantation should undergo evaluation on admission and daily to monitor for acute neurocognitive changes.

FAQ4: What tools are useful to evaluate neurocognitive deficits and diagnose TAME?

For pre-HCT assessment, see FAQ9. For adult HCT recipients, we recommend the Confusion Assessment Method (CAM) tools, which are widely verified, highly validated, and designed for providers, nursing, and support staff to use in evaluating hospitalized (not in an intensive care unit) adult patients for signs of delirium, including hypoactive delirium, which can be easily overlooked [15-18]. Multiple CAM tools are available (help.agscocare.org), the choice of which can be tailored to the individual institution. These assessments are designed to be performed during rounds, shift transitions, or within shifts. Although the Delirium Rating Scale (delirium = score >12) and the Memorial Delirium Assessment Scale (delirium = score ≥8) [19,20] can define the presence and severity of delirium and have been studied in HCT recipients, they are clinician-performed, require training, and take an estimated 30 minutes to more than 1 hour to complete accurately, all of which can impact their feasibility for use in common HCT practice models.

For screening children for altered cognition, we recommend the Cornell Assessment of Pediatric Delirium (CAP-D), with score of >9 identifying those with features of delirium. This tool takes less than 2 minutes to complete, has been studied in HCT patients, and can be used in children from birth to age 21 years [7,8,21] (Appendix A).

Because of the nature of neurocognitive changes in HCT recipients, collaboration among nursing, support staff, family/caregivers, providers, and pharmacists is critical to the prompt recognition of alterations in attention and cognition. Although regular, formal assessments are recommended, input from family and caregivers should be welcomed as a valuable addition to these tools.

FAQ5: What are potential risk factors for developing TAME?

Established predisposing factors for delirium in hospitalized non-HCT patients that may be relevant to TAME in the HCT population include age ≥65 and age <5 years, physical debility, preexisting cognitive impairment, and presence of certain comorbidities [22,23]. HCT-specific data are limited, but reported significant risk factors for delirium and its severity include low blood counts, electrolyte and renal abnormalities, older age, poorer reduced pretransplantation cognitive test performance, female sex, prior alcohol and drug use, acute leukemia diagnosis,

and physical debility [4-7,13,24]. Pre-HCT recognition of certain predisposing factors allows for potential mitigation approaches, for example, interventions for physical debility or extra care when considering medications that can impair cognitive function.

Formal pre-HCT evaluation for predisposing factors (as discussed in FAQ9), including preexisting cognitive impairment, allows for the identification of potentially unrecognized risk factors and should facilitate a full discussion of the risk of TAME with patients and caregivers and the ability to establish a robust program for optimizing environmental and treatment factors before and during the HCT hospitalization.

FAQ6: What are potential inciting/precipitating factors for TAME?

Several factors that increase the risk of delirium in HCT and non-HCT hospitalized patients have been identified (Table 3). Many of these factors are potentially modifiable, even during HCT, including intentionally minimizing the use of specific medications (eg, anticholinergic drugs, sedative hypnotics); encouraging mobility; optimizing sleep quality, hydration, nutritional status, and electrolyte levels; and minimizing the use of catheters/lines. Studies in non-HCT patients have shown that hospital length of stay also impacts the risk of delirium, and while prolonged HCT-hospitalization is often necessary, recognizing this risk factor for TAME is important. Therefore, when extended hospitalization is necessary, modifying the environment of care as noted above to preserve daytime and nighttime routines, maintain physical and cognitive stimulation, and minimize polypharmacy (via diligent and iterative medication reconciliation) are potentially important mitigation strategies.

Of particular importance are medications known to impact cognition, including glucocorticoids, opioids, antiemetics, sedative-hypnotics, and antihistamines, that often are administered during HCT to alleviate symptoms and/or treat GVHD. Dosing and drug choice can impact rates of sedation and other negative impacts of polypharmacy; Table 4 highlights common drugs used in HCT and alternative options. Additionally, it should be noted that when addressing patient analgesic needs, a multimodal, balanced approach is recommended, which includes regular pain assessment and nondrug approaches to minimize opioid use [30]. We recommend thoughtful consideration of substitutes, or at least dose reductions, to decrease the risk for altering mentation in this high-risk population.

It is important to recognize that in older adults and immunocompromised patients of any age, a neurocognitive change may be the sole symptom of a serious medical condition, such as sepsis, infection, myocardial infarction, stroke, metabolic derangements, drug toxicity, and renal or liver failure. Thus, recognition of TAME should prompt further evaluation in HCT recipients.

Table 3
Predisposing and Precipitating Factors for Delirium [4,7,8,13,22,24–29]

Risk Factors	Identified in Non-HCT Patients (May be HCT-Relevant)	Identified in HCT Patients
Patient-related	• Age ≥65 yr • Cognitive impairment • History of delirium • Sensory impairment • History of stroke • Depression • History of falls • Low level of activity • Polypharmacy • Chronic renal or hepatic disease	• Age <5 yr • Age >60 yr • Lower cognitive function • Renal dysfunction • Elevated alkaline phosphatase • Lower oxygen saturation (<92%) • Lower physical functioning • Decreased blood counts • Higher magnesium • Falls within the last year • HCT Comorbidity Index ≥3
Treatment-related	• Severe acute illness • Metabolic derangements • Dehydration • Poor nutritional status/low albumin • Infection • Admission to intensive care unit • Indwelling catheters • Pain	• HHV-6 • Medications: ◦ Antiepileptics ◦ Antipsychotics ◦ Anticholinergics ◦ Tacrolimus ◦ Steroids ◦ Greater opioid use ◦ Benzodiazepines • Fludarabine • Thiotepa
Environmental- related	• Use of restraints • Disrupted sleep • Lack of family/caregiver visitation	

Table 4
Commonly Used HCT Medications Impacting Cognition and Alternative Choices

Drug/Drug Class	Anticholinergic Burden	Alternative	Comments
Anti-infectives			
Antibiotics			Reports of quinolones and sulfa antibiotics associated with delirium, reconsider cefepime if renal dysfunction is significant
Delirium			
Haloperidol		Antipsychotics are recommended only for managing psychotic features that place patients or staff at risk or are disturbing to the patient	
Olanzapine			Increased syncopal risk, only use short term for antiemetic or for documented psychiatric illness
Quetiapine			Antipsychotics associated with increased risk of death
Depression and anxiety			
Amitriptyline	High	Low-dose SSRI	Sedation, orthostasis
Citalopram, fluoxetine, paroxetine		Sertraline or escitalopram	Higher risk in older adults, recommend sertraline or escitalopram first
GI symptoms			
Dicyclomine	High		
Famotidine	Medium	Proton pump inhibitor	Avoid in patients with delirium
Diphenoxylate with atropine	High	Loperamide	Confusion, dry mouth
Insomnia			
Benzodiazepines			Minimize use of benzodiazepines; or limit to lorazepam due to short half-life
Zolpidem, eszopiclone, zaleplon	Low	Ramelteon or mirtazapine	Confusion, falls, minimal sleep benefit
Miscellaneous			
Cyclobenzaprine	High		Confusion, falls, unknown benefit
Diphenhydramine, hydroxyzine	High	Loratadine, cetirizine, fexofenadine	Clearance reduced with age, risk for confusion, dry mouth, and constipation
Oxybutynin	High	Trospium, darifenacin, solifenacin	Use agent with low CNS penetration and/or M3 selectivity
Nausea and vomiting			
Meclizine	High	None	Confusion, dry mouth, constipation
Metoclopramide	Low	Ondansetron	
Prochlorperazine	Low	Ondansetron	Preferred over promethazine, scopolamine, or meclizine
Promethazine	High	Ondansetron	Confusion, sedation
Scopolamine	High	None	Confusion, dry mouth, constipation
Pain			
Acetaminophen	Low	N/A	Total daily dose <4 grams
Celecoxib			COX-2 selective NSAIDs preferred in HCT due to

(*continued*)

Table 4 (*Continued*)

Drug/Drug Class	Anticholinergic Burden	Alternative	Comments
			thrombocytopenia and renal dysfunction
Diclofenac			Watch with renal dysfunction, topical use only
Gabapentin, pregabolin			Increase risk of severe sedation when used with opioids
Lidocaine			May reduce opioid needs
Meperidine			Avoid as analgesic
Opioids (morphine)		Hydromorphone, oxycodone, or fentanyl	Use minimal effective dose; oral may be less deliriogenic than IV
Tramadol			Avoid as analgesic

COX indicates cyclooxygenase; EPS, extrapyramidal symptoms
References: Sugiyama Y, et al. Am J Hospice & Pall Care 2022 [31]; American Geriatrics Society 2019 Beers Criteria Update Expert panel. American Geriatric Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatric Soc. 2019 [32]; Drugs for Overactive Bladder The Medical Letter on Drugs and Therapeutics 2023 [33]; American Geriatrics Society 2023 updated AGS Beers Criteria Update Expert panel. American Geriatric Society 2023 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatric Soc. 2023 [30].

FAQ7: What tests and evaluations are indicated in a patient diagnosed with TAME?

Guidance for the workup of TAME, offered in Table 5, highlights testing for infection, organ dysfunction, electrolyte abnormalities, and central nervous system pathology, along with a careful review of medications and dosing. Assessment for additional complications of treatments, including urinary retention, constipation, dehydration, and sleep disruption, is important for a thorough

Table 5
Recommended Evaluations and Treatment of Early and Late TAME

Potential Etiologies	Workup and Management
CNS pathology	• Head CT scan • Brain magnetic resonance imaging • Lumbar puncture depending on the extent of immunosuppression or risk for CNS malignancy
Infection	• Blood and urine cultures • Chest X-ray and/or chest CT • Workup for viral reactivation (depends on extent of immunosuppression) • Lumbar puncture for bacterial, fungal, viral including HHV-6, toxoplasmosis, and broad microbial PCR (depending on the extent of immunosuppression)
Uncontrolled pain	• Assess for nonverbal findings of pain • Evaluate response to scheduled acetaminophen with or without scheduled low-dose opioids if uncontrolled pain is a consideration
Elimination problems	• Bladder scan/postvoid residual to evaluate for urinary retention • Monitor frequency and quality of bowel movements to assess for constipation
Medications	• Partner with pharmacist and nursing to review use and response to medications for symptom management. • Deprescribe all nonessential agents • Evaluate the use of as needed medications and where possible minimize anticholinergic medications. • Assess benzodiazepine and opioid use/needs and consider alternatives (eg, topical lidocaine or diclofenac, or acetaminophen) • Check levels of cyclosporine, tacrolimus, and sirolimus as appropriate • Have the pharmacy team review the full medication list for drug-drug interactions, total anticholinergic burden, other agents that can impact cognition, and use of potentially inappropriate medications.
Sleep disturbance	• Attempt to provide undisturbed sleep for at least 4-6 hours. • Open window blinds and provide cognitive stimulation during daytime hours. • Mobilize patient/up to chair 3 times daily with meals. • Avoid sedative-hypnotics.
Hepatic injury	Liver function testing
Acute kidney injury	Renal function testing
Electrolyte abnormality	Electrolyte testing

CT indicates computed tomography.

evaluation. One study found that the etiology of delirium in HCT recipients was most often multifactorial (50% of patients), followed by medication (31%), infection (7%), and toxic-metabolic (5%) [6]. Heterogeneity in HCT approaches, including autologous versus allogeneic and varied conditioning intensity, impacts the differential diagnosis for TAME, and therefore a workup should consider the HCT approach and other patient risk factors. For example, HHV-6-associated delirium is reported primarily after allogeneic HCT, most frequently after receipt of cord blood and unrelated donor grafts [25,34]. While much rarer, HHV-6 reactivation after autologous HCT is more closely associated with a thiotepa, busulfan, and cyclophosphamide-based conditioning regimen [35]. It follows that not every HCT recipient requires HHV-6 testing to explore it as a cause of altered cognition, but those at highest risk should undergo early testing.

FAQ8: What are the potential complications of TAME?

Delirium may be disruptive to optimal patient care, and although it has not yet been studied intensively, patients with TAME can manifest nonadherence to critical medications or experience functional decline, goal-discordant care for treatment-related toxicities, and excessive and invasive diagnostic testing. Subsequently, patients with TAME may be at risk for increased morbidity/mortality due to falls, development of pressure ulcers or aspiration pneumonia, iatrogenic infectious complications, nutritional compromise, and complications from procedures and medications. Studies of patients with delirium during their initial HCT course have shown increased nonrelapse mortality [6], higher rates of 1-year mortality [5], worse neurocognitive functioning at multiple time points in the first year post-HCT, higher rates of cancer and treatment distress after HCT, and decreased health-related quality of life during the first year post-HCT [9,10].

FAQ9: What are pre-HCT nonpharmacologic strategies for preventing TAME?

The focus here is on recognizing risk factors for delirium, followed discussing TAME risk and potential mitigating factors with the patient and caregiver, and then individualizing treatment plans in an effort to mitigate TAME (Figure 2). This strategy always includes a detailed evaluation of prescription and over-the-counter medications, partnering with the patient and the caregiver, along with the patient's primary care provider if relevant, to minimize or discontinue medications associated with altered mentation, including those with high anticholinergic activity, benzodiazepines, sedative-hypnotics, and drugs with central nervous system activity. Although no studies to date have investigated the impact of active deprescribing of higher-risk medications on HCT outcomes, a recent report identified a high rate of polypharmacy and potentially inappropriate medications in a cancer patient population [36]. Working with pharmacy and nursing to identify areas of concern and help educate patients and families about TAME facilitates a supportive, patient-focused care plan.

In HCT and non-HCT adult patients, cognitive impairment has been identified as a risk factor for delirium. Between 20% and 50% of adults formally tested for cognitive changes prior to HCT have evidence of cognitive impairment [37–40], with rates up to almost 70% in those age >60 years [41]. Testing to evaluate for subtle or significant cognitive impairment can identify those patients at highest risk for TAME and prompt discussions regarding HCT risks versus benefits, and also optimize supportive and environmental factors to reduce that risk. Therefore, before proceeding with HCT, we recommend screening for cognitive impairment using such tools as the Mini-Cog [42] (Appendix B) or Blessed Orientation Memory and Concentration (BOMC) [43] tests. The advantage of the BOMC is that it can be performed via phone and in patients with visual impairment [44]. For those patients who have a decrement in scoring (Mini-Cog score ≤2; BOMC score ≥8), this can be a marker of significant cognitive impairment, and thus we recommend further intervention, which may include referral to neurology or neuropsychology based on institutional standards or administering the Montreal Cognitive Assessment (MoCA), a 30-point test of multiple cognitive domains [45] that also has been studied in adult HCT candidates [46]. Although the MoCA is a good test of executive function, memory, and attention and has been validated in multiple languages, and serial testing helps illuminate trends and impacts of specific interventions, it might not perform ideally in ethnoculturally and linguistically diverse populations [47–50]. Although as-yet unstudied, patients with suspected cognitive impairment may benefit from referrals to cognitive therapy and testing for potentially reversible causes, such as depression, medications, vitamin B12 deficiency, thyroid disease, and sleep apnea.

The impact of cognitive challenges prior to HCT and the risk of delirium has not been studied in children. However, there is growing research and clinical efforts to identify cognitive changes in

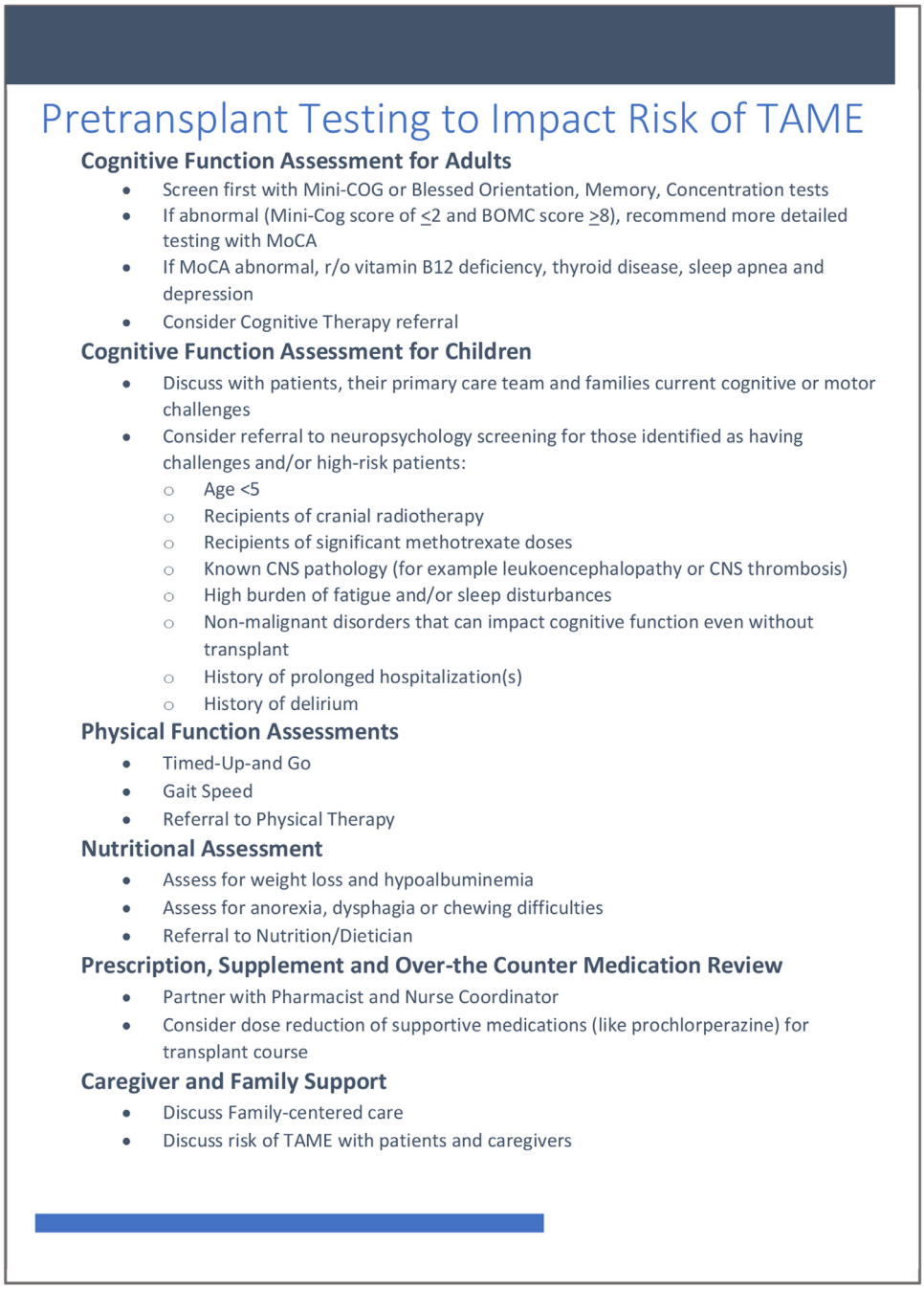

Figure 2. Pretransplantation testing to impact the risk of TAME.

children undergoing HCT. Recommendations for the pretransplantation assessment of pediatric cognitive challenges, focusing on those considered at highest risk [51], are listed in Figure 2. Of note, the MoCA has been studied in noncancer patients as young as age 14 years [52] and could be an additional tool for uncovering cognitive impairment in this younger population.

Poor physical function has been identified as a risk factor for HCT-associated delirium [6]. Pain, cancer, treatment-related fatigue, and weight loss are known contributing factors to deconditioning and sarcopenia after HCT, and physical functioning and performance status contribute to HCT outcomes [53,54]. Pre-HCT evaluation of physical functioning either within HCT clinics, using the Timed Up & Go, 6-minute walk (gait speed), and Sit-to-Stand tests, or through formal physical therapy assessments can identify unrecognized areas of weakness, fall risk, and predisposition to immobility during HCT. These tests, plus a formal frailty evaluation, can distinguish patients who are at highest risk for TAME or falls from those who are best supported with interventions (eg,

physical/occupational therapy and/or nutrition) before proceeding to HCT and throughout their initial transplantation course.

Caregiver and family support has a critical role in delirium prevention. Family-centered care involves partnership between family members and medical staff, in which family members participate in patient care activities, and has been studied in both critically ill patients [55] and hospitalized patients with dementia [56]. These studies showed a benefit in delirium prevention, with improvement in markers of functional status in patients with dementia. Although unstudied in HCT, transplantation requires the engagement and support of caregivers for an optimal chance of success. Given the intensity of HCT and its high risk for complications, HCT patients are required to have caregiving support during their early transplantation course, especially when they are outpatients. During hospitalization, especially the initial HCT treatment and engraftment period, caregivers and family members may be able to be present and directly contribute to the daily care and patient routine, while others may be unable to be present due to work or family constraints. Educating medical staff, social work, patients, and caregivers on ways that family caregivers can contribute to the nonpharmacologic support of HCT patients through mobilization, cognitive stimulation, nutritional support, and adding familiarity and routine to the environment may contribute to reductions in the risk and severity of TAME.

FAQ10: What are the nonpharmacologic strategies during HCT hospitalization to minimize and manage TAME?

Multicomponent nonpharmacologic treatment strategies have been studied in non-HCT hospitalized adults and shown to be effective in reducing the number and duration of delirium episodes [57]. While no HCT studies have been performed, we recommend extrapolating these low-risk multicomponent approaches to prevention and treatment of TAME. These approaches include supporting staff and family caregivers to provide daytime stimulation and orientation, ensuring support for vision and hearing, reducing nighttime disruptions, and maintaining a calming nighttime environment. Figure 3 highlights nonpharmacologic and pharmacologic options to help optimize sleep quality and timing. In addition, frequent movement and mobilization during the daytime should be pursued, even in bedbound patients. Working with the patient, care team, and family to promote time out of bed, multiple episodes throughout the day of walking, sitting

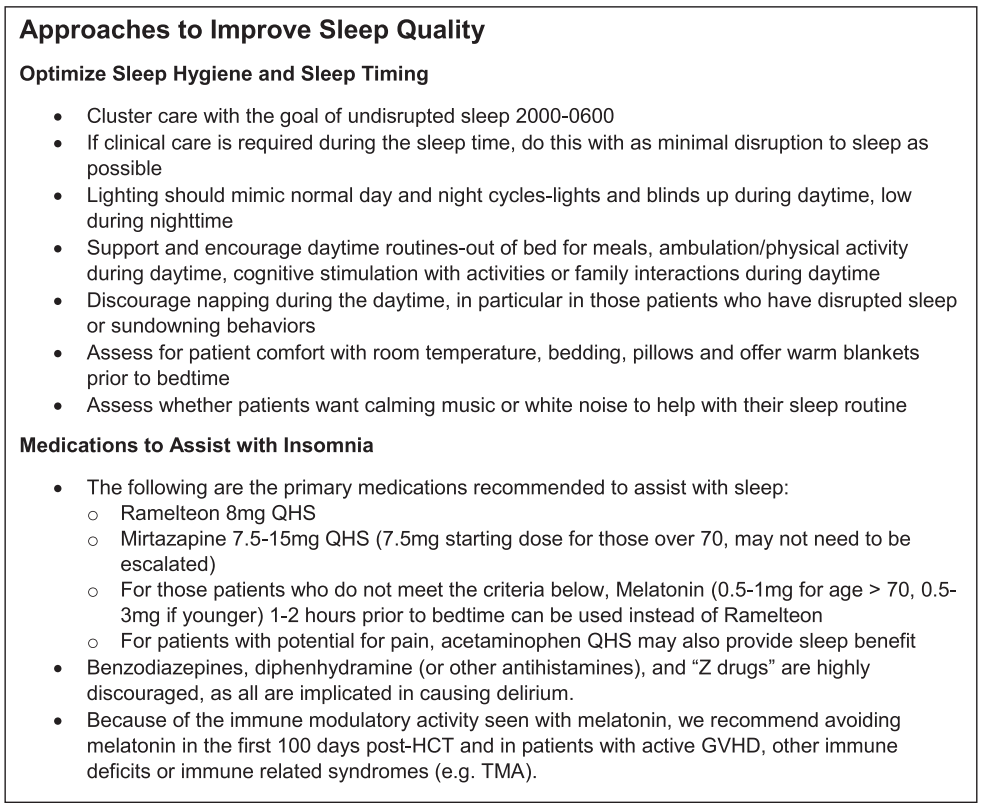

Figure 3. Approaches to improving sleep quality.

Table 6
Antipsychotic Dosing for Delirium Treatment in Adults Adapted from References

Drug	Dose	Frequency	Comments
Aripiprazole	5-30 mg	Every 24 h	Limited experience, may work in hypoactive as well as hyperactive delirium
Haloperidol	0.5-2 mg	Every 2-12 h	May be given i.v.; QT interval-prolonging.
Olanzapine	2.5-5 mg	Every 12-24 h	Dissolvable tablet available. Elderly and hypoactive delirium tolerate poorly.
Quetiapine	12.5-50 mg	Every 12-24 h	Only available orally.
Risperidone	0.25-1 mg	Every 12-24 h	Orthostatic hypotension with higher doses. Elderly tolerate poorly; don't use if age >70 yr.
Regardless of agent selected, the lowest effective dose should be used			

Breitbart W et al. Psychosomatics 2002 [58]; Tanimukai H et al. Am J Hosp Pall Care 2016 [59]; Prommer E. J of Hospice and Pall Med 2017 [60].

up out of bed, and eating 3 meals per day can help establish a routine. Coordinating with a dietician and speech therapist to maintain nutritional intake after HCT can support the patient and their caregiving team. Finally, if TAME has already developed, the foregoing interventions should be maintained, and the patient should be continuously evaluated for modifiable factors, including uncontrolled pain, elimination disturbances, disrupted sleep cycles, poor nutrition, occult infections, medication side effects, and electrolyte abnormalities.

FAQ11: What are the indications and pharmacologic options for treating TAME?

Patients with TAME experiencing hyperactive delirium pose specific management challenges for care providers, family members, and caregivers. In addition to nonpharmacologic interventions (see FAQ10), medications are indicated when patients have disturbing or frightening hallucinations or delusions or if their behavior calls for medical treatment or poses a risk of harm to staff or themselves (Table 6). However, the appropriate use of chemical restraints must be balanced against the increased morbidity and mortality associated with delirium.

Caring for an HCT patient with hypoactive delirium can be particularly challenging, as these patients are unable to fully report symptoms, and ongoing receipt of oral medications may be disrupted. In addition, patients with hypoactive delirium must be evaluated and managed for aspiration risk/airway protection, monitored for nutrition and hydration status, and supported with positioning and mobilization to prevent pressure sores and venous thrombosis. The use of lines, tubes, and other tethers that act as physical restraints should be minimized whenever possible.

CONCLUSIONS

We propose a new classification for acute neurocognitive changes that commonly complicate HCT and impact its trajectory of recovery. TAME is an inclusive diagnosis, capturing those with acute encephalopathy, manifesting clinically as delirium and subsyndromal delirium, and occurring in early and late forms based on post-transplantation timing. Further research is needed to understand the acute and long-lasting cognitive risks of HCT. Our goal is to establish a uniform framework for recognition, diagnosis, evaluation, and management of cognitive changes found early and late after HCT. We also highlight risk factors for TAME, and although these are more common in older adults, especially those with lower functional status, cognitive impairment, and multiple comorbidities, children and young adults are also at significant risk for developing TAME during their initial transplantation course. Treatment factors also impact TAME risk and outcomes, and the care environment together with medication choices likely have critical roles. Recognition of TAME as a potentially modifiable HCT-associated complication is the first step toward reducing its incidence and enhancing its recovery. Talking about TAME and potential contributing factors with care teams, patients, and their caregivers is an important component of the risk discussion and supports their engagement with mitigating factors to optimize overall HCT outcomes.

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APPENDIX A: CORNELL ASSESSMENT OF PEDIATRIC DELIRIUM (CAP-D)-REPRINTED WITH PERMISSION BY CRITICAL CARE MEDICINE

RASS Score _____ (if -4 or -5 do not proceed)

Please answer the following questions based on your interactions with the patient over the course of your shift:

	Never	Rarely	Sometimes	Often	Always	Score
	4	3	2	1	0	
1. Does the child make eye contact with the caregiver?						
2. Are the child's actions purposeful?						
3. Is the child aware of his/her surroundings?						
4. Does the child communicate needs and wants?						
	Never	Rarely	Sometimes	Often	Always	
	0	1	2	3	4	
5. Is the child restless?						
6. Is the child inconsolable?						
7. Is the child underactive—very little movement while awake?						
8. Does it take the child a long time to respond to interactions?						
					TOTAL	

Figure 1.
Cornell Assessment of Pediatric Delirium revised. RASS = Richmond Agitation and Sedation Scale.

APPENDIX B: MINI-COG REPRINTED WITH PERMISSION BY DR. SOO BORSON

Mini-Cog©

Instructions for Administration & Scoring

ID: _____ Date: _____

Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies.[1-3] For repeated administrations, use of an alternative word list is recommended.

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below.

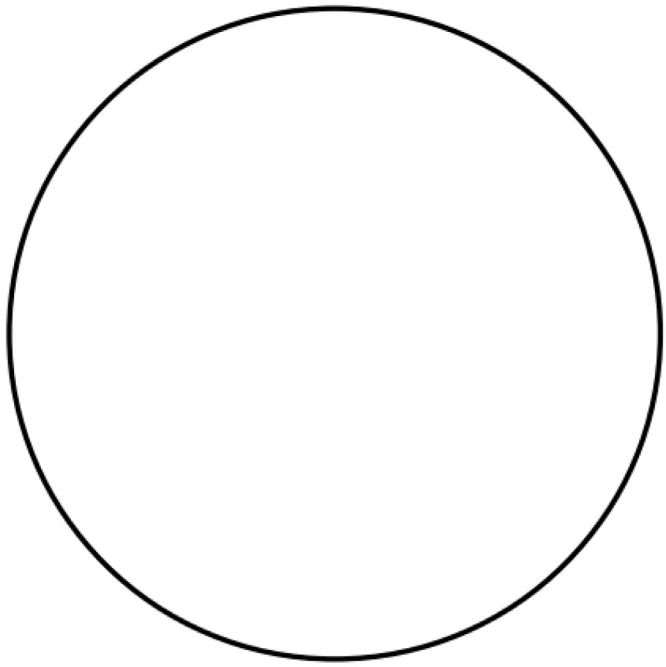
Word List Version: _____ Person's Answers: _____ _____ _____

Scoring

Word Recall: _____ (0-3 points)	1 point for each word spontaneously recalled without cueing.
Clock Draw: _____ (0 or 2 points)	Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored. Inability or refusal to draw a clock (abnormal) = 0 points.
Total Score: _____ (0-5 points)	Total score = Word Recall score + Clock Draw score. A cut point of <3 on the Mini-Cog™ has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status.

Clock Drawing

ID:_____ Date:_____



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