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Psychiatric Care in Hematopoietic Stem Cell Transplantation

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Abstract

Background: Patients with cancer frequently experience neuropsychiatric symptoms due to their medical illness or its treatment. In recent decades, psychiatrists have become increasingly involved in the care of patients with cancer. However, psychiatrists may be less familiar with hematopoietic stem cell transplantation (HSCT), a distinct cancer treatment modality associated with multiple neuropsychiatric sequelae.

Objective: To provide an overview of HSCT, and describe the prevalence, impact, risk factors, and suggested management of psychiatric consequences of HSCT.

Methods: We performed literature searches in PubMed and PsychInfo to identify articles describing neuropsychiatric symptoms, including depression, anxiety, distress, post-traumatic stress disorder, delirium and cognitive impairment, resulting from HSCT in adults. Those articles most relevant to this manuscript were included.

Results: Psychiatrists may be involved in the treatment of patients before, during, or after inpatient hospitalization for HSCT. Each phase of treatment introduces unique stressors that may lead to or exacerbate psychiatric disorders. Appropriate management requires evaluation of HSCT-related medications, an understanding of the impact of complications from HSCT, and

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consideration of how the patient's underlying medical condition should influence psychiatric recommendations.

Conclusion: To optimize patient outcomes, consulting psychiatrists should be familiar with the basic principles of HSCT and the neuropsychiatric sequelae that may result from treatment. Further research is needed to identify strategies to manage psychiatric complications in this unique population.

Keywords

cancer; oncology; neoplasm; hematopoietic stem cell transplantation; bone marrow transplantation; neuropsychiatry

Introduction

Hematopoietic stem cell transplantation (HSCT), also known less specifically as bone marrow transplantation (BMT), is a routine part of cancer care for many patients with hematologic malignancies.¹ The psychological stress of HSCT begins during the pre-transplant period, is exacerbated during inpatient hospitalization, and is perpetuated by a close surveillance period over several months following HSCT. Given the prevalence of hematologic disorders and increasing indications for HSCT, it is imperative for consultation-liaison psychiatrists to be familiarized with HSCT, its many associated pharmacologic treatments, and the range of neuropsychiatric presentations in these patients.

Overview of Hematopoietic Stem Cell Transplantation

Over 50,000 people undergo HSCT annually throughout the world, a number that continually increases with advances in technology and access to care.² In the United States, over 22,000 transplants occur each year.³

HSCT is delineated by graft type, with a primary differentiation between autologous and allogeneic HSCT. Autologous transplantation (auto-HSCT) refers to the reinfusion of the patient's own cells back into the patient. The primary intent of auto-HSCT is to deliver very high doses of chemotherapy, and to utilize the patient's own cells to re-establish progenitors within the bone marrow to prevent profound myelosuppression.¹ Auto-HSCT is well tolerated with published transplant-related mortality for most diseases of less than one percent.⁴ Overall benefit of transplant varies by disease type.

Allogeneic transplantation (allo-HSCT) refers to the infusion of cells collected from a donor into the patient.¹ Patients and donors are matched across human leukocyte antigen types. The graft can be obtained from either related donors or unrelated donors identified through the National Marrow Donor Program. In addition to safely delivering very high doses of chemotherapy, allo-HSCT also offers potential additional immune-related benefits at the cost of additional immune-related side effects, principally graft-versus-host-disease (GVHD). GVHD refers to the damage of host organs by graft cells (predominantly T-cells) and can result in a spectrum of clinical manifestations ranging from minor rashes to fatal complications. Over 40% of patients will develop chronic GVHD.⁵ Complication rates are

higher among patients undergoing allo-HSCT as compared to auto-HSCT, with transplant-related mortality often thought to approach 40% over two years for higher risk patients.⁶ For patients with significant comorbidities or of advanced age, reducing the intensity of chemotherapy may be an option to mitigate acute side effects, but this is often at the expense of an increased risk of disease relapse. Similar to auto-HSCT, potential overall benefit of allo-HSCT varies primarily by disease type, as well as disease stage and cytogenetics. For example, three-year survival probability following sibling-matched allo-HSCT is 78% for aplastic anemia as compared to 59% for early-stage acute myeloid leukemia (AML) or 27% for advanced stage AML.³ Further, adverse cytogenetics have been shown to negatively impact survival in many hematologic disorders.^{7,8}

Due to the high morbidity of HSCT, all patients should ideally undergo comprehensive pre-transplantation screening, including an assessment of comorbidities, functional status, and psychosocial well-being and support.⁹ Several psychosocial screening tools, such as the Transplant Evaluation Rating Scale,¹⁰ are used in HSCT. Exclusion of patients based on psychosocial risk factors, such as a history of addiction or the absence of a reliable caregiver for the first 90 days post-transplant, is common practice, though somewhat controversial.¹¹

The HSCT process is both physically and emotionally challenging for patients. Patients undergoing auto-HSCT typically spend at least three weeks in the hospital while allo-HSCT patients often spend more than a month hospitalized. The acute physical side effects are largely due to chemotherapy and GVHD and include fatigue, nausea, vomiting, diarrhea, malaise, weakness, mucositis, and infection.¹ Long-term, HSCT patients may face a myriad of potentially serious physical effects secondary to their transplant that elevate mortality risk and can have a major impact on quality of life. For example, chronic GVHD can cause malabsorption, cholestasis, and cytopenias.¹ Of note, both acute and chronic GVHD are independently associated with worse functional status, occupational outcomes, mental health, and overall quality of life (QOL).¹² To mitigate risk of GVHD, patients often require long-term immunosuppression, including with corticosteroids, which can result in osteoporosis and elevated infection risk. Finally, after transplantation infertility is common, and patients are more likely to develop several secondary cancers, including myelodysplasia and acute leukemias after auto-HSCT for lymphoma or cancers of the skin, oral mucosa, brain, thyroid and bone after allo-HSCT.^{1,12} Despite advances in supportive care that have led to improved recovery for patients with adverse side effects, the prolonged and potentially unpredictable post-HSCT course can lead to post-transplant decisional regret in some patients,¹³ as well as a myriad of psychiatric symptoms requiring careful consideration in this medically complex population.

Anxiety, Depression, and Distress

Anxiety and depressive symptoms are the most commonly reported psychiatric concerns during HSCT, seen in 15-40% of patients before, during, or after transplant.¹⁴ Anxiety is typically highest prior to transplant and then gradually decreases during inpatient hospitalization and after discharge.¹⁵ Depression, on the other hand, tends to be less prevalent than anxiety prior to transplant, but then increases during hospitalization for HSCT and may remain elevated for years.¹⁶ Distress, a similar but more wide-ranging construct

that also includes feelings of vulnerability, social isolation, and spiritual crisis, can be experienced by patients for several years after transplant.¹⁴

Several disease and treatment-related outcomes have been shown to be impacted by mood and anxiety symptoms. Pre-transplant depression and anxiety may lead to slower white blood cell recovery¹⁷ and higher incidence of acute GVHD.¹⁸ Pre-transplant distress has been shown to predict post-transplant distress, utilization of prescription drugs for depression and anxiety, and engagement in care with a mental health professional.¹⁹ Pre-transplant distress is also predictive of need for inpatient psychiatric consultation and likelihood to be given a formal psychiatric diagnosis during inpatient hospitalization.²⁰ The presence of mood and anxiety disorders during inpatient hospitalization is associated with an increased length of stay,²¹ and depression has been associated with a two- to three-fold mortality risk in the three years following transplant.²²

Several risk factors have been identified for increased distress in HSCT patients; female gender, chronic GVHD, chronic pain, and worse functional status increase the likelihood of disturbances in mood and anxiety.²³ The mechanisms underlying the likely bidirectional relationship between heightened distress and these factors has not been well elucidated and is worthy of future study. In recent years, researchers have begun to identify the financial impact of HSCT and its downstream consequences. In one study, evaluating 325 HSCT recipients, 46% reported decline in income post-HSCT, with worse QOL and stress in those reporting financial hardship.²⁴ Regarding potential immune system related effects, the Bone Marrow Transplant Survivor Study found that exposure to prednisone for prevention or treatment of GVHD was associated with increased psychological distress in survivors.²⁵ Further, compared to non-depressed recipients of HSCT, depressed HSCT patients demonstrate elevated levels of IL-6 and IL-10, again suggesting that immune dysfunction may potentially contribute to these patients' mood disturbance.²⁶

Management

Data on the management of mood and anxiety symptoms in HSCT is extremely limited. A systematic review by Baliousis et al. described nine "psychological" intervention studies for the management of distress in adults who had received HSCT.²⁷ Seven of these studies evaluated a cognitive behavioral therapy intervention and almost all showed benefit. A randomized controlled trial (RCT) of inpatient palliative care during HSCT hospitalization improved depressive symptoms, as measured by the Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire 9 (PHQ-9), at six months post-transplant.²⁸ Short-term benefits in depression and anxiety have also been demonstrated with massage,²⁹ relaxation exercises,³⁰ and music therapy.³¹

There have been almost no studies evaluating pharmacologic interventions for depression and anxiety in HSCT patient populations. Of interest, in an RCT of 56 adult HSCT candidates with depression or anxiety, those who received sertraline had a shorter time to engraftment and demonstrated lower mortality and readmission rates at six months compared to placebo.³² Although Selective Serotonin Re-uptake Inhibitors (SSRIs) carry theoretical risks of bruising and bleeding, raising concern in HSCT patients with cytopenias, we use them widely in our clinical practice, and find them to be safe and well-tolerated.

Because HSCT patients often experience nausea, decreased appetite, and insomnia, mirtazapine is another good option for depression and anxiety management. The extremely rare risk of agranulocytosis described in isolated case reports with mirtazapine, as well as its association with thrombocytopenia, is often outweighed by its potential benefit in our clinical experience. However, the risk-benefit ratio of using mirtazapine, or any medication associated with blood dyscrasias, in HSCT should be made on an individual patient basis. While we highly advocate treating depression and anxiety in symptomatic patients, it is important to be cognizant of the feasibility of this approach during transplant hospitalization. Patients may be unable to tolerate oral medications in the setting of severe chemotherapy-induced mucositis or emesis and potential drug-drug interactions with other medically-necessary medications commonly exist. Finally, patients with hematologic malignancies are at increased risk for delirium, which is further compounded during HSCT by exposure to numerous centrally-acting medications. Therefore, delirium should be ruled out prior to assessing for mood or anxiety disorders and potentially introducing another centrally acting medication to patients' regimen. Table 1 provides an overview of medications commonly used in HSCT and their risk of adverse psychiatric effects. Overall, there is a significant need for large, randomized studies to identify evidence-based interventions that can be implemented in this unique population.

Post-traumatic Stress Disorder

Patients undergoing HSCT face a series of life threatening events, starting with their initial cancer diagnosis. HSCT is associated with a high risk of potentially fatal side effects, and those who survive still face high mortality rates during the years following treatment. Prior research on the prevalence of PTSD in patients undergoing HSCT reveal that 3-28% of HSCT patients meet the Diagnostic and Statistical Manual of Mental Disorders (*DSM-5*) criteria for PTSD, which is higher than in the general population and similar to the general cancer population.^{14,33,34} Efforts to identify HSCT-specific risk factors for PTSD have revealed that limited social support or family strain, pre-morbid psychological distress, financial demands, overall health burden, and tendency towards avoidance-based coping strategies are associated with PTSD following HSCT.^{14,34,35} However, it is still unclear what the most common or likely PTSD triggers may be in HSCT patients. Additional attention to mental health factors, including PTSD, during pre-treatment screening for HSCT may clarify the true prevalence of PTSD attributable to HSCT.

For cancer patients who suffer from PTSD, their traumatic experience(s) are often not isolated external events, but diagnosis- and treatment-associated traumas which the patient can re-experience during repeated medical encounters.³⁶ Physical sequelae of anti-neoplastic therapies (e.g. peripheral neuropathy) can serve as constant reminders of their diagnosis and treatment and can make avoidance of triggers difficult, thus increasing their level of distress. Avoidance symptoms can also be dangerous if they lead to reduced compliance with post-transplant follow-up care. Symptoms of hyper-arousal (e.g. insomnia, difficulty concentrating) may be due PTSD, co-occurring mood and anxiety disorders, or even complications from HSCT and other anti-neoplastic therapies. This confluence of symptoms can complicate the accuracy of PTSD diagnoses and estimates of PTSD prevalence. Also, a certain level of "sensitivity" to physical symptoms, which could be mistaken as

“hyperarousal” due to PTSD, is often encouraged by the patient’s oncology and BMT teams in order to facilitate timely evaluation of transplant-related complications or cancer recurrence.

Management

There are no pharmacological options for PTSD that are specifically designed for HSCT patients. Telephone-based CBT shows promise in reducing multiple PTSD-associated symptoms in this population.³⁷ More recently, inpatient integrated palliative care has been shown to improve a variety of mental and physical health symptoms acutely and in the long-term, including decreasing prevalence of clinically significant PTSD symptoms (Post-Traumatic Stress Disorder Civilian Checklist score ≥ 32) at six months post HSCT.²⁸ When treating PTSD in those undergoing HSCT, the psychiatrist should consider the multitude of stressors that the patient has faced, and continues to face, while focusing on symptoms that appear to be interfering with ongoing cancer treatment. However, treatments targeting PTSD in this unique population are a needed area of research and clinical development.

Delirium

Delirium is the most common neuropsychiatric problem in this population, affecting between 40% and 73% during hospitalization for their transplant.^{38,39} The risk of developing delirium is greatest within the first four weeks after transplant, with delirium episodes typically lasting between two to ten days.^{38,40} Though delirium in HSCT may present in a variety of ways, in our experience it is typically hypoactive. This is supported by one study which reported that 86% of delirious patients after transplant exhibited psychomotor retardation, worsening cognitive function, inattention, confusion, and disruption of sleep-wake cycle, all of which are more commonly associated with hypoactive delirium.⁴⁰

HSCT patients are at higher risk for developing delirium than the general hospitalized patient due to several unique risk factors. Specifically, several agents used in conditioning chemotherapy regimens, as well as total body irradiation, are associated with encephalopathy (Table 1).^{41,42} Patients experience prolonged immunosuppression, which can lead to delirium as a direct consequence of exposure to the immunosuppressive agent, and indirectly, through increased risk of infection and Posterior Reversible Encephalopathy Syndrome (PRES). As a consequence of myeloablative chemotherapies and immunosuppressant medications, patients are prone to rare infections of the central nervous system, such as HHV6 encephalitis. Furthermore, many medications used during hospitalization for HSCT, including opioid analgesics, sedatives, corticosteroids, and anticholinergics, further elevate delirium risk.

Delirium that occurs during transplant hospitalization for HSCT has been shown to lead to higher levels of distress and fatigue, poorer neurocognitive functioning, and lower health-related QOL at both six months and one year post-transplant.⁴³ In the only study examining the impact of delirium on mortality in HSCT, delirium within four weeks after transplant conferred a 14-fold greater mortality rate, making it of significant concern for HSCT patients and their providers.³⁸

Management

Despite the pervasive and long-term impact of delirium in HSCT, almost no studies have investigated delirium management in this patient population. As with suggested delirium management in all hospitalized patients, we recommend behavioral interventions, limiting exposure to deliriogenic medications, and evaluation for infectious and metabolic derangements. In addition, we suggest psychiatric consultants evaluate for contributors more unique to the HSCT population (Table 2). The limited evidence for pharmacotherapy interventions demonstrates that several antipsychotics (including haloperidol, risperidone, olanzapine, and quetiapine), lead to decreased delirium severity scores on validated measures.⁴⁴ For behavioral management of agitation in the setting of hyperactive or mixed delirium, we do recommend using neuroleptics. The evidence to support any particular antipsychotic medication is lacking, but we favor olanzapine, given that it is sedating, available as a dissolvable tablet (useful in the setting of mucositis), and widely prescribed by oncologists for chemotherapy-induced nausea.⁴⁵ In patients who cannot tolerate oral medications or are severely agitated, haloperidol, which is available in intravenous, intramuscular, and oral formulations, is also an excellent option. Benzodiazepine use should be minimized, unless a GABA-withdrawal delirium is suspected. Finally, given the high risk of Wernicke's encephalopathy in this population,⁴⁶ high dose intravenous thiamine can be considered for both treatment or prophylaxis of delirium. A RCT evaluating the efficacy of a prophylactic approach is currently underway at our institution.⁴⁷ Other agents, such as gabapentin and alpha 1 agonists, have not been studied to target delirium in HSCT.

Other Cognitive Disorders

The cognitive consequences of HSCT extend beyond the acute mental status changes of delirium to include long-term cognitive changes. Recent studies reveal that many patients actually demonstrate cognitive impairment prior to their transplant,⁴⁸ and the cognitive outcomes for patients are diverse, ranging from improvement post-transplant⁴⁹ to long-term cognitive impairment.⁴⁸ Of great importance, patients receiving HSCT identify lack of information about treatment-induced cognitive impairment as one of their primary concerns.⁴⁹

The extant literature indicate that patients who experience delirium during HSCT are at increased risk for persistent cognitive impairment.⁵⁰ Older age, male gender, and lower pre-malignancy IQ are all negative prognostic factors for long-term objectively measured cognitive function after HSCT.^{48,51} In contrast, younger age appears to be a risk factor for greater self-reported cognitive concerns.⁵¹

The impact of cognitive impairment on disease-related outcomes in HSCT is not well defined. A prospective cohort study of 58 allo-HSCT patients by Mayo et al. did demonstrate that poor performance on objective tests of executive function/working memory predicted impaired medication management ability;⁵² however, subjective reports of cognitive impairment did not appear to impair medication adherence. Due to the complicated nature of post-transplant medication regimens, patient confusion over these regimens can have fatal implications.

As the number of patients receiving HSCT increases, and post-HSCT survival improves, the longer-term side effects of this therapy, including the impact on cognitive function, are becoming more prominent.⁵³ The most robust evidence for cognitive recovery of cancer-related cognitive impairment is with behavioral strategies, such as cognitive rehabilitation, cognitive behavioral therapy, cognitive training, meditation, and physical activity.⁵⁴ To our knowledge only one study has evaluated interventions (computer and group-based cognitive rehabilitation programs) for patients with cognitive problems after HSCT, which showed improvement in memory, processing speed, and subjective cognitive performance.⁵⁵ In addition, while pharmacotherapies, such as methylphenidate, modafinil, donepezil, and memantine, can be considered, they carry a degree of risk and have yet to be studied in the HSCT population. As a result of the prevalence of both pre- and post-HSCT cognitive impairment, we encourage psychiatrists to conduct routine cognitive screening with HSCT patients. Useful cognitive assessments include the Montreal Cognitive Assessment, Mini Mental Status Exam, and Repeatable Battery for the Assessment of Neuropsychological Status.⁵⁶ Early identification of at-risk patients can facilitate referral to neuropsychology for further characterization, as well as management of modifiable risk factors and involvement of caregivers to provide additional support for these at-risk patients.

Conclusions

Patients receiving HSCT experience a high prevalence of psychiatric comorbidity. To optimize identification and management of these neuropsychiatric issues, psychiatrists can familiarize themselves with the medications and treatments that these patients receive, complications that they experience, and how different phases of their treatment course present unique risk factors for disturbances in mood, anxiety, and cognition. While the prevalence and impact of these psychiatric disorders have been well described in the HSCT literature, this review underscores the ongoing need to strengthen the evidence base for the management of these disorders. Further research is needed at all levels of management: from studies focusing on individual pharmacologic treatment interventions, such as the use of neuroprotective agents for cognitive disorders, to adaptive design studies that use algorithms to guide treatment decisions for a variety of interventions. Similarly, additional studies evaluating systems-based care approaches, such as collaborative care models or proactive psychiatric consultation, will facilitate much-needed research to establish standard of care treatment of psychiatric disorders among HSCT recipients.

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Table 1:

Psychiatric complications and pharmacologic features of medications commonly used in hematopoietic stem cell transplantation^{41,42}

Medication	Exposure Period			Psychiatric Complications	Significant DDI	QT Prolongation
	Pre-transplant	Transplant hospitalization	Post-engraftment			
Antibiotics						
Fluoroquinolones (e.g. Levofloxacin, Ciprofloxacin)	x	x	x	delirium, psychosis	1A2 inhibitor	x
SMX/TMP (Bactrim)	x	x	x	anxiety, insomnia, delirium, depression, psychosis	3A4 inducer	
Antifungal agents					3A4 inhibitor	x
Fluconazole (Diflucan)	x	x	x			
Posaconazole (Noxafil)	x	x	x	1-17%: insomnia		
Voriconazole (Vfend)	x	x	x	2-12%: psychosis		
Antiviral agents						
Valacyclovir (Valtrex)	x	x	x	7%: depression		
Valganciclovir (Valcyte)		x	x	6-20%: insomnia 5%: anxiety, depression < 5%: agitation, delirium, psychosis		
Immunosuppressive agents						
Alemtuzumab (Campath)		x	x	16%: insomnia 7%: anxiety		
ATG (Thymoglobulin)		x		12-20%: insomnia 7%: anxiety		
Corticosteroids (e.g Dexamethasone, Methylprednisolone, Prednisone)	x	x	x	insomnia, depression, mania, emotional lability, personality changes		
Cyclosporine (Neoral, Gengraf)	x	x	x			x
Mycophenolate mofetil (Cellcept)	x	x	x	41-52%: insomnia 28%: anxiety 3-20%: agitation, delirium, depression, psychosis		
Tacrolimus (Prograf)		x	x	> 10%: anxiety, agitation, insomnia, delirium, depression, psychosis		x
Gastrointestinal symptom management						
D2 Antagonists (e.g Prochlorperazine, Promethazine)	x	x	x			x
Lorazepam (Ativan)	x	x	x	16%: sedation Anxiety, agitation, irritability, insomnia, mania, suicidal ideation, delirium, memory impairment, psychosis		
Ondansetron (Zofran)	x	x	x	6%: anxiety, agitation		x
Opioids	x	x	x	Serotonin syndrome (tramadol, meperidine, fentanyl)		

Medication	Exposure Period			Psychiatric Complications	Significant DDI	QT Prolongation
	Pre-transplant	Transplant hospitalization	Post-engraftment			
Chemotherapy						
Busulfan		x		84%: insomnia 72%: anxiety 23%: depression agitation, delirium, psychosis		
Carmustine		x		delirium		
Cyclophosphamide		x		< 1%: delirium		
Cytarabine		x		delirium, leukoencephalopathy		
Etoposide		x		delirium		
Fludarabine		x		1%: depression < 1%: agitation, delirium		
Methotrexate		x		delirium, memory impairment		
Thiotepa		x		< 1%: delirium, depression, psychosis		
Seizure Prophylaxis						
Levetiracetam (Keppra)		x		7-13%: anxiety, agitation, irritability, emotional lability, depersonalization 3-5%: depression 2-3%: delirium		

Abbreviations: DDI – Drug-Drug Interaction, 1A2 – cytochrome P450 1A2, 3A4 – cytochrome P450 3A4, D2 – dopamine receptor 2, SMX/TMP – sulfamethoxazole/trimethoprim

Note: The above table is not intended to be comprehensive. It includes common medications used in hematopoietic stem cell transplantation and the most likely periods patients will be exposed to them with an emphasis on relevant psychiatric side effects, significant potential for drug-drug interactions, and well-documented risk for QT prolongation.

Table 2:

Recommended evaluation and management of delirium in hematopoietic stem cell transplantation

Suggested initial diagnostic tests for common etiologies	Management	If symptoms persist or worsen
• Blood chemistries: electrolytes, glucose, albumin, blood urea nitrogen, creatinine, transaminases, bilirubin, alkaline phosphatase, magnesium, phosphorus • Complete blood count • Oxygen saturation or blood gases • Urinalysis and urine culture • Chest x-ray • Blood culture • Serum levels of immunosuppressant medications (e.g. tacrolimus, cyclosporine) • Folate, vitamin B12, vitamin D • Thyroid function tests • Peripheral venous ultrasound • Review of all medications including potential drug-drug interactions	• Treat any identified reversible etiology • Discontinue all non-essential centrally acting medications • Decrease benzodiazepines and narcotics to minimum effective dose • Evaluate for potential sleep disorders • Consider initiation of antipsychotic medication for patients with agitation or other dangerous behavioral disturbance • Consider high dose intravenous thiamine, especially in patients with weight loss or decreased oral intake • Institute environmental/supportive interventions - Open blinds every morning. - Encourage use of patient's own glasses, hearing aide, and shoes. - Encourage fluids by mouth when appropriate, keep fluids within reach - Early and frequent ambulation - Request staff assess orientation to person, time and place every morning and as needed throughout the day. - Extend visitation hours with family/friends as feasible. - Minimize disturbances at night. Turn off television when patient asleep or when not in use.	• Magnetic Resonance Imaging of the brain (to evaluate for Posterior Reversible Encephalopathy Syndrome or stroke). <i>Gadolinium may be helpful, but not necessary.</i> • Electroencephalogram (to confirm encephalopathy, rule out seizure activity) • Lumbar puncture (to evaluate for Human Herpes Virus 6, other viral or bacterial infections, or less likely paraneoplastic syndrome)

Note: Bolded items indicate aspects of delirium management more unique to hematopoietic stem cell transplantation