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Immune-Compromised Patients: Human Immunodeficiency Virus and Organ Transplantation

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The consultation-liaison psychiatrist (CL) has no greater opportunity and obligation to contribute to patient care, practitioner training, and research than in advancing the work with immune-compromised patients. This area of health care has grown enormously in the past quarter century with the global emergence of the acquired immune deficiency syndrome (AIDS) epidemic. New case numbers continue to rise in the established geography of the disease, and AIDS continues to enter areas heretofore untouched by the condition. Current projections suggest that by the year 2030, AIDS will take more lives than were lost in any of the other great plagues of humanity (UNAIDS, 2006).

In contrast to the viral assault on the immune system associated with human immunodeficiency virus (HIV) disease, the compromise of immune regulation and response associated with transplantation medicine is induced by the interventions developed by the field. Success in expanding the organ types and their posttransplant longevity has increased the number of potential beneficiaries and the population of living organ transplant recipients.

The AIDS and organ recipient patient populations will grow and increasingly reflect the clinical challenges of caring for the chronically ill. As such, the consultation psychiatrist provides expertise regarding the psychosocial aspects

of illness experience and coping, transplant candidacy and care, and health behaviors, including treatment adherence. The psychiatrist also plays a critical role in the assessment, referral, and ongoing treatment of preexisting or newly developing mental and substance use disorders. This is a special need in immune-compromised patients, given the nature of the high-risk groups with AIDS or organ failure. Psychiatric treatments are considered and provided in a behaviorally and medically complex context. In providing effective treatment of coexisting mental disorders and dysfunctional health behaviors, the consultation psychiatrist may alter quality of life, have impact on treatment decisions, and extend patient longevity.

As the scale and dimensions of mental health care for the immunocompromised patient have grown, the research field of psychoneuroimmunology has emerged. This rapidly growing area of investigation provides sound evidence that psychosocial and behavioral factors can modulate immune function (Glaser, 2005). Observation and intervention studies are advancing our understanding and creating a framework for the optimal provision of clinical evaluation and treatment of the patient with immune dysregulation.

20.1 Human Immunodeficiency Virus Patients

20.1.1 Case Vignette

J.K. is a 33-year-old man referred by his internist for psychiatric assessment after an initial medical evaluation revealed that he was infected with HIV. The patient had presented for medical evaluation, knowing that his sexual and drug use habits had significantly increased his risk of infection. Recently, he had met someone with whom he hoped to begin a new romantic relationship and was encouraged by this individual to clarify his HIV status. With the disclosure of the positive HIV test result by the internist, the young man became intensely overwrought; he seemed both surprised and exquisitely apprehensive. Summoning all the advantages of his lengthy experience working with HIV-infected patients, the physician tried to calm, reassure, and support the patient in his first response to the test results. As the patient's distress remained largely refractory to the physician's approach, the internist decided to refer the patient for psychiatric consultation.

Days later, the patient met with the consulting psychiatrist and expressed fear of a decline in his health, rejection by others, especially by his newfound friend, and a sense of terror, reflective of his having received a "deadly" diagnosis. J.K. reported experiencing shortened, restless sleep, general nervousness including waves of discouragement, and behavioral withdrawal. He admitted special difficulty refraining from drug use since his meeting with the internist. He sketched out a history of occasional days-long episodes of mild depressive symptoms that cleared without special action or intervention, but otherwise denied a significant personal or family history of psychiatric disorder.

The consultant's diagnostic impression of the episode was a subsyndromal depression or perhaps an adjustment disorder with mixed emotional features. The primary care provider was advised to continue to emphasize in subsequent appointments with the patient the elements of the medical monitoring and treatment plan and their potential positive impact on J.K.'s quality of life and longevity. It was suggested that monitoring include checks on the patient's

affect, attitude about his illness and prognosis, and screening for elements of suicidal ideation or impulse. The psychiatrist underlined the need for psychosocial screening in the event of missed medical appointments or deteriorating adherence to treatment.

The patient met twice more with the psychiatrist. In the sessions, added sources of apprehension were identified and addressed. Special emphasis was placed on effectively managing the disturbing effects of disclosure of HIV status on key relationships. Recognizing the increased risk of major depression in those with subsyndromal depression, the psychiatrist considered suggesting that the patient begin an antidepressant medication trial. However, J.K.'s dysphoria subsided and the antidepressant trial was not undertaken.

Over the next 9 months, the patient saw his internist three times, apparently content with the care he was receiving. At the third of the visits, his internist revealed that the patient's CD4 cell count had fallen below 350, raising the need to begin antiretroviral treatment. The patient became apprehensive and very dispirited with this news. The need for specific HIV treatment represented a fearful downturn and confirmation of the relentless progression of his condition. Both the patient and the practitioner agreed that further consultation with the psychiatrist was indicated.

The psychiatrist met with the patient 10 days later. By then, J.K. was despondent and apprehensive on a daily basis. He was experiencing sleep-onset difficulties, compromised energy to carry out daily activities, and considerable withdrawal from contacts with others. The patient's presentation suggested the leading edge of a probable major depressive episode. Despite some reluctance, the patient agreed to a trial of fluoxetine.

Over the next 3 months and three visits to the psychiatrist, the patient experienced a gradual improvement in mood, energy, behavior, and sleep quality. The visits provided a setting for J.K. to identify sources of pathological fear and despair and reduce their influences. During the same period, the patient and his internist were able to review and prepare for the challenges and complexities of initiating three-drug antiretroviral treatment. Over the following 6 months, J.K. managed to effectively integrate the antiretroviral protocol, the antidepressant regimen, and his response to a new phase of his illness and its treatment into his ongoing perspective and activities.

20.1.2 Psychosocial Issues and Treatment Considerations

The HIV illness experience is unique for each infected individual, yet there are common issues and themes across the various illness phases. In this subsection, we explore aspects of illness experience and response, illness narratives, and psychosocial treatment considerations relevant to the CL psychiatrist. As the meaning of illness, social support, and adaptive coping have been associated with improved psychological and physical outcomes in HIV illness (Farber et al., 2003), we look at specific interventions that address these areas.

Patients with psychiatric disorders, including personality disorder (especially borderline and antisocial personality disorders), are at higher risk of HIV infection (Perkins et al., 1993). For infected individuals, psychiatric disorder can impact the subjective experience of infection, as well as the treatment of HIV and related illness. Therefore, appropriate assessment and effective treatment of psychiatric conditions is of paramount importance. The diagnosis and

treatment of certain psychiatric disorders can be similar to that in noninfected individuals. There are also unique diagnostic and treatment considerations in the setting of HIV infection. Finally, there are unique neuropsychiatric manifestations of HIV/AIDS and related medical sequelae. We address these issues related to psychiatric and neuropsychiatric illness in a later subsection.

There are common intrapsychic and interpersonal conflicts and issues that are illness-phase specific. Some familiarity with these themes affords us a better understanding of our HIV-infected patients and facilitates more appropriate psychosocial treatment. Sensitivity to these dynamics can guide therapeutic contacts, which can provide support and be a powerful facilitator of growth and healing. In addition, during longer hospitalizations there can be a role for more structured, brief psychotherapy. Themes that are identified during this work can be further explored and addressed in subsequent outpatient psychotherapy.

20.1.2.1 New Diagnosis

Patients' responses to HIV diagnosis depend on their awareness of pretesting risk behaviors. For those unaware of their high risk, there may be disbelief or concerns that the results are inaccurate. Once a patient tests positive, there may be periods of denial and also significant anxiety related to issues of mortality, impact on life ambitions, uncertain disease course and treatment, and uncertain response from family and loved ones (including feared rejection). There may be guilt related to high-risk behaviors and feelings of shame in relation to social stigma. Patients and their loved ones can also exhibit other symptoms associated with loss, including guilt, sadness, anger, bargaining, and acceptance (Cohen, 1990).

Once diagnosed, patients must also deal with the issue of whether or not to inform friends and family. Sometimes this involves acknowledging sexual or drug-related lifestyles that were previously undisclosed. Patients should be encouraged to inform their sexual partners, current and past, once they have processed the diagnosis adequately themselves; some states require this disclosure. At the appropriate time, patients must also be counseled on safe-sex practice, to decrease their likelihood of transmitting the virus and contributing to the epidemic.

Suicidality should be evaluated. The suicide rate in patients with AIDS has been reported as 36 times that of the general population (Cohen, 1990). Patients with no history of suicidal ideation may talk of suicide when they are overwhelmed and trying to manage feelings of despair, loss of control, helplessness, and fear of the future. The major intervention here is to help the individual manage and work through the overwhelming anxiety. As well, lowered self-esteem, impact on one's sense of identity, and alienation from friends and family can also contribute to suicidal ideation; crisis intervention, communication, and support are important here (Cohen, 1990). Patients with a preinfection history of depression, anxiety, personality disorder, and suicide attempts can be at much higher risk for suicide and need to be managed appropriately (Sheridan and Sheridan, 1988).

20.1.2.2 Early Illness

After being diagnosed, patients struggle to integrate the diagnosis and its treatment into their life. Here it becomes important to explore the meaning of illness, including illness-related fears. Fears of unknown illness and treatment, lack of cure, and the possibility of premature death can lead to significant anxiety (Cohen, 1990). Complexes related to earlier interpersonal loss can become

constellated, especially when these losses have not been adequately worked through. There can be significant anxiety and anticipatory mourning regarding the potential impact of HIV infection on previously held ambitions. It is important to create a safe space for these painful feelings to be expressed, both allowing for mourning and providing hope.

Patients also often struggle with larger existential questions such as, “Why did this happen to me?” Even in the time-limited setting of consultation psychiatry, it can be invaluable to create a safe space to begin gentle exploration and engagement with these questions. If the consultant is not comfortable with transpersonal and existential themes, and if it seems appropriate, pastoral, spiritual, or religious support can be recruited.

Patients often have misconceptions regarding HIV infection and treatment. Many are unaware that modern antiretroviral treatment has transformed HIV infection from a death sentence to a chronic illness. It can be important to provide education regarding this aspect, or to facilitate the exchange of this information via the primary team and hospital educational resources.

The psychiatric consultant can also encourage the patient to seek out community resources and support groups. The Internet can be invaluable for locating phone numbers and other information. It is important to be aware of medical clinics or providers in the community who specialize in work with HIV-positive individuals. Social work can often assist with educating the patient and making referrals to resources that can help with insurance issues, legal aid, and other HIV-related services.

20.1.2.3 Chronic Illness

There are other common themes that may need to be explored and addressed when relevant, such as dealing with social stigma and the interpersonal response to the patients’ infection, the need for chronic medical care and medical morbidities, the worsening of medical condition when it occurs, AIDS-related cognitive changes, and processing the impact of HIV/AIDS on educational and vocational pursuits. For some of these issues it becomes important to draw from grief work and both mourn the loss as well as facilitate and co-construct new meanings and life goals with the patient. In addition to these themes, HIV-related symptom onset and an increase in symptoms can be key triggers for hopelessness and demoralization, which need to be addressed.

20.1.2.4 Terminal Illness

There is significant existential anxiety around death in American culture, which often leads to avoidance in caregivers who are uncomfortable with emotional engagement with the dying patient. At the time that the patient needs human contact the most, the opposite often happens. This can be especially true in busy public hospital settings, with indigent and often homeless populations who have limited, if any social network. When these networks exist, even if in the form of case managers, they should be recruited and attended to. When these networks do not exist, the psychiatric consultant is often the primary source of human contact (in teaching hospitals, medical students can be valuable allies). It is critical to engage with the dying patient in a sincere and compassionate way. The consultant can work with the primary team in addressing treatable issues, such as poorly managed pain. The consultant can help facilitate communication with relationships that have been strained or broken. Patients often need help in

deciding which people they wish to contact, in deciding what needs to be expressed, and in making these connections.

Exploring patients' spiritual beliefs can be crucial, especially their perspectives on the afterlife. For patients with significant guilt, forgiveness and self-compassion work can also be crucial to facilitate a less tormented and anxious passing. For spiritually inclined patients, culturally syntonetic rituals can be co-constructed and engaged in. Appropriate spiritual bibliotherapy can be carefully integrated in some instances; for patients who identify with specific religious belief systems, relevant texts can be requested or spiritual figures can be incorporated into the care. Finally, when a patient dies, consultants must tend to their own emotional responses. Ideally, the consultant has engaged with this inevitable existential reality beforehand. It is important to take time, even in the busy workday, to mourn the loss of a patient, to find ways to take care of one's own grief response, and to find ways to restore one's own energy and then move forward (Sheridan and Sheridan, 1988).

20.1.2.5 Special Issues

20.1.2.5.1 Adherence to Antiretroviral Treatment: Compliance with highly active antiretroviral therapy (HAART) can be challenging, even for patients without significant psychological distress. Often patients are taking multiple medications, some of which have multiple dosing times each day. Therefore, the complicated dosing regimens often have impact on patients' other daily activities. In addition, HAART often has significant side effects that can be distressing and have other psychosocial impact. For some patients, the medications are a constant reminder that they have a disease. There can also be anxiety that people will find out and discriminate against them if the medications are seen, which can also negatively impact medication compliance. Thus, compliance with HAART requires a serious commitment from even the most well-compensated patient.

Major depression can further reduce adherence (Singh et al., 1996). Depressed patients often have decreased interest in self-care and may ignore medical symptoms and problems. They may be too withdrawn to present for care and medical follow-up. Depression can interfere with problem solving, which is important to negotiate complex medication regimens and approach issues such as medication side effects. With a sense of hopelessness and negative thinking, some patients may doubt the potential benefits of treatment. In HIV-positive patients with depressed mood, Safren et al. (2001) found that a single-session that targeted the rehearsal of adherence-related behaviors led to enhanced HAART compliance. In addition to interventions that specifically address medication nonadherence, it becomes crucial to treat major depression

20.1.2.5.2 The Role of Spirituality: Spirituality is a potentially important component and dimension at every level and phase of care. Studies have looked at spirituality and religiosity in the setting of HIV infection. Nelson et al. (2002) studied 162 patients with terminal illness, 78 patients of whom had terminal AIDS, and assessed spirituality, religiosity, and depression in these patients. There was a strong negative association between spiritual well-being and depression (i.e., higher spirituality was associated with lower depression), especially on the existential subscale that looked at meaning and depression. The authors recommended existential or spirituality-based interventions for terminally ill individuals with HIV.

20.1.2.6 *Illness Narratives*

“Narrative is a fundamental human way of giving meaning to experience. In both telling and interpreting experiences, narrative mediates between an inner world of thought-feeling and an outer world of observable actions and states of affairs” (Garro and Mattingly, 2000, p. 1). Telling stories enables patients to represent and understand their experience, and to expand and reshape their concepts and values, creating a personal narrative that is more cohesive, enriching, and meaningful. These revised stories create new understandings of self and others that can reshape one’s experience of the past, present, and anticipated future.

In telling stories, certain parts are left out because of attentional biases. As a person’s story is explored, neglected and forgotten aspects as well as new perspectives and lines of inquiry can allow for new stories to be created. “Patient and doctor together reconstruct the meaning of events in a shared mythopoesis . . . Once things fall into place; once experience and interpretation appear to coincide, once the patient has a coherent ‘explanation’ which leaves him no longer feeling the victim of the inexplicable and the uncontrollable, the symptoms are, usually, exorcised” (Eisenberg, 1981).

Farber et al. (2000) looked at resilience factors associated with adaptation to HIV disease, focusing on the construct of “hardiness”. They describe hardiness as having three dimensions: (1) commitment, which relates to one’s sense of meaningful and purposeful engagement with life; (2) challenge, which relates to one’s sense that change is fundamental and can allow for growth, and (3) control, which is the sense that one can influence one’s life course as it unfolds. In their study of 200 patients with symptomatic HIV, they demonstrated that high hardiness was associated with lower psychological distress, higher perceived quality of life in physical health, good mental health and overall functioning domains, and more positive personal beliefs.

In a subsequent study, Farber et al. (2003) looked at 203 symptomatic patients with HIV and AIDS, measuring the meaning of the illness, problem-focused coping, social support, psychological well-being, and depressed mood. Positive meaning was associated with a higher level of psychological well-being and a lower level of depressed mood. This contribution of positive meaning of illness was over and above the contributions of problem-focused coping and social support. The authors suggest the use of psychotherapy that supports problem-focused coping when appropriate, but also pays attention to HIV-related meaning, which can help decrease distress and increase psychological well-being. Therapy interventions that focus on meaning and purpose and on the articulation of meaning and purpose may reduce distress, facilitate coping, and increase positive adaptation.

20.1.3 Psychosocial Treatments Relevant to Consultation-Liaison Psychiatry

20.1.3.1 *Narrative Therapy*

Much of psychotherapy in general can be considered a form of narrative work, whether this is schema-focused work in cognitive-behavioral traditions or an implicit orientation guiding approaches such as Jungian psychoanalysis.

Narrative therapy is characterized by telling one’s story; examining the roots of that story; seeking aspects of that story previously overlooked; exploring how incorporating new aspects of the story changes the meaning attributed to different events; anticipating

how self-image, priorities, and relationships change as a result of the new meanings; and finding an appreciative audience for the new growth. . . . Engaging in telling the story desensitizes patients to threatening cues that trigger anxiety, decreasing fear and avoidant behavior. . . . While retelling provides some comfort and momentary relief, the story must change in order to add therapeutic advantage. [Petersen et al., 2005]

Appraisals are labeling of experience that shape emotional and behavioral response. Positive reappraisal results in assigning new meaning to the event and integrating confusing aspects into a coherent conceptualization, which can then lead to emotional and cognitive resolution (Petersen et al., 2005).

This co-creation of a more adaptive and meaningful narrative can be engaged via questioning in a way that promotes contemplation of potential growth or lessons learned through the illness process. The idea of transformative suffering can be brought up, including the Jungian concept of the “wounded healer.” Sometimes amplification can be attempted with fairy-tales and myths, for example, the mythological tale of Chiron, who drew his strength from a poisoned arrow inflicted upon him by Zeus. Patients can find it interesting and useful to hear that in shamanic cultures, the healer often gained their power through an encounter with severe suffering. These myths can provide cognitive models that can shape the appraisal of illness experience in more adaptive ways. The important skill or art is to not disavow the pain or suffering as well, as this can be an important part of the grieving and mourning process. If these feelings are prematurely or superficially dealt with, they often return in a variety of ways including delayed grief reactions, projections, or psychosomatic responses. As Edwards (1993) states,

Countertransference from our own fear or pain may prompt us to get ahead of the patient by focusing on empowerment or hardiness. Anger and sorrow must be expressed and relieved before natural restitutive urges appear. There is a natural rhythm to grieving. . . . After patients have expressed and worked through their intense diagnosis-related feelings, they are often intrigued and mobilized by the suggestion that, although they cannot change the fact that they are HIV-positive, they do have control over their response to the disease.

20.1.3.2 Addressing Relational Deficits and Conflicts

The lack of perceived social support is associated with low self-esteem, depression, and poor quality of life (Safren et al., 2002). It is therefore important to explore and address this issue when possible. The consulting psychiatric team can provide an important relationship. Supportive visits can be very powerful, even when there are constraints on provider time, as long as one conveys to patients that they are cared for and are being listened to. It is also important to assess for community relationships—friends, family members, and case managers—that can be integrated in patient care. Sometimes problem solving or work targeting suspended or damaged relationships can be helpful (and followed through in subsequent outpatient psychotherapy). The consulting psychiatrist can attempt to arrange family meetings. Sometimes it is possible to involve families even after many years of separation. “The support from family and loved ones can make the difference between dying with despair and dying with dignity and love. The fact that this does not always work is never a reason not to try” (Cohen, 1990). Depending on the patient’s unique needs, referrals can be made to outpatient mental health programs, to individual psychotherapy or counseling, to religious or spiritual groups, to 12-step groups, or to HIV-specific resources—all which can provide relationship.

20.1.3.3 Adaptive Coping Techniques

Coping refers to mechanisms that regulate distress, and there are three categories described (Clarke et al., 2002): problem-focused (e.g., information-seeking, problem-solving, direct action), emotion-focused (e.g., escape and avoidance, seeking social support, cognitive reframing), and meaning-focused. Active and adaptive coping styles are associated with improved outcomes, including decreased depression (Safren et al., 2002). Thus, it is important for the psychiatric consultant to evaluate the patient's coping repertoire, expanding it when needed. Important work that addresses coping skills can be initiated even in time-limited consultations. The patient can further develop this after discharge, sometimes with the support of community resources (meditation centers, stress management groups) or in individual psychotherapy.

It is first helpful to question patients about what has helped them cope with difficulty in the past, including prior experience with mindfulness and relaxation exercises. Often, exploration of approaches appraised as "not helpful" reveal that they were not tried sufficiently or that normal responses (e.g., the mind wandering repeatedly during meditation) were labeled as signs of ineffectiveness or failure. Here it can be useful to provide corrective information, since that particular technique may be valuable to revisit.

Some specific approaches that can be powerful include mindfulness and acceptance-based work. Mindfulness is a form of practice that cultivates a gentle attention in the present and looks at arising thoughts and sensations as fleeting events in the mind to be neither attached to nor averse to, but to simply "be with" as they rise and fall. There is a substantial literature on the use of mindfulness in a spectrum of conditions, including anxiety, depression, chronic pain, borderline personality disorder, and psychosis. Acceptance-based work has various shades, including cultivating self-acceptance, as well as acceptance of one's experience in the moment. Basic exercises utilizing these approaches are not difficult to learn, but to be most effectively utilized they require additional training and personal practice by the provider.

There are other relaxation techniques, different from mindfulness, that can be taught in single sessions and assigned as "homework" between sessions. This often shifts the locus of control onto the patients and strengthens their sense of agency, which can be crucial for patients who are struggling with bodies and medical courses that may seem out of control. Some relaxation techniques include deep, diaphragmatic breathing; visualization and guided imagery exercises; the use of relaxing music or ambient sounds; and yoga or other physical movement.

Having patients list their concerns and needs can help break down large, overwhelming problem areas into more manageable parts. Utilizing written cognitive-behavioral therapy handouts on problem solving can be something concrete that allows goals to be broken down into a series of steps, sometimes with pros and cons for branch points. This can also provide patients more active involvement in breaking through overwhelming states. Sometimes patients need the gentle and active coaching style encouraged in cognitive-behavioral approaches, even when one is also simultaneously attending to deeper psychodynamic conflicts and themes, or to transference projections and even dream material.

Finally music and expressive arts modalities can be effective. Nonverbal communication and expression can provide access and enable processing of material that is otherwise threatening and defended against. It is also a way to give shape

to and digest as of yet unformulated emotion and psychic material. As Aldridge (1993) states, "By painting, singing, dancing, acting or making music together we can bring the emotion of suffering into the world in concrete form. Suffering made external as expression and brought into form as art gives the individual the chance to grapple with the meaning of that suffering and thereby to bring about change." Artistic involvement can also provide refuge, and a place where creativity and play are nourished.

20.1.3.4 Brief Psychotherapy and Additional Considerations

We often have a limited number of sessions available with our patients, especially in this age of managed care, which pushes for short hospital stays. Despite this, patients are sometimes hospitalized for longer time periods, in which case more formal brief psychotherapies can be attempted. The narrative approaches we've discussed can be expanded into these longer courses. There are also brief psychodynamic, interpersonal, and cognitive-behavioral approaches that can be helpful and that often explore and address previously mentioned themes. If there are specific psychiatric disorders, one can utilize evidence-based psychotherapeutic approaches. Sometimes grief work can be engaged. Some patients with HIV have significant punishment beliefs for which techniques such as positive affirmations or cognitive restructuring can be attempted. If there are particular skill deficits, skill-building work can be attempted (for example, the skills utilized in dialectical behavior therapy for borderline personality disorder, including distress tolerance, interpersonal effectiveness, and mindfulness skills). Antiretroviral medication adherence issues can be targeted in brief therapy.

20.1.4 Specific Psychiatric Syndromes in Human Immunodeficiency Virus Patients

20.1.4.1 Mood Disorders

Depression is the most common psychiatric disorder for which HIV-positive individuals seek treatment, and there is evidence that mood disorders are more prevalent in HIV-positive individuals. In part this reflects higher rates of mood disorder in the main risk groups: intravenous drug users and homosexual men.

20.1.4.1.1 Depression: Diagnostic Considerations: Diagnosis and treatment of depression in HIV infection can be complicated by somatic symptoms shared by both disorders, including concentration and attentional difficulties, sleep disturbance, appetite disturbance, and fatigue. Comorbid substance abuse can also complicate the diagnosis. It is also imperative to differentiate demoralization and adjustment disorder from other forms of depression, as the treatment approach can be quite different, with more focus on psychotherapeutic intervention. Especially with demoralization, it becomes important to not pathologize what can be considered a normal response to intense circumstance. In addition, one must also consider unresolved grief issues, dysthymic disorder, major depression, and bipolar depression.

20.1.4.1.2 Demoralization and Adjustment Disorder: In demoralization, the patients' sadness is often specifically related to a particular event or circumstance. Sometimes this can be difficult to differentiate from major depression. Unlike in major depression, the patients often report feeling fairly normal when they are distracted from thinking about the event or circumstance causing their

distress (Angelino and Treisman, 2001) and this sadness dissipates if the event or circumstance achieves some resolution or improvement. In one HIV clinic, the distinction between depression and demoralization was explored, and approximately half of the patients with depressive complaints were felt to have major depression, whereas the other half experienced demoralization (Lyketsos et al., 1994).

At the heart of demoralization is a breakdown in coping; when these mechanisms are insufficient, distress and helplessness ensue (Clarke et al., 2002). Breakdowns in hope and meaning are also important contributors to demoralization; a breakdown in one's assumptive world, with loss of meaning, can happen in response to events such as major illness or bereavement (Clarke et al., 2002). When demoralization is due to illness, it abates as the patients' health improves; even when there is a terminal illness, demoralization improves if the physician understands their concerns and addresses them (Slavney, 1999). Demoralization may also be common in the context of addiction, when during periods of sobriety the person struggling with addiction faces losses and also from a sense of powerlessness over the drug craving (Angelino and Treisman, 2001).

An important distinction between major depression and demoralization is that the former is characterized particularly by anhedonia, whereas the latter is characterized by a subjective feeling of incompetence. "A depressed person has lost the ability to experience pleasure generally, whereas a demoralized person, while being unable to look forward with pleasant anticipation, may laugh and enjoy the present moment. The demoralized feel inhibited in action by not knowing what to do, feeling helpless and incompetent; the depressed have lost motivation and drive even when an appropriate course of action is known" (Clarke et al., 2002).

It has been argued that demoralization is a normal response under certain circumstances; though people differ in their vulnerability to it, even the most resilient have their breaking point (Slavney, 1999); others argue that this minimizes the importance of demoralization and that though it can at times be understandable, it is always abnormal (Clarke et al., 2002). Patients who are estranged from family and friends, and patients with physicians who are distant or condescending may be more vulnerable to demoralization (Slavney, 1999).

Demoralization, when diagnosed, needs to be explained and validated to both the patient and the physician as a normal response to a difficult situation. Sometimes physicians are uncomfortable with emotional distress and want the psychiatrist to recommend an antidepressant; there is a great opportunity for psychoeducation here and it should be made clear that the patients are not suffering from a psychiatric disorder (Slavney, 1999). Adjustment disorder, on the other hand, is diagnosed when marked distress that is in excess of what would be expected, given the nature of the stressor, or when significant impairment in social or occupational (academic) functioning is present. For billing purposes for demoralization syndrome, the International Classification of Diseases (ICD-9) code V71.09 ("other suspected mental condition") can be used (Slavney, 1999).

Clarke et al. (2002) describe some important therapeutic tasks in demoralization: (1) symptomatic relief of physical and mental symptoms; (2) cognitive work that includes information and reassurance, reality testing, problem solving, exploring appraisals and meanings, identifying and challenging cognitive distortions, and looking at meaning and purpose; (3) a behavioral component that links the exploration of meaning and purpose with goal setting and

scheduling of positive activities, which can assist in redeveloping a sense of mastery and control, reengagement in relationships, and enjoyment of pleasurable activities; and (4) providing an empathic understanding of patients, which reduces alienation and reinforces their value as a person.

20.1.4.1.3 Secondary Depression: This depression is secondary to medical conditions, such as medication-induced depressive symptoms and substance-induced depression. Careful history taking, physical exam, and appropriate medical workup are important to investigate these etiologies of depressive symptoms. In addition to the usual organic workup, testosterone deficiency should be considered and antiretroviral medications with potential mood effects should be assessed, for example efavirenz (Sustiva). When there is significant substance abuse, clear diagnosis can be challenging. It can be helpful to inquire about periods of sobriety and assess the presence of mood symptoms during these periods. It can also be helpful to inquire about the temporal sequence; that is, did the depressive symptoms predate the substance abuse or vice versa?

Testosterone deficiency, present in up to 50% of men with HIV, is a specific medical condition that is associated with HIV infection, which can lead to depressive symptomatology. Symptoms of hypogonadism can include depressed mood, fatigue, diminished libido, decreased appetite, and loss of body mass. Evaluation includes testing for serum testosterone (below 300 to 400 ng/d is abnormal) and treatment is testosterone. Depot testosterone (400 mg IM biweekly) has been shown to improve mood in HIV-positive men with major depression in a double-blind placebo-controlled study.

20.1.4.1.4 Mania: Diagnostic Considerations and Differential: As with manic-like states in non-HIV patients, substance-induced (e.g., psychostimulants) etiologies need to be considered, as well as medication-induced etiologies (e.g., corticosteroids). In primary mania, there is often a preexisting bipolar disorder or at least family history of a mood disorder. In secondary mania, there is less association with family history, but more association with progression of underlying HIV disease and central nervous system (CNS) involvement. The symptomatology of secondary mania is different and may include more irritability, less pressured speech, more psychomotor slowing, and more cognitive impairment (Ferrando and Wapenyi, 2002).

20.1.4.2 Mood Disorders: Treatment Considerations

20.1.4.2.1 Depression: In addition to improving general quality of life in HIV-positive individuals, treatment of clinical depression has been shown to increase health-related quality of life and increase antiretroviral adherence (Elliot et al., 2002). There is now growing data to support the pharmacologic and psychotherapeutic treatment of major depression in the setting of HIV-infection.

Tricyclic antidepressants (TCAs), such as imipramine, have been shown to be effective in HIV depression, but significant side effects lead to frequent discontinuation. Coupled with potential lethality in overdose, TCAs have become second-line agents (Ferrando and Wapenyi, 2002). Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline, and citalopram, have been shown to be effective in HIV, across HIV illness stages, in both open label and double-blind, placebo-controlled trials. They have been shown to be as effective as TCAs but with more tolerable side-effect profiles. The response rates and adverse effects do not vary as a function of CD4 count (Ferrando and

Wapenyi, 2002). There is some evidence that HIV-positive patients receiving antiretroviral treatment and SSRI treatment may be at increased risk for developing serotonin syndrome (DeSilva et al., 2001). Mirtazapine, venlafaxine, and bupropion have been studied in small, open-label trials with major depression and HIV with favorable response rates (>70%) and few adverse effects (Ferrando and Wapenyi, 2002).

For augmentation in partial response, one can consider lithium, thyroid hormone, bupropion, antipsychotic medications, or methylphenidate (Angelino and Treisman, 2001). There are open-label and placebo-controlled studies that support the use of psychostimulants in advanced HIV, demonstrating quick response and good tolerability. Caution should be exercised with substance abusers, given the abuse potential, though there are no published reports of abuse of prescription psychostimulants in HIV patients under medical supervision (Ferrando and Wapenyi, 2002).

Regarding so-called alternative or complementary treatments, St. John's wort is not recommended as it may decrease levels of protease inhibitors.

One study of psychotherapy and HIV compared interpersonal psychotherapy, cognitive-behavioral therapy, supportive therapy plus imipramine, and supportive therapy alone. Interpersonal therapy and supportive therapy plus imipramine were superior to the other treatments (Markowitz et al., 1998). Interpersonal therapy works with four themes: role transition, interpersonal deficit, interpersonal conflict, and grief/loss. When the major depression is treated, there are often other issues that can still benefit from psychotherapy.

20.1.4.2.2 Mania: Practice guidelines recommend lithium, valproic acid, or carbamazepine. Lithium has been shown to be effective in HIV-positive individuals, but it has a low therapeutic index and can be neurotoxic and poorly tolerated in HIV-positive individuals (Cruess et al., 2003). Valproic acid has been the best studied, with one study using doses up to 1750 mg/day and serum levels >50 µg/L, and another study finding efficacy at levels between 90 and 100 µg/L (Ferrando and Wapenyi, 2002). There is some in vitro evidence of increased HIV replication, but this has not been shown in vivo, including an in vivo trial that showed valproic acid does not affect viral load in patients on antiretroviral therapy (Maggi and Halman, 2001). Newer data have shown that valproic acid may ameliorate neurotoxicity associated with AIDS dementia complex (ADC) (Schifitto et al., 2006). In addition to anticonvulsants, atypical antipsychotics, including risperidone, olanzapine, and quetiapine, can be effective mood stabilizers. One needs to be mindful of potential metabolic side effects, especially with olanzapine and clozapine. Finally, benzodiazepines can be a useful short-term adjunct; there is a case report using clonazepam 2 mg po t.i.d. with success in controlling HIV-related manic symptoms (Ferrando and Wapenyi, 2002).

20.1.4.3 Anxiety Disorders

Patients at various illness phases can have significant anxiety relating to HIV infection and its sequelae. Current anxiety symptoms are present in up to 11% of HIV patients (Sewell et al., 2000). Somatic etiologies need to be considered, such as substance intoxication and withdrawal states, medication side effects [e.g., interferon, pentamidine, azidothymidine (AZT), Lamivudine (3TC)], opportunistic illness-related anxiety symptoms, and other medical conditions such as anemia, hypoxia, and various metabolic disturbances. Anxiety and agitation can frequently be seen in the setting of delirium and ADC. In addition to anxiety

secondary to somatic etiologies, the differential includes adjustment disorder with anxious features and other anxiety disorders including social phobia, generalized anxiety disorder, posttraumatic stress disorder (PTSD), panic disorder, and obsessive-compulsive disorder. There has been recent interest in PTSD in patients, resulting from illness, and in caregivers for the ill and dying, in whom PTSD is quite common. In addition to subjective distress, PTSD has been shown to negatively affect medical outcome. Special attention should be paid to evaluating illness-related PTSD symptoms.

20.1.4.3.1 Treatment Considerations: The SSRIs are first-line agents for generalized anxiety disorder, social phobia, panic disorder, obsessive-compulsive disorder, and post-traumatic stress disorder. Mirtazapine (Remeron) and venlafaxine (Effexor) are also good options. Other options include gabapentin (Neurontin) and buspirone (BuSpar), though the efficacy of the latter is questionable. Atypical antipsychotics can be considered, but they have potential metabolic side effects.

Patients often seek benzodiazepines because they provide immediate relief, but safety concerns, cognitive side effects, and abuse potential need to be addressed. For patients who request benzodiazepines but who are at high risk of negative consequences (e.g., patients with substance abuse or dependence), it is important to express an intention to treat their anxiety but also to set gentle but firm limits. For non-high-risk patients, benzodiazepines can be considered for short-term use, or as a time-limited agent to bridge the gap before the antidepressant effect has taken place. Lorazepam, oxazepam, and temazepam are the agents of choice for patients taking protease inhibitors.

Relaxation and meditation techniques can be effectively taught to patients in the hospital setting and can be powerful, nonpharmacologic anxiety-management tools. For patients with longer anticipated hospital stays, cognitive-behavioral techniques specific to their anxiety disorder can be incorporated. The advantage of these nonpharmacologic approaches is that they can allow the patient a sense of internal control, helpful in countering demoralization, and there are usually no side effects to deal with. Music can be a useful relaxation tool as well, and other expressive arts modalities should also be considered.

20.1.4.4 Psychotic Disorders

20.1.4.4.1 Diagnostic Considerations: Psychosis in HIV can have multiple etiologies including substance intoxication and withdrawal states; it also can be medication induced, opportunistic infection related, or secondary to other organic etiologies. HIV patients with delirium or dementia can have psychotic symptoms. Given the higher prevalence of antisocial personality disorder in HIV-positive populations, malingering also needs to be considered.

It is important to rule out substance-induced and organic etiologies before making a primary psychiatric diagnosis. Primary psychiatric disorders that can involve psychotic symptoms include mood disorder with psychotic features, schizoaffective disorder, schizophrenia, as well as certain personality disorders—mainly borderline-personality disorder.

20.1.4.4.2 Treatment Considerations: Patients who are HIV positive can be more susceptible to extrapyramidal side effects (EPSs) as a consequence of HIV-induced neuronal damage to the basal ganglia (Work Group on HIV/AIDS, 2000). Also, movement disorders such as acute dystonias and parkinsonism can

be seen in advanced HIV in the absence of neuroleptic treatment (Ferrando and Wapenyi, 2002). With regard to typical antipsychotics, haloperidol has been shown to be effective in HIV-positive patients with schizophrenia, but with high EPS incidence. With regard to atypical antipsychotics, both clozapine and risperidone have been shown to be safe and effective in HIV-positive patients (Lera and Zirulnik, 1999; Singh et al., 1997). Overall, atypical antipsychotics are preferable given the lower rate of EPSs.

20.1.4.5 Substance Abuse/Dependence Disorders

In substance use disorders, substance use often impairs judgment and leads to impulsivity and high-risk sexual behaviors. Certain substances such as cocaine and methamphetamine can increase sexual desire and lead to high-risk situations. In the context of intravenous drug use, the sharing of contaminated needles is a major risk factor for HIV infection. Substance abuse and dependence can increase the risk of infection and also decreases compliance with HIV treatment. Substance intoxication and withdrawal states can also complicate the diagnosis of psychiatric disorders.

20.1.4.5.1 Treatment Considerations: Treatment can be similar to that for non-HIV-positive substance abusers. Motivational enhancement techniques can be especially valuable for ambivalent patients. Patients should be informed that longevity is now possible with properly treated HIV, and which also involves treating chemical dependency. For patients who previously viewed an HIV diagnosis as a death sentence, this corrective information can partially address feelings of illness-related hopelessness and thus affect their motivation toward treatment.

The overall treatment can be seen as consisting of four steps: detoxification, rehabilitation, treatment of comorbid conditions, and relapse prevention. Referral to 12-step groups can be helpful, especially linking the patient with a sponsor. Education on safe-sex behavior (condom use) and high-risk drug behaviors (needle-sharing) to decrease the risk of spread is important. Finally, vocational rehabilitation, social rehabilitation, and the creation of a drug-free environment are essential to preventing relapse (Angelino and Treisman, 2001).

20.1.4.6 Personality Disorders

Patients with a personality disorder, especially borderline and antisocial personality disorder, are more likely to contract HIV due to impulsivity and increased high-risk behavior. Once the patient is infected, the personality disorder affects all aspects of HIV infection and its treatment. Intrapsychic issues such as the meaning of the illness, behavioral responses including coping, and interpersonal dynamics including those between patients and care providers are all affected. A thorough examination of this topic is beyond the scope of this chapter and can be found elsewhere (Singh and Ochitill, 2006).

In the hospital, the “difficult patient” is a common cause for psychiatric consultation. There are interventions that can be implemented with both patient and providers. For providers, including ward staff, it is often important to create an opportunity for angry and hostile feelings arising in providers to be voiced, minimizing the chance that they will be disowned and projected completely onto the patient. As well, it becomes important to frame the patient as a wounded individual who is both deserving of compassion and needing limits. Gentle, strict, but nonpunitive limits need to be set on inappropriate patient behavior, and sometimes formal contracts need to be constructed. There is often

room for direct skills-building work with the patient. If some relationship can be established with the patient, distress tolerance and interpersonal communication skills can be worked on. Mindfulness and stress-management techniques can be introduced to deal with distress and affective dysregulation, and thus decrease acting-out behaviors. Through chain analysis and therapeutic conversation, patient behaviors that detract from receiving deserved care can be addressed and new avenues of getting needs met can be explored.

Sometimes patients who are otherwise higher functioning can regress in hospital settings and appear personality disordered. Other times, taking a history, including consulting with collateral sources, clarifies a long-standing pattern of frank personality disorder. In this case, it is critical to make referral to psychotherapy and to consider referral to HIV specialty clinics where there is psychiatry and psychology presence. This is critical because the personality disorder will undoubtedly surface in areas of medication and treatment compliance and provider interactions, and in high-risk behaviors that may entail further spread of HIV in the community.

20.1.4.7 Cognitive Disorders: Delirium and Dementia

20.1.4.7.1 Delirium: When the HIV-positive patient presents with altered mental status, special attention should be paid to ruling out organic processes associated with HIV infection, including direct HIV infection of the CNS, opportunistic infections associated with HIV, other disorders related to HIV, as well as neuropsychiatric side effects of HIV treatment. As well, when a patient with unknown status (but high risk) has altered mental status of unclear etiology, HIV-testing should be done, as positive status necessitates additional evaluation.

Delirium is one of the most common diagnoses in HIV-positive patients evaluated by consultation psychiatry. These patients have less cognitive reserve and are more likely to develop delirium. Delirium is characterized by rapid onset of fluctuating level of consciousness, markedly poor attention, disorientation, and perceptual disturbances. This diagnosis should be suspected even in patients with preexisting psychiatric diagnoses. Practitioners often focus on more obvious phenomenon such as delusional content or hallucinations, deeming the etiology as psychiatric. Disorientation and waxing/waning consciousness are not typical of a primary psychiatric illness and should be a tipoff to delirium. There is often a significant role for the consultant in providing education to the staff regarding delirium and its medical nature, despite neuropsychiatric and behavioral phenomenon.

As with non-HIV-positive patients, the etiology is often multifactorial and the differential can include withdrawal/intoxication states, medication effects (especially anticholinergic medications, benzodiazepines, and narcotic analgesics), metabolic disturbances (e.g., hypoxia), electrolyte imbalances (hyponatremia, hypercalcemia), liver and renal failure, infection and sepsis [in HIV, one needs to consider herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and HIV encephalitis, as well as cerebral cryptococcus and toxoplasmosis], cerebral hypoperfusion (e.g., from shock and severe hypotension), postictal states, and other CNS events (e.g., ischemic and hemorrhagic stroke).

The workup should include careful gathering of the history from friends, family, case managers, and care providers in the community, to establish a better baseline and course of cognitive decline. A careful physical examination should be performed, including a detailed neurologic exam. Lab testing should be done and include evaluation of electrolytes, renal and hepatic function, syphilis

serology, vitamin B₁₂ level, and toxicology screen. Head imaging and, unless contraindicated, lumbar puncture should also be performed. Review of current medications and evaluation of recreational drugs and alcohol consumption are also important. Electroencephalogram can be helpful if epileptiform activity is suspected, and diffuse slowing is consistent with delirium.

Lumbar puncture in HIV-positive individuals is complicated by frequent nonspecific findings (e.g., mild elevations in white blood cell count, mild elevations in protein, mild decrease in glucose). Regardless, lumbar puncture can be critical for detecting treatable CNS diseases including cryptococcal, syphilitic, tuberculous, or lymphomatous meningitis. Cerebrospinal fluid polymerase chain reaction for tuberculosis, VZV, HSV, CMV, and JC (a type of human polyomavirus) virus [in progressive multifocal leukoencephalopathy (PML)] can be useful tools when available.

Regarding imaging, magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT), but CT with double-dose contrast can be a good alternative. Diffuse white-matter abnormalities can be suggestive of PML or HIV encephalitis. Periventricular contrast enhancement is sometimes seen with CMV or VZV. Focal cerebral lesions are often abscesses (e.g., toxoplasmosis) or primary CNS lymphoma.

20.1.4.7.1.1 Treatment Considerations: Attempts should be made to treat the underlying disease(s) and other potentially exacerbating factors. Pharmacologic approaches can be useful for managing the delirium, especially the use of atypical antipsychotics, which have a lower risk of EPS. Haloperidol and chlorpromazine in small doses have also been shown to be effective in HIV/AIDS delirium without much EPS (Breitbart et al., 1996). Nonpharmacologic approaches are also useful, including providing frequent reorientation; avoiding sensory overstimulation or deprivation; providing soothing music; and having friends, family members, or community providers providing contact and presence. Once the delirium has cleared, it is important to process the experience of delirium with the patient, who can often experience it as intensely frightening and sometimes as indication that they are “going crazy.”

20.1.4.7.2 AIDS Dementia Complex: Some investigators maintain that HIV-1 proliferation in the brain is needed for development of ADC, while others argue that a macrophage-initiated cascade of events leads to brain dysfunction, even when the activated macrophages are not infected with HIV. In the era of potent antiretroviral therapy, many CNS opportunistic infections have decreased. Yet the incidence of ADC in HIV-infected individuals with higher CD4 counts (200 to 350 cells/mm³) has increased, and the prevalence of HIV encephalopathy is also rising (Dore et al., 1999). For patients with ADC on effective antiretroviral regimens, it has been shown that macrophage secretions cause a dysregulation of proteins critical for regular function, but not outright neurotoxicity. Thus for patients on antiretroviral therapy ADC is typically milder and a more slowly progressing deterioration in mental functioning. Some HIV-infected individuals manifest a dementia more similar to Alzheimer disease than typical ADC, for example, demonstrating deficits in long-term memory. Some theories include the following: as patients with AIDS are living longer and aging, they may be developing Alzheimer's disease; some of the newer antiretroviral drugs might be increasing the risk of Alzheimer's disease by affecting lipid metabolism and the processing of amyloid; and chronic, low-grade brain inflammation, as occurring

in HIV-associated brain disease, might be contributing to a vulnerability to Alzheimer's disease. Patients now need to be evaluated for cortical dysfunction as well as the subcortical dysfunction of more classical ADC.

Early manifestations of ADC include (1) cognitive dysfunction, including forgetfulness, slowing, impaired concentration and attention, sequencing problems; (2) behavioral issues, including withdrawal and disinhibition; and (3) motor dysfunction, including slowing, unsteady gait, weakness, and poor coordination. Later manifestations can include (1) cognitive dysfunction including memory loss, word-finding problems, poor attention/concentration, and impaired judgment; (2) behavioral issues including withdrawal, apathy, irritability, agitation, and disinhibition; (3) psychiatric issues including mania, depression, and psychosis; and (4) motor dysfunction, including slowing, spasticity, paraplegia, and incontinence.

The AIDS dementia complex needs to be differentiated from delirium, which can sometimes be difficult in the acute setting. Collateral history can be helpful in this regard, as delirium has an acute or subacute onset, whereas ADC has a more gradual decline. Of course, the two conditions can often be comorbid. Thus, when a patient with ADC develops an acute worsening in mental status, a delirium workup should proceed.

20.1.4.7.2.1 Treatment Considerations: Highly active antiretroviral therapy can lead to significant improvement in AIDS-related cognitive deficits and AIDS dementia, provided the particular agent has good CNS penetrations. Case reports have described the use of risperidone (up to 6 mg/day) and clozapine in psychosis associated with HIV dementia with significant improvement in symptoms and low EPS (Dettling et al., 1998; Zilakis et al., 1998). Behavioral and nonpharmacologic approaches should also be integrated (see Chapter 7).

20.1.5 Drug Interaction Issues in Psychopharmacologic Treatment

Drug interactions are an important consideration and one needs to have an index of suspicion and investigate potential interactions prior to initiating psychotropic treatment (Ferrando and Wapenyi, 2002). An increase in plasma concentration does not always translate into clinical significance; it depends primarily on the therapeutic index of the drug involved (Ferrando and Wapenyi, 2002). Most documented interactions involve ritonavir, a potent inhibitor of the cytochrome P-450 IIIA enzyme (Ferrando and Wapenyi, 2002). Ritonavir causes a 145% increase in the area under the plasma concentration curve (AUC) of desipramine, so dose reduction and plasma level monitoring is recommended. Bupropion was listed as contraindicated with ritonavir, but this has been removed since it is metabolized by the 2B6 isoform, and is not significantly affected by ritonavir. Clozapine, pimozide, and several benzodiazepines (clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, and zolpidem) are listed as contraindicated since ritonavir presumptively raises their serum levels. One study did show insignificant effects with zolpidem, so this contraindication is questionable. Methadone levels may be decreased by rifampin (used for TB treatment) and also the antiretrovirals ritonavir, nevirapine, and possibly efavirenz. It is advisable to follow serum methadone levels before and after initiation of HAART (Ferrando and Wapenyi, 2002). Sildenafil levels may be raised by concurrent administration of ritonavir, saquinavir, and indinavir, resulting in potentially dangerous cardiac side effects. Despite the need to be cautious, there

have been few serious drug interactions documented, and it is important to provide treatment when needed (Ferrando and Wapenyi, 2002).

20.2 Organ Transplantation Patients

20.2.1 Unique Psychosocial Issues and Treatment Considerations

While HIV is an unanticipated “acquired” condition, transplantation-related immunodeficiency is often a long contemplated, desired, and required condition for survival. The field of transplantation is based on the ability to adequately suppress a transplant recipient’s immune system to allow tolerance of the graft, ensuring function, while minimizing infectious risk.

Since first attempted in the 1950s, transplantation has become a more common treatment and accepted by the public. Discussion of transplant candidacy and issues such as adherence to medication are beyond the scope of this chapter, but are well described in the literature (Chisholm, 2002; Levenson and Olbrisch, 1993; Olbrisch and Levenson, 1995). The focus of this section is on general characteristics of transplant recipients of all organ systems. Balanced information is presented to allow practitioners who have not previously treated transplant recipients to approach them with a sense of confidence that they can evaluate and initiate appropriate treatment plans.

A tenuous state of pharmacologically controlled immune function is required for survival among solid organ transplant recipients. This delicate balance requires ongoing vigilance of the recipient and health care team for warning signs of rejection and infection, which are primary threats to survival. Strict adherence to medications, diet, and self-surveillance are a way of life among those who adjust well, while constant depression and anxiety may plague those who are unable to adjust (Perez-San-Gregorio et al., 2005).

Improving the side effect and efficacy profile of immunosuppressive agents has been a focus of attention over the last 30 years. The numbers and types of agents available have grown as a result, but they remain limited in scope. All immunosuppressive agents are associated with potentially serious toxicity and side effects that impact short- and long-term functional ability (Hathaway et al., 2003). Table 20.1 summarizes agents, mode of action, general, and neuropsychiatric side effects that may be observed.

20.2.2 Psychiatric Comorbidities: Diagnostic Issues

Individuals who undergo transplantation are generally very ill and often exhausted by their chronic conditions; the stress and concomitant physiologic dysfunction associated with chronic organ dysfunction may be associated with adjustment, anxiety, cognitive, and mood disorders addressed in other areas of this text. Preexisting symptoms and syndromes are frequently exaggerated posttransplantation if treatment is not rendered. Willingness to accept mental health care is often challenging posttransplantation. Preoperative psychosocial assessment can have beneficial effect by alerting potential recipients of the likelihood of exaggerated symptoms posttransplantation.

20.2.3 Specific Assessment Considerations

Each individual who has undergone solid organ transplantation is unique. Those referred for psychiatric assessment and treatment are manifesting

Table 20.1 Immunosuppressive agents commonly used in transplantation with associated medical and psychiatric side effects (Trzepacz, 1991; Trzepacz, 1993a,b)

Class	Agent	Mode of action	General side-effect profile	Psychiatric side-effect profile
Corticosteroids (Cerullo, 2006; Hathaway et al., 1996; Prasad et al., 2003; Viswanathan, 1989)	Prednisone, methyl prednisolone	Antiinflammatory	Diminished signs of infection, osteoporosis, impaired glycemic control, hypertension, hyperlipidemia	Depression (especially with late-phase weaning), insomnia, cognitive decline Mania, confusion, agitation (prominent in pulse dosing for rejection)
Antimetabolites (Crawford et al., 1996)	Azathioprine	Blocks DNA synthesis	Neutropenia, increased likelihood of infection, bone marrow suppression	None noted in the literature
Calcineurin inhibitors (CNI) (Chegouchi, 2006; Ciancio et al., 2004; de Groen et al., 1987)	Cyclosporine, tacrolimus	Inhibit calcineurin phosphatase and T-cell activation	Nephrotoxicity, vulnerability to viral infection, hypertension, diabetes, hyperlipidemia	Depression, confusion, cortical blindness, quadriplegia, seizures, and coma
Purine synthesis inhibitors (Prasad et al., 2003)	Mycophenolate mofetil	Prevent B- and T-cell proliferation	Gastrointestinal cramping diarrhea, neutropenia	Distress from GI side effects
Target of rapamycin inhibitors (TORI) (Kasner et al., 2005)	Sirolimus	Inhibit interleukin-2, T-cell proliferation	Hyperlipidemia, thrombocytopenia	None noted in existing literature
Depleting antibodies	ATG (antithymocyte globulin), OKT3 (muromonab-CD3)	Deplete T or B cells that have been activated and are acutely injuring graft	Allergic reaction, fever, flushing, hypotension, aseptic meningitis, coma	Confusion, lethargy, coma

symptoms that are generally significant enough to have raised the attention of their families or transplant providers. Attention to detail of pretransplant, peri-operative, and posttransplant courses provides the necessary information to accurately diagnose and treat individuals who present for care.

There are general caveats that should guide the approach to all transplant recipients with new onset psychiatric symptoms: (1) symptoms are of an organic etiology unless (and occasionally, even if) medical evaluation is negative; (2) a full review of somatic symptoms often guides further necessary evaluation; and (3) attention to the timeline of all prescribed medications, supplements, and herbal remedies with respect to psychological symptoms often provides a clue for iatrogenic symptoms. Table 20.2 presents acute medical mimics referred for psychiatric evaluation.

Table 20.2 Psychiatric referrals, symptoms, and examples of medical mimics (C. Skotzko, personal observation)

Psychiatric symptom	Symptom delineation	Medical mimic
Depression	Fatigue, low energy, difficulty concentrating	Anemia: hemoglobin of 6 or less, severe B ₁₂ deficiency, posttransplant, lymphoproliferative disorder
Anxiety	Apprehension, inability to relax, frequent dyspnea	Sepsis, rejection (pulmonary/cardiac), pulmonary embolism
Psychosis	Hallucinations, delusions	Stroke, CMV infection, cyclosporine toxicity
Mania	Impaired sleep, motor agitation, racing thoughts, impulsive behavior	Thyrotoxicosis, rejection treated with steroid bolus, central nervous system, herpetic infection
Dementia	Forgetfulness, confusion, difficulty concentrating	Hypothyroidism, vascular insufficiency, stroke in evolution

Unlike more routine evaluations, exposure histories are essential in teasing out potential infectious etiologies for psychiatric symptoms. Inquiry regarding adherence to medications and utilization of herbal remedies should be addressed to the recipient (and support persons if available), as the complexity of treatment regimens leaves little room for error. Up-to-date medication lists are essential in determining if medications have been added by outside physicians not associated with the transplant program. Immunosuppressive toxicity and organ rejection related to suppressed immune systems are easily induced by the addition of a medication that interacts with transplant regimen.

20.2.3.1 Cognitive Disorders/Organic Brain Syndrome and Delirium

Organic brain syndrome (OBS) and delirium are common in early transplant recipients. The full range of symptoms from quiet, withdrawn states to acutely agitated psychotic states may be seen in posttransplant recipients and often serves as an “early warning sign” of impending graft dysfunction or an as-yet-undeclared infection. The effect of chronic immunosuppressive agents on cognitive decline noted posttransplantation remains unclear (Borlongan et al., 1997; Cupples and Stilley, 2005). Prior addictions may be linked to the unmasking of cognitive deficits in the posttransplant period, while pretransplant decline attributed to organ dysfunction may not remit, indicating as-yet-unrecognized dementia (Sorrell et al., 2006).

Common underlying medical illnesses associated with transplantation, including hypertension, diabetes, and hyperlipidemia, place the recipient at an increased risk for CNS small vessel ischemic disease. Stepwise progressive decline suggests small vessel disease. Sudden profound or progressive decline requires evaluation for progressive leukoencephalopathy, which has been noted with utilization of calcineurin inhibitors (Munoz et al., 2006). Additionally the potential for rare but debilitating progressive multifocal leukoencephalopathy associated with polyomavirus is a concern in the absence of other definable causes for decline (Shitrit et al., 2005).

20.2.3.2 Mood Disorders

Posttransplantation depressive disorders have been reported in the range of 17% to 40% across organ systems (Dew et al., 1996; Tanriverdi et al., 2004). Presentation of mood disorders range from subtle return to smoking or other unhealthy behaviors to pronounced indications such as mania, suicidality, or sudden nonadherence to medications or necessary followup. The degree of psychological mindedness often defines the language and symptoms noted.

Essential evaluation should include a careful review of symptoms and physical evaluation prior to ascribing a primary psychiatric etiology for the symptoms. Physicians often prematurely assume that somatizing complaints are associated with a mood disorder.

20.2.3.3 Anxiety Disorders

Anxiety symptoms are also prevalent, with rates ranging from 14% to 40% (Dew et al., 1996; Limbos et al., 2000; Tanriverdi et al., 2004). Acute presentation of anxiety symptoms may herald an imminent life-threatening illness, and the potential for acute physiologic decompensation needs to be considered. Despite the conviction of many physicians, it is unusual for a panic disorder to develop late in life. Thus, new-onset anxiety should be viewed as of primary organic etiology until proven otherwise. Substance abuse and withdrawal may contribute to anxiety states. Posttraumatic stress disorder secondary to medical illness and treatment has been recently appreciated, and needs to be considered and treated appropriately.

20.2.3.4 Psychotic Disorders

Transplant centers rarely accept individuals with a known history of schizophrenia or schizoaffective disorder. As such, the number of recipients with these illnesses is small. New-onset psychotic disorders are usually of organic etiology (Chegounchi et al., 2006; Hotson and Enzmann, 1988; Southworth and Dunlap, 2000). Central nervous system infection, drug toxicity, systemic infections, and delirium may present with hallucinations, paranoid delusions, disorganized behavior, and thought disorder.

20.2.3.5 Substance Abuse/Dependence Disorders

Resumption of prior addictions needs to be considered in evaluating new-onset cognitive, mood, anxiety, or psychotic illnesses, especially when substances were utilized in the pretransplant period. The extent of substance use is important and should be clarified. Chronic pain and neuropathic sequelae of illnesses such as diabetes and zoster require coordinated management to optimize quality of life and ensure controlled use of substances of abuse.

Return to alcohol consumption has been studied extensively in the liver transplant population (Beresford et al., 2004; DiMartini et al., 2002, 2006; Kelly et al., 2006). Noted predictors of resumption are diagnosis of mental illness, lack of insight into substance problem, lack of a stable partner, daily quantity consumed in years prior to transplant assessment, active substance use at time of evaluation, and prior alcohol rehabilitation (Bellamy et al., 2001; DiMartini et al., 2006; Kelly et al., 2006). Resumption of disordered alcohol consumption increases the risk for nonadherence to medications and inattention to self-surveillance, which may have devastating consequences.

Of equal importance, although less frequently addressed, is return to nicotine dependence. Recidivism is common posttransplantation, which can negatively

affect graft function and place individuals at higher risk for infection (DiMartini et al., 2005; Mehra et al., 2005).

Currently limited numbers of individuals are transplanted while participating in methadone maintenance treatment (MMT) (Koch and Banys, 2001, 2002). Opiate abuse recidivism appears to be low, with variable reports of survival (Kanchana et al., 2002; Liu et al., 2003). Recently released data of MMT recipients of liver transplant are troubling, as survival and infection rates appear appreciably worse (Weinrieb et al., 2004).

20.2.4 Approaches to Treatment

The adage “start low, go slow, and be aware of side effects” is appropriately applied in transplant recipients. Symptom identification and treatment are the primary goals of evaluation. An inclusive biopsychosocial approach facilitates appropriate diagnosis and treatment planning.

Considering side-effect profiles benefits treatment tolerability. Use of an activating agent is imprudent in an agitated depression, while a sedating agent would be ill advised in someone who is unable to get out of bed or attend to activities of daily living. Collaborative planning with a transplant pharmacist is beneficial in establishing a treatment regimen. There are potential drug–drug interactions, competition for cytochrome system in excretion, and the need for appropriate drug level surveillance in using some of the newer antidepressant agents (Vella and Sayegh, 1998). In general, newer psychotropics should be used with special caution in transplant recipients.

The recovery and return to function in familial, community, and employment environments simultaneously present the potential for added complications. The recipient’s support system can be severely challenged by the procedure and recuperative period. The role adjustment for patients and those around them can generate significant distress for all.

With an already complex medication regimen to follow, patients may be more open to psychosocial interventions for mood and anxiety symptoms. Psychotherapeutic interventions to treat posttransplant recipients have demonstrated promise (Baines et al., 2004; Gross et al., 2004; Kreitzer et al., 2005; Lisson et al., 2005; Rodriguez et al., 2005; Wallace et al., 2004). Individual and group psychotherapies provide an environment for recipients and their support persons to address the challenges that they face in the future.

The solid organ transplantation field strongly requires assessment studies that accurately evaluate the impact of psychosocial factors present prior to on a variety of outcomes. Despite the obvious need for psychiatric involvement, psychiatrist participation has declined (Levenson and Olbrisch, 1993). One consequence of the decline in specialist transplant psychiatrists will be increasing numbers of transplant recipients seeking care in general psychiatry practices, generating greater need for the kind of overview presented herein.

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