

## Mini-review

# Mismanaging the gift of life: noncompliance in the context of adult stem cell transplantation

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### Summary:

**In this paper, we address the issue of noncompliance with medical regimens in adult stem cell transplant patients. We review the definition, prevalence, and consequences of noncompliance and address whether or not we should alter our medical decision-making with regard to stem cell transplantation based on patient noncompliance. We discuss how the health care team should handle noncompliance issues and propose clinical guidelines for stem cell transplant programs to consider regarding evaluation and management of medical compliance.**

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### Overview of noncompliance

#### Definition

The most quoted definition of compliance is probably that of Haynes *et al.*<sup>1</sup> ‘the extent to which a person’s behavior (in terms of medication, following diets, or executing life-style changes) coincides with medical or health advice’. This useful definition encompasses both the range of possible patient behaviors, as well as the degree to which a patient is compliant. Medical regimens include a variety of behaviors, such as taking medication, attending clinical appointments, following exercise and diet plans, abstaining from or limiting substance use, and engaging in preventive health behaviors. Thus, ‘noncompliance is the degree to which behavior fails to coincide with medical recommendations in each of these areas’.<sup>2</sup> Compliance can be complete or partial, erratic or patterned.<sup>3</sup> Noncompliance is usually inadvertent, but can be intentional. Because of the range and number of health behaviors asked of patients, in most cases a patient cannot be described globally as non-compliant. Thus, health professionals should distinguish between compliers, partial compliers, and noncompliers, and not assume that patients who are noncompliant with one aspect of the regimen will be noncompliant in others.

#### Prevalence

Although rates of patient noncompliance are highly variable because of difficulties in assessing compliance and defining adequate compliance, noncompliance with general medical regimens is common, ranging from 20 to 82%.<sup>4</sup> Noncompliance rates for heart, liver, and kidney transplant patients are also frequent, ranging from 20 to 50%.<sup>5</sup> Specifically, reports indicate post-operative immunoprophylaxis noncompliance from 3 to 36%, appointment non-compliance after transplantation between 3 and 79%, and noncompliance with post-operative smoking cessation 10–50%, depending upon type of transplant, time since the transplant, and how noncompliance was assessed. The prevalence of noncompliance post SCT, however, is unknown, and should be a priority for future research. One might expect noncompliance rates for SOT recipients to be lower than the general medical population given the ‘higher stakes’ involved. On the other hand, the treatment regimens

The ultimate success of a medical therapy is dependent upon patients’ ability and willingness to engage in and maintain certain health behaviors. Noncompliance with medical regimens can result in increased morbidity, mortality, unnecessary healthcare costs, and ultimately, loss of life. Given the advances of stem cell transplantation (SCT), now used successfully to treat a variety of once fatal diseases, very little attention has focused on factors that may maintain or maximize the life that is prolonged by this procedure. We are aware of no published studies that describe the compliance behaviors of adult SCT recipients. In this paper we review the definition, prevalence, and consequences of noncompliance and extrapolate from the general medical and solid organ transplantation (SOT) literatures, how these data could relate to post-SCT outcomes. We then pose two key questions. First, should we alter our medical decision-making based on patient noncompliance? Second, how should the health care team handle noncompliance issues? In conclusion, we propose clinical guidelines for SCT programs to consider regarding evaluation and management of medical compliance.

are more toxic and disruptive of routine activities of living and necessitate a substantially greater commitment to weather the rigors of therapy, making compliance more difficult. The degree to which these competing considerations influence behavior may vary from patient to patient. As yet, an a priori prediction remains unclear and needs to be tested empirically.

### Consequences

The impact of noncompliance is far reaching and includes elevated rates of morbidity and mortality, increased use of medical and economic resources, and may cause clinicians to misinterpret the response to a given medical regimen. Schweizer *et al*<sup>6</sup> found that for those who were noncompliant with medication regimens, 91% of kidney patients, 66% of liver patients, and 50% of heart patients, died or lost their graft. Fifty-seven percent of appointment noncompliant renal transplant patients experienced one or more late acute rejection episodes compared to 2% of compliant patients.<sup>7</sup> For health behaviors, dramatically different survival rates among post-heart transplant smokers *vs* non-smokers were found at both 5 (36% *vs* 76%) and 10 years (22% *vs* 70%).<sup>5</sup> Such morbidity is accompanied by increased economic costs related to additional diagnostic tests and treatments, and results in loss of physical functioning and ability to work. Bunzel and Laederach-Hofmann<sup>8</sup> observed that the 'Royal Pharmaceutical Society of Great Britain noted that health costs could be cut by 30% or more if noncompliance was considerably reduced'. Studies suggest it costs more than \$180 billion a year to treat complications of medication errors made by patients in the United States alone.<sup>9</sup>

Medical practitioners who are unaware of compliance problems may incorrectly ascribe poor therapeutic outcomes to inadequacies in the regimen,<sup>10</sup> and then possibly prescribe more potent medicines with the potential for greater adverse reactions. In a similar vein, the intra- and inter-individual differences in drug absorption that are often reported in ambulatory drug trials, may be in part due to variability in compliance.<sup>11</sup>

### Should we alter medical decisions based on compliance information?

Given the serious consequences of noncompliance, it is not surprising that it is a major consideration in determining eligibility for solid organ transplantation. Medical compliance, psychiatric status, and history of substance use are the psychosocial areas that most often constitute the focus for decision making pre-SOT.<sup>12</sup> Forty-three percent of kidney, 62% of cardiac, and 73% of liver transplant programs surveyed viewed medication noncompliance as an absolute *vs* relative contraindication to transplantation (Table 1).<sup>13</sup>

Should stem cell transplant programs follow suit? Although we can assume that the potential health and economic consequences of noncompliance after SCT are also severe, there are several issues that are fundamentally different from SOT. First and foremost, there are no published data on the incidence, predictors, and consequences of non-

compliance in adult SCT patients, nor on the predictive value of pre-transplant compliance in determining post-transplant behavior. Second, the substantial shortage of organs available for SOT necessitates that some potential recipients be denied transplantation whereas provision of stem cells to one individual does not deny it to another. Third, SOT requires that patients engage in lifelong immunoprophylaxis to prevent rejection of the organ while SCT patients usually only need immunosuppressants in the first 6 months post transplant. Finally, there is little consensus within the medical community as to which post-SCT behaviors are critical for continued health, as well as what constitutes adequate compliance with those behaviors.

There is considerable variation among SOT programs in terms of absolute contraindications for transplantation, even with respect to behaviors known to significantly impact outcomes (see Table 1). For example, 96% of lung and 76% of heart transplant programs, but only 8% of kidney and 20 % of liver programs,<sup>13</sup> surveyed viewed current cigarette smoking as an absolute contraindication to transplantation. These figures suggest that the impact of certain health behaviors may be different depending upon the medical condition or type of transplant (although it is unclear from the data if this reflects actual differences in medical outcomes or simply differences in the issues that have been studied across transplant types). In order to understand non-compliance in the SCT patient population, it is critical to identify which behaviors are most relevant to maintaining post-SCT health (eg abstinence from tobacco and marijuana, wearing a mask in public, reduction of sun exposure). Of equal importance, the correlates of compliance, the impact of compliance on therapeutic outcomes, and the interventions that effectively increase compliance all need to be determined.

Given the noted void in the SCT compliance literature, we believe that a decision to deny a candidate SCT based on noncompliance behaviors alone is premature. However, the data available from the SOT and general medical literatures can guide us in the identification of general non-compliance risk factors and the incorporation of appropriate assessments and interventions into the clinical care of SCT patients, until such time that we have information specific to SCT.

### How should the health care team handle noncompliance?

#### *Take a patient-centered approach*

Understandably, practitioners can become frustrated with noncompliant patients and perceive them as 'difficult' or 'ungrateful'. It may be helpful to remember that patient noncompliance is usually not intentional. A certain degree of noncompliance may be inevitable given the complexity of post-transplant medical regimens, and all patients, including health care professionals, are susceptible to 'irrational' health behaviors at times.<sup>14</sup> Developing a better understanding of noncompliance and recognizing the patient as a partner in decision-making, rather than as a passive recipient of prescriptive advice, should improve

**Table 1** Percent of US solid organ transplant programs surveyed for which the listed items are absolute contraindications for transplantation

Contraindications	Type of transplant program			
	Kidney %	Liver %	Cardiac %	Lung %
Medication noncompliance	43	73	62	37
Dietary noncompliance	13	0.0	12	19
AMA hospital discharge Hx	8	17	35	27
Current cigarette smoking	8	20	77	96
Current heavy ETOH use	55	94	88	85
ETOH abuse in 6 months	15	54	28	35
Current illicit drug use	27	54	55	50
Marijuana use current	24	49	71	81
HIV-STD risk behaviors	17	31	43	27
No support person	4	31	22	39
Denial of illness severity	23	31	36	35

From Olbrisch, Levenson, Fischer & Kulstad (2001).<sup>13</sup>

patient compliance, as well as patient and practitioner satisfaction.<sup>15</sup>

#### Perform appropriate assessment

The easiest way to assess compliance is to ask the patient. However, how patients are asked about compliance to treatment regimens influences how compliant they appear.<sup>10,16</sup> Patients tend to tell health providers what they believe providers want to hear.<sup>3</sup> Leading or biased inquiries (eg ‘You’ve been taking your medication as directed, right?’) may contribute to this problem. As an alternative approach, providers can make a statement which allows patients to ‘save face’, followed by a question. For example, ‘Patients usually have some difficulties taking all their medications. How’s it been going for you?’ Because patient predictions of future noncompliance are significantly correlated with actual compliance levels,<sup>17</sup> one can ask a patient directly if s/he anticipates any difficulty with a prescribed regimen. For those patients who anticipate difficulties, problem solving can be offered a priori. It should be noted that assessments made by patients of their failure to take medication tend to be accurate, whereas denials of noncompliance are not.<sup>3</sup> Overall, unbiased queries regarding compliance followed by nonjudgmental discussion can provide the best information.

Several other methods have been used in assessing patient compliance. These include patient interviews, pill counts, blood and urine assays, and medication monitoring systems. Each method has specific limitations and none is totally reliable. The accuracy of pill counts in monitoring compliance is dependent on the number of doses actually ingested by the patient vs the number of doses removed from the bottle. Measurement of drug concentration in blood and urine has several limitations,<sup>3</sup> particularly with SCT patients who may have gastrointestinal absorption problems secondary to GVHD. Electronic medication monitoring systems can be extremely useful,<sup>3,18</sup> but are rather costly. However, missed appointments or questionable drug levels can be used as indicators for further compliance assessment.

#### Identify risk factors

There are several consistent and identifiable risk factors for medical noncompliance that have appeared in the general medical and SOT literatures. In addition, Dew *et al*<sup>19</sup> found a strong ‘dose effect’ in studying compliance in heart transplant patients; as the number of psychosocial risk factors accumulated, compliance problems increased exponentially. Noncompliance risk factors are included in Table 2, and include treatment- and disease-related factors, as well as factors that are patient-related.

**Table 2** Evaluation of noncompliance in SCT patients

A. Use a patient-centered approach
1. Noncompliance usually nonintentional
2. Recognize patient as partner in decision-making
B. Assess appropriately
1. Nonjudgmental query/discussion with patient
2. Observe behavior, monitor laboratory results, drug levels
3. Seek corroborative information from family members
C. Identify risk factors
1. Disease- and treatment-related
a. multiple medications
b. frequency of dosing
c. duration of treatment
d. adverse side-effects
e. severity of disease
2. Patient-related
a. age (young, old)
b. low socioeconomic status
c. lack of spouse or significant support person
d. past noncompliance (need to be careful to evaluate appropriately and determine if pre- and post-transplant regimens are similar)
e. patient belief or attitudes
f. distress
g. untreated or poorly controlled psychiatric disorder (affective or personality disorders, substance dependence/abuse)

### *Treatment- and disease-related factors*

Post-transplant regimens are complex, involving multiple medications and significant life-style changes. Increasing the number of medications, frequency of dosing, and duration of treatment all increase the likelihood of non-compliance.<sup>5,17</sup> Patients who are prescribed several medications tend to take them all at the same time and so if they miss a dose they miss all the medications.<sup>3</sup> In this way, the number of medications may not be as critical as the number of doses per day. In fact, a linear decline in compliance rates has been demonstrated with increasing number of doses per day.<sup>3,5</sup> In addition, the longer the duration of the treatment regimen, and the longer time since transplant, the less compliant patients tend to be.<sup>10,16,20</sup>

Complex medical regimens and multiple medications can make it more likely that patients will misunderstand or forget instructions, or become confused about dosing. They may be too embarrassed to ask for help especially if they have reading difficulties or have already asked for clarification in the past. Compliance may be particularly difficult to sustain with prophylactic medications since a patient experiences no symptoms of the condition being prevented and patients may not fully appreciate the reason for taking the medication. Patients may discontinue medications because of adverse side-effects, fear of addiction, and concerns about long-term consequences. These types of concerns may be particularly relevant for SCT patients whose medications are known to cause impotence, cataracts, Cushing's syndrome, moon face, acne, and hirsutism.

Severity of the disease seems to affect compliance. Patients with mild forms of disease, or those who perceive their disease to be in milder form, tend to comply less with regimens than patients with moderate and moderately severe disease.<sup>21</sup> Conversely, patients with severe or terminal disease usually comply less than the moderate group. Thus, prognosis, type of transplant, and GVHD may all be important factors in determining differential compliance rates.

### *Patient-related factors*

Age, socioeconomic status, and social environment can affect compliance. Elderly patients and those under 20 appear to be at risk.<sup>8</sup> Low socioeconomic status may be a barrier<sup>6</sup> if a patient does not have resources for transportation to clinic appointments, or to cover medication costs. Absence of social and family support can be a significant contributor to noncompliance<sup>16–18,22</sup> and may explain why the presence of a caregiver was a prognostic indicator of survival following allogeneic SCT.<sup>23</sup>

Intuitively, one would think that pretransplant compliance history would be the best indicator of post-transplant behavior, but empirical evidence from the SOT literature does not bear this out.<sup>2,12</sup> The circumstances surrounding, and requirements for, pretransplant compliance may be qualitatively different than post-transplant regimens. For example, renal patients may show a higher rate of clinic appointment compliance pretransplant because of the structured nature of dialysis as well as the natural consequences to not attending. Post-transplant regimens do

not include such externally imposed structure, and thus, noncompliance may surface for the first time. In other circumstances, such as heart transplant, a patient might feel so ill pretransplant, that compliance with lifestyle modifications (eg smoking cessation) is easy. Restoration of physical health, however, may bring feelings of invulnerability and relapse to previously poor health behaviors may occur. Patients may be more motivated to follow medical recommendations and make necessary lifestyle modifications in preparation for transplant, but become complacent or less diligent about such health-related matters months or years following transplantation.

Patient perceptions, beliefs, and attitudes play a critical role in medical compliance. These include patient beliefs about the severity of the illness, their susceptibility to the illness, the efficacy or benefits of the medication or treatment regimens, their perceptions about their role as patient, and perceived barriers to taking necessary actions.<sup>15,18,20</sup> In fact, patient perception of disease severity is associated with compliance but physician-assessed disease severity is not.<sup>10</sup>

Distress, anxiety, poorly controlled psychiatric conditions, and substance use can all affect compliance. SCT patients and families experience significant stress secondary to prognosis, demands of treatment, temporary dislocation, and financial strain. The resulting distress, no matter how 'normal', can have a considerably negative impact. Distress was found to be the strongest predictor both for medical and appointment noncompliance in renal transplant patients<sup>8</sup> and a high level anxiety was reported to be the most important predictor of noncompliance in the first year after heart transplantation.<sup>8</sup> Patients with high distress may find it difficult to assimilate information, engage in adaptive problem solving, and remember medical regimens. Not unlike treating nausea, a 'normal' adverse effect of chemotherapy, distress should be directly treated, even though it is an expected consequence of the SCT experience.

Psychiatric disturbances, distinguishable from distress, can also impair compliance. These can include affective disorders, personality disorders, and substance dependence or abuse. Post-transplant depression has been found to trigger post-transplant noncompliance.<sup>8,22</sup> Personality disorders, which by definition are characterized by maladaptive behaviors and interpersonal difficulties, may contribute to poor patient-practitioner communication and purposeful manipulation and noncompliance. The psychological, cognitive, and physical consequences of substance abuse can all be detrimental to compliance.

## **Intervene**

### *What can health providers do?*

There are a number of ways providers can positively impact patient compliance behavior (Table 3) including: (1) simplify treatment, the overall best predictor of compliance,<sup>3,5</sup> by reducing the number of medications and/or doses when possible; (2) prioritize environmental precautions and health behaviors to circumvent patients using their own logic to prioritize overwhelming lists of rec-

**Table 3** Practical interventions for noncompliance in SCT patients

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<p>A. Employ patient-centered approach</p> <ol style="list-style-type: none"> <li>1. Explain treatment plan and rationale</li> <li>2. Elicit questions</li> <li>3. Prepare patients for adverse reactions</li> <li>4. Emphasize rationale for prophylactic regimens even though no symptoms are present</li> <li>5. Provide positive feedback for adequate compliance</li> </ol> <p>B. Simplify treatment</p> <ol style="list-style-type: none"> <li>1. Limit number of medications and doses</li> <li>2. Provide dose checklist, pill box, or electronic reminder</li> <li>3. Educate patient on the use of reminder cues taking into account patient life-style</li> <li>4. Prioritize recommendations</li> <li>5. Provide consistent messages across providers</li> </ol> <p>C. Involve the patient's spouse, family, or support person</p> <p>D. Reassess compliance and presence of risk factors periodically</p> <p>E. Use allied-health providers on transplant team (social work, clinical and health psychology, psychiatry) to treat reversible risk factors</p> <ol style="list-style-type: none"> <li>1. Distress</li> <li>2. Maladaptive coping and problem solving</li> <li>3. Depression and anxiety</li> <li>4. Substance use, abuse, and dependence</li> <li>5. Practical problems (ie transportation, money for medications)</li> </ol>	<hr/> <p>ommendations; (3) suggest ways to combat forgetfulness, the most patient-cited reason for noncompliance,<sup>3,5</sup> such as pill organizers, dose checklists, electronic or watch-based reminders, post-it notes, and involvement of a spouse or friend; (4) tailor the regimen as much as possible to the lifestyle of the patient (eg daily routines, sleep schedule, etc).<sup>3</sup></p> <p>Consensus and coordination of recommendations across health providers is critical to compliance, as is continuity of care, and good patient-provider communication.<sup>15,17,18</sup> The patient-provider exchange should include assessment of the patient's understanding of the illness and treatment regimen, encouragement of questions, and positive reinforcement of good compliance. 'Inoculation' against noncompliance can be achieved through provision of clear and consistent information of what the treatment regimen is, rationales for the prescribed regimen, written materials or encouragement to take notes, and preparative warnings about possible adverse side-effects and how to reduce them. Specific information as to why consistent compliance is beneficial (eg to reduce need for future diagnostic tests, readmissions, painful medical procedures, relapse) often serves as an adequate motivator. A toll-free number for patients and family members to call with concerns or a transplant program web site with pertinent information could be useful.</p> <p>In summary, assessment of compliance and distress levels is critical to patient care and should not be ignored. Assessment and education should be ongoing, and not limited to discharge planning or to initial outpatient visits. Those at greatest risk for noncompliance, (eg patients of particular age, limited socioeconomic resources or social support, or have a history of noncompliance) should be monitored closely. Those that exhibit distress or anxiety,</p>
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substance use problems, relationship difficulties, or maladaptive coping should receive immediate psychotherapeutic services from the allied health professionals on the transplant team.

*What can allied health specialists do?*

One of the great advantages of many transplant centers is that they involve allied health professionals as part of the transplant team. This reflects recognition that the transplant experience has a profound impact on multiple dimensions of the patient and family life. Involving professionals whose expertise lies in addressing the social, psychological, and behavioral aspects of the transplant experience reduces the burden of the medical team and vastly improves patient care and health outcomes. Most health care facilities have social workers trained in helping patients obtain resources to assist with practical needs, such as transportation, housing, community-based instrumental and social support. If additional social support is needed within the treatment center, social workers and psychologists can provide counseling. Psychologists are important team members that can more fully assess barriers to compliance, help patients adopt more adaptive beliefs and attitudes, assist with coping and problem solving skills, reduce distress, treat anxiety and depression, and modify relevant health behaviors (eg smoking cessation, substance abuse treatment, exercise regimens). Psychiatrists can provide pharmacotherapy for psychiatric and affective disturbances.

**Conclusions**

Due to an absence of information, noncompliance should not be used as an absolute contraindication to SCT at this time. However, given what we know from the relevant literature, patient noncompliance post-SCT is likely to be a prevalent and 'costly' problem that must be addressed. Appropriate assessment and intervention is likely to reduce the morbidity that results from noncompliance and facilitate improved outcome.

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