WEB BASED RENAL TRANSPLANT PATIENT MEDICATION EDUCATION

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Abstract

Purpose: The aim of this study was to assess whether or not an interactive educational program about immunosuppressive medications would improve medication compliance in renal transplant recipients. The educational program chosen as the experiment intervention was an interactive, Internet based program.

Scope: This study investigated two different renal transplant populations. The first was new transplant recipients and the second was established renal transplant recipients. The inclusion criteria were broad, age greater than 18, sixth grade reading level and ability to use a computer without special assistant devices. Specific to our patient population the study modules and all materials were written in both English and Spanish.

Methods: Both study groups were randomized and followed prospectively at pre-determined intervals. Patient compliance was assessed by testing recall for both type of medication and its purpose. To avoid bias, both groups were administered the test prior to the study group receiving the educational module.

Results: Use of an interactive, internet based learning tool did not improve medication compliance as compared to usual care. Overall medication compliance was better than anticipated suggesting that participation in a research study on medication compliance stressed the importance of medication compliance and had a positive effect (Hawthorne Effect).

Word Count: 199

Key Words: Renal Transplantation, Medication Compliance, Internet, Patient Education.

Purpose:

We hypothesized that the most effective means of addressing medication non-compliance was education of the patient regarding fundamental elements of prescription drug use. We proposed to conduct two clinical studies (only the first study was performed) to demonstrate that a web enabled educational module could reduce medication errors. We identified 6 potential error types in the chain of medication use; availability, compliance, dosage (strength of tablet, # of tablets, frequency of administration), identification (non-recognition of medication by patient), prescription (errors in prescribing by physicians resulting in drug-drug interactions) and delivery (errors by pharmacists in dispensing and by nurses in administration). We proposed to study education modules on two separate patient populations. First, a newly transplanted group of patients to demonstrate the efficacy of these teaching modules when patients are beginning a new medical regimen. *Given the complexity of the medication regimen for the renal transplant population, if value is proven in this group, these HIT tools will have general use in all patients beginning new medical regimens.*

We also hypothesized that there was a value to improving medication compliance in patients who are already on established medication regimens. Therefore, we proposed to test our educational modules on patients with established kidney transplants. *Value of the medication quiz and educational modules in this setting would relate to all patients with chronic disease.*

During the course of this investigation only the first part, study1, was performed. Study 2 was not performed due to the principal investigators departure from Yale.

Scope:

To the kidney transplant patient, the daily, lifelong requirement for a complex regimen of medications is fundamental. Without the uninterrupted use of immunosuppressive drugs, the transplanted organ will be interpreted by the host's immune system as a foreign invader that must be attacked and destroyed (through the process called rejection). Other medications are needed to control comorbid diseases such as diabetes (present in 37% of recipients by 36 months)[i] and hypertension (present in 90% of recipients and linked to chronic rejection)[ii] that either lead primarily to the state of kidney failure, or have developed following the transplant. For these and other health conditions the average recipient of a renal allograft takes between 6 and 12 types of maintenance medications, with a total daily count often reaching as high as 30 to 40 pills and capsules (see Appendix 1).

Under the best of circumstances, accurate use of these medications is a consuming task. It is known that increased complexity of a drug regimen reduces drug adherence.[iii] Preventable errors in the dose or method of using one or more of these drugs, regardless of cause, put the patient's organ and life at risk and are not acceptable, consistent with the 1999 report, *To Err is Human: Building a Safer Health System* of the Quality of Health Care in America Committee of the Institute of Medicine.[iv]

For all patients with endstage renal disease (ESRD), healthcare stakes are very high. With the availability of dialysis and transplantation often taken for granted today (in the United States), it is important to realize that overall mortality rates with ESRD are 10-20% per year. Kidney transplantation affords an excellent chance of attaining a near normal life style.[v] More importantly, it offers the greatest likelihood of achieving longevity among available maintenance renal replacement therapies.[vi] For diabetics, in particular, the survival benefit is so pronounced that transplantation is unequivocally accepted as the standard of care.

In addition to affording the patient superior survival and lifestyle, transplantation is considerably more cost effective than maintenance dialysis.[vii] As might be expected, the initial twelve months of transplantation are the most expensive, costing approximately $7,500 per Medicare member per month

(PMPM) in 2001. Beyond the first year, however, PMPM costs for those with functioning allografts are only $1,000, in contrast to maintenance dialysis costs of $4,300.[viii] With proper medication use, rehospitalization of the transplant recipient is unusual and the principal maintenance costs are for the expensive medications. When medication errors occur, (collectively referred to as "non-compliance" in the transplantation literature) the odds of graft failure increased seven-fold.[ix] In one retrospective study of 260 kidney recipients, 91% of patients who were noncompliant with medications and follow-up care lost their grafts or died.[x] Some have argued that noncompliance is the most significance cause of long-term renal allograft failure.[xi] If the renal transplant fails and the patient survives, the fiscal benefits of this initial investment are lost. With loss of the transplant, the higher level of maintenance expenses supporting the return to dialysis are resumed. In the U.S., Medicare supports roughly 70% of the $22.8 billion costs of the ESRD program. The overall cost benefit of successful transplantation is so significant that medical caretakers of the ESRD patient are specifically required by Medicare to regularly document consideration of the appropriateness of transplantation in the long-term care plan for that individual.

Requiring the utilization of society's fiscal and organic resources, and the patient's physical and emotional tolerance for innumerable challenges for success, transplantation is a therapy offered with the intent of providing sustained function of the allograft and survival of the person serving as its host. This renal replacement modality represents society's investment in medical therapy for the ESRD patient's future. Unfortunately, in addition to the dilemma caused by the vast inadequacy of organs for transplantation, success is limited by the many factors contributing to the successful utilization of the prescribed medication.

Fifty years after its advent,[xii] the principal goals of transplantation still depend entirely on the patient's ongoing use of an individualized, complex and evolving medication regimen, as seen above.

Dramatic improvement has occurred during this half century. With modern drugs the frequency of acute rejection has been reduced to less than 15% in the first year at many centers.[xiii] Yet, to achieve this low rate, the complexity and expense of the drug regimens patients receive, have increased profoundly. Simultaneous reductions in supportive resources, have served to compound greater demands on the patient who strives to comply fully with all of the transplant team's expectations.

In practice, errors in the use of these medications have been difficult to either prevent[xiv] or verify. Likely often unrecognized, non-adherence to medications is now estimated to be implicated in as many as 36% of graft losses.[xv] Premature graft failure that results from avoidable errors compromises immediate patient safety,[xvi] shortens overall survival of that individual[xvii] and, as discussed above, represents an untimely loss of profits from society's resources that have been invested to achieve long-term health care gains for the ESRD afflicted recipient.

Few data are available for use in identifying the specific cause (s) of these failures in transplantation. Non-adherence, or non-compliance are, at best, vague terms referring to the patient's responsibility for not taking the medication precisely as intended by the physician. Previously, little consideration has been given to other causative factors.

Principle among uncaptured causes of "non-compliance" after transplantation is the failure of communication between the patient and physician. Prescriptions and associated instructions are, infrequently today, conveyed directly to hospitalized patients by the attending doctor. Instead, rising pressure on the physician to increase productivity and to minimize the length of inpatient stay, especially in the high cost field of transplantation,[xviii],[xix] has made prolonged interactions at this level lamentably uncommon. Even among primary care physicians, preventive care has become impractical, consuming 7 hours per physician per day to accomplish at the advised rates.[xx] Yet patients specifically implicate the lack of physician education, even with a simple medication as well tolerated as eye drops for glaucoma, in their own medication compliance.[xxi] Nevertheless, in today's environment, it is junior doctors, nurses

and other physician extenders who fill the gap between medical experts and their patients, introducing potential for increased error because of their own understandably lower level of knowledge and familiarity with complex medications. In an era of enforced resident work restrictions, there is limited opportunity for education of these junior physicians who deliver immediate in-hospital care for the new transplant patient and are often responsible for writing the discharge prescriptions, often with little expertise.[xxii] Continuity of care, one of the most important principles of overall patient safety in transplantation, has been similarly compromised by new work hour limits and involvement of numerous additional personnel.[xxiii] Accordingly, previous assumptions that physicians accurately write prescriptions, and fully communicate instructions and expectations to the overwhelmed transplant recipient, may well be compromised. The IOM's Committee on Health Literacy has just reported that nearly half of all American adults have difficulty understanding and using health information, and called for a concerted effort to improve health literacy.[xxiv] *In no arena can the urgency of this need be greater than in the complex field of organ transplantation.*

Equally important in the avoidance of preventable medication errors following transplantation is the recipient's ability to communicate with healthcare providers. If the patient is unable to inform treating physicians about which medications they are taking, recognition of problems caused by too much or too little of a drug or drug-drug interactions is impossible.[3] Failure to detect the contribution of non-compliance to an insufficient response, may result in wrong measures being taken to try to improve outcomes.[xxv] It is not uncommon for transplant patients labeled "non-compliant" to tend to forget the names of the medications they are supposed to take.[xxvi, xxvii]

Prevalence of medication non-compliance

Approximately 80/year new and 700 established renal transplant recipients are followed actively at the Yale New Haven Organ Transplant Center. Review of the patient's medication list is a key component of every encounter (both inpatient and outpatient) with the transplant team. Errors identified are individually addressed with a combination of focused education and corrective medical interventions. During the two-month period from 02/01/04 to 3/31/04, the following specific medication errors were identified by the Principal Investigator. Specific patient identifiers are excluded for HIPAA compliance.

MEDICATION ERRORS IN NEW KIDNEY TRANSPLANT RECIPIENTS (<6 months): Yale New Haven Organ Transplant Center 2/1/04 – 3/31/04

Patient	# Meds	Error Type	Error Source	Real Adverse Event	Potential Adverse Event	Description	Preventable ?
1	10	Delivery	Pharmacist	None	Hyperlipidemia atherosclerosis	Pharmacist refused to dispense Lipitor due to potential interactions	Yes
2	12	Compliance	Patient	BP 190/100	Stroke, heart attack	Didn't take BP meds in am: BP 190/100	Yes
3	12	Dosage	Patient	K – 3.0 mEq/L	Arrythmia	Unable to report how much KCl he's taking	Yes
4	11	Dosage	Patient	None	Loss of a 3rd kidney transplant	Believed each rapamycin tab 5mg, not 1 mg.	Yes
5	17	Compliance	Patient	None	Adrenal crisis, loss of kidney transplant	Preloaded pill box: took Pepcid instead of Prednisone x 6 days	Yes

Patient	# Meds	Error Type	Error Source	Adverse Event	Potential Adverse Event	Description	Preventable?
6	12	Dosage	Patient	BP 150/90	Stroke, heart attack	Unable to report Lisinopril strength of 10 or 20 mg	Yes
7	14	Prescription	Other MD	None	Cyclosporine toxicity, renal failure	14 day course of Clarithromycin without cyclosporine level monitoring	Yes
8	7	Compliance	Patient	None	Infection, lymphoma	Did not stop cyclosporine with addition of rapamycin (took 4 instead of 3 immunosuppressants,	Yes
9	14	Compliance	Patient	BP 170/110, 20 lb gain	Stroke, heart attack	Morbidly obese patient (BMI 48) stopped lasix for 3 days to "get a better creatinine"	Yes
10	13	Availability	Patient	Chronic rejection	Premature graft loss	Ran out of rapamycin x 48 hours	Yes
11	16	Compliance	Patient/ insurance	Anemia hct 28%	Heart failure, transfusion	Taking ½ of erythropoietin dose due to expense. Did not request assistance.	Yes
12	12	Dosage	Patient	None	Stroke, heart attack	Unable to report whether Toprol was "XL" or not	Yes
13	12	Availability	Patient	Chronic rejection	Adrenal crisis, Premature graft loss	Missed "a couple of days" of prednisone due to delayed mail order delivery	Yes
14	9	Availability	Patient	Chronic rejection	Premature graft loss	Ran out of mycophenolate x 48 hours. dialysis imminent	Yes
15	12	Delivery	Nurse	None	Rejection, premature graft loss	Subacute care facility refused to administer everolimus because of unfamiliarity with drug profile	Yes

Overall, 16 medication errors in 15 patients were identified. In 15/16 (94%) cases the error should have been preventable. Nearly one third (5/16) involved the patient's lack of knowledge or inability to communicate one of the five basic elements of the drug prescription. An additional one third (6/16) of errors involved patient compliance or drug availability. Both categories represent the patient's failed responsibility for the portion of care that depends on their own motivation and efficacy or to behave appropriately. *Overall, this survey of medication error types suggests that improved patient education about the elements of prescription medication knowledge can prevent errors*.

To determine the extent to which healthcare literacy contributes to medication compliance, the staff of the Yale New Haven Organ Transplant Center was selected to represent a population at the highest end of the spectrum. A Human Investigation Committee approved, voluntary and confidential 12 question survey was circulated to all 42 personnel on 3/10/04.

The response rate of 71% (30/42) was considered acceptable. The mean age was 40.5 years; 1 respondent declined to provide her age. The study group was predominantly female; 23 (77%) women, 7 men. As expected, this was a highly educated population: 100% of respondents had at least a high school diploma. The highest degree received was high school in 4/30, college in 13/30, graduate school in 10/30, and other degrees in 3/30. Profession was self reported to be physician 6/30, nurse 4/30, other clinical healthcare provider 9/30, scientist 3/30, administrator 2/30, clerical worker 6/30.

This population was also generally healthy with only 14/40 (47%) taking one or more chronic medication (including contraceptive hormones). The mean number of chronic meds taken by these 14 respondents was 1.5. However, 97% reported having been prescribed a medication for an acute illness (e.g., antibiotic).

Chronic Medication		**Acute Medication**	
	8/14 (57%)	Followed instructions exactly	21/30 (70%)
Sometimes missed dose (1-3 times/month)	4/14 (29%)		7/30 (23%)
Often missed dose	1/14 (7%)		1/30 (3%)
Usually do not take as prescribed	1/14 (7%)		

Among this highly educated population, only 57% of individuals were fully compliant with chronic medications. There was improved compliance with the use of acute medication.

We conclude that, even highly educated individuals who have a high degree of health literacy are frequently less than compulsive in using a small number of prescribed medications.

Methods:

Study Design:

Study 1

The null hypothesis was: interactive web based education modules would have no effect upon a renal transplant patient's knowledge of their medication regimen and secondary markers of medication compliance.

Patients were invited to participate in this study on post kidney transplant day number two. If they agreed to participate, a detailed explanation of the study requirements and the expected risks and benefits were given and informed consent obtained. The patients were randomized to receive either the standard of care discharge and out patient teaching, or standard of care discharge and out patient teaching plus interactive web enabled education modules. Prior to hospital discharge both groups were given a test (**Transplant Medication Quiz**) to assess whether or not the pre discharge teaching accomplished the goal of educating patients about their discharge medications and to serve as the baseline comparison for future tests. This test assessed knowledge for five elements: name of medication; the strength of pills (or capsules, or concentration of liquid): the number of the pills required to make the dose: the frequency of use: and the duration of use. Additionally patients were tested for knowledge of when the medication was last changed and by whom. The study group (interactive web enabled teaching group) used the first interactive web based education module prior to discharge.

On the first and subsequent clinic visits both the experimental and control groups were given a computerized test of their knowledge of their medications. This medication list was verified against the medication list generated by the prescribing physicians - the transplant team - and graded for accuracy on the above listed items. The experimental group then proceeded to interactive web based education modules followed by a clinic visit. The control group received a standard of care clinic visit. The test was administered prior to the education module at each visit to assess the long-term recall of the medication regimen.

The test and web based teaching was repeated at the following clinic visits, visit 1, week one, week 2, week 4, month 2, month 4 month 6.

The primary end point was-
The score on the **Transplant Medication Quiz** of medications which served to quantify how successful our education modules had been in teaching patients 1) about the regimen and 2) the ability to communicate the elements of this regimen to healthcare providers.
Secondary endpoints were-
1. Serum creatinine- an important measure of kidney function, because we hypothesized that improved medication compliance results in better graft function.
2. Rejection events-as with serum creatinine, we hypothesized improved medication compliance results in fewer rejection episodes.
3. Drug levels-immunosuppressive medication, cyclosporine, tacrolimus and rapamycin drug levels served as a quantifiable measures of medication compliance both with regards to having therapeutic drug levels and the consistency of these levels.
4. Hospitalizations-all hospitalizations and hospitalizations that occurred specifically for medication errors are tracked. All hospitalizations were followed in case there was a beneficial effect that results from the education modules that we had not anticipated. Medication error related hospitalizations were a measure of the effectiveness of our intervention.

5. Blood pressure control, Serum lipid control, Hemoglobin A1c- these measures served as additional markers of improved medication compliance.
6. Patient satisfaction-as measured by a survey that had been validated in the Yale Medical Group as reliably and reproducibly assessing patient satisfaction with the experience at Yale.

Study 2 (Not conducted)

The null hypothesis was: an interactive web enabled education modules would have no effect upon a patient's level of satisfaction with their healthcare experience in a busy renal transplant practice and would result in no improvement in medication compliance.

Renal transplant patients greater than one year out from their transplant will be invited to participate in this study. If they agree to participate, a detailed explanation of the study requirements and the expected risks and benefits will be given and informed consent obtained. The patients will be randomized to continuing to receive standard of care or to receive interactive web enabled education modules that instruct them in the importance of their medical regimen. Both the control group and the experimental group receive a computerized **Transplant Medication Quiz** to assess their knowledge of their medications at the beginning of their clinic visit that occurs every three months. After the test, the experimental group continues on with an education module while the control group will have a normal clinic visit. The test administration occurs prior to the education module at each visit to assess the long-term recall of the medication regimen.

After being randomized and prior to any interventions, both groups take a patient satisfaction survey. This survey has been validated in the Yale Medical Group as reliably and reproducibly assessing patient satisfaction with the experience at Yale. At each three month interval clinic visit, both groups of patients will be administered the survey.

The primary endpoint of this study is-
Improving patient satisfaction throughout the year and overall patient satisfaction at one year.

The secondary endpoints are-
1. Drug levels-immunosuppressive medication, cyclosporine, tacrolimus and rapamycin serum drug levels will serve as a quantifiable measure of medication compliance. Particularly we will look for consistency of levels.

2. Blood pressure control, serum lipid control and hemoglobin A1c are additional markers of improved medication compliance.

Educational Module:

The educational module developed was set up so that it ran from a centralized server. This allowed test results to be collected and stored automatically. The module consisted of text and video clips covering the various aspects of medication compliance that we had identified. To reinforce these we developed a “pill box game” where study participates were required to allocate varying dosages of different medications into an electronic

pillbox. We also developed an interactive prescription where study participates could drag the cursor over various parts of the prescription and receive an explanation of what it was.

Data Sources and Collection:

Data was collected directly from the patient taking the Internet based test of medication compliance and stored in a central server for analysis later.

Interventions/Measures:

The interview was taking the educational modules and the measured output was the score on the test of medication compliance.

Limitations:

1. A research assistant was assigned to be with the study subject during the taking of the test as well as during the education module. This created a bias due to the natural tendency of the research assistant wanting to help the patient. This lead to a significant dilution of the differences in scores as all patients tended to perform the same on the tests of medication compliance.
2. The mere fact they were participating in a research project on medication compliance raised the level of the importance of medication compliance in the minds of both study and control patients and they performed better than expected (Hawthorne Effect). Because of the above issue any potential benefit from the educational modules was unable to be detected.
3. The research was limited by insufficient patient accrual. For the first project power calculations indicated that 50 patients were needed in each group to detect a significant difference. Only 76 patients total were enrolled in the study.
4. The departure from Yale of the principal investigator has hindered data analysis.

Results:

Study 1

No definitive conclusions can be drawn from this project because enrollment was not completed prior to the expiration of the grant and the data that was obtained does not point to any benefit.

The overall quiz scores to assess medication compliance were:

Number		Quiz0	Quiz1	Quiz3	Quiz6	Avg Quiz
38	**Control**	76%	97%	94%	95%	90%
38	**Study**	74%	93%	96%	94%	89%

The similarity in quiz scores, which was the primary end point implies the education modules had no positive effect over usual care in improving a renal transplant patients understanding of their medication. However, if having recall of ones medications and an understanding of their function is a proxy for medication compliance, then it seems that participation in the research project has resulted in better over compliance than would have been anticipated.

The educational modules did not result in a significantly lower serum creatinine.

Number		Cr1	Cr3	Cr6
38	**Control**	1.7	1.6	1.7
38	**Study**	1.7	1.7	1.7

The educational modules did not result in a lower number of rejections per patient.

Number		Rej1	Rej3	Rej6
38	**Control**	0.08	0.13	0.08
38	**Study**	0.08	0.13	0.11

The educational modules did not result in a lower number of hospitalizations per patient.

Number		Hos1	Hos3	Hos6
38	**Control**	0.61	0.53	0.45
38	**Study**	0.39	0.58	0.66

When analyzed by age there does not appear to be a significant difference in test scores.

Age	Quiz0	Quiz1	Quiz3	Quiz6	Avg Quiz
<65	76%	96%	95%	96%	91%
>=65	65%	83%	94%	81%	79%

Similarly for race:

Race	Quiz0	Quiz1	Quiz3	Quiz6	Avg Quiz
Black	88%	90%	92%	84%	89%
Hispanic	70%	96%	90%	98%	87%
White	71%	96%	96%	97%	90%

Study 2

There are no results to report for study 2 as this study was not performed.

Discussion:

In conclusion, the preliminary results of this project do no support the hypothesis that an interactive Internet based education program results in better medication compliance than usual care. It should not be inferred from this conclusion that the educational module was of no value because both groups performed well and better than would have been

anticipated from the preliminary data. Therefore a reasonable explanation is that bias was introduced into this study and the control population did not received usual care but rather more teaching and reinforcement about the importance of medication compliance. This resulted in an elevation in the control group's performance and a decrease in the observed effect of the experimental intervention. This may have masked any positive effect the educational module would have had. Certainly, if it is accepted that education itself helps to improve compliance then the educational module has a value because it can be self administered by patients. A hypothetical model would be to use a computer on wheels in the waiting area of a medical practice. While waiting for an appointment a patient could use the educational module and improve their understanding of their medical regimen. At the very least, use of the educational module in this way may prompt the patient to ask questions regarding their medications to their providers.

The implications to these findings are that medication compliance is something that can be improved upon by raising the patient's awareness of its importance and engaging them actively in the process. There is a need for continued research to find the most efficacious way to accomplish this and how to integrate it into standard medical practice.

No publications resulted from this work.

Respectfully submitted,

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[i] http://www.usrds.org/2003/pdf/07_tx_03.pdf, 4/20/04

[ii] Opelz G, Wujciak T, Ritz E. Association of chronic kidney graft failure with recipient blood pressure. Collaborative Transplant Study. Kidney Int. 1998 Jan;53(1):217-22.

[iii] Dusing R, Weisser B, mengden T, Vetter H. Changes in antihypertensive treatment the role of adverse effects and compliance. Blood Press 1998; 7:313-315, 1998.

[iv] To err is human: Building a safer health system. http://www.nap.edu/books/0309068371/html/

[v] Cameron JI, Whiteside C, Katz J, Devins GM. Differences in quality of life across renal replacement therapies: a meta-analytic comparison. Am J Kidney Dis: 35(4):629-37, 2000.

[vi] Djamali A. Premasathian N. Pirsch JD. Outcomes in **kidney transplant**ation. *Seminars in Nephrology. 23(3):306-16, 2003*

[vii] Winkelmayer WC, Weinstein MC, Mittleman MA, et. al. Health economic evaluations: the special case of end-stage renal disease treatment. Med Decis Making 22:417-430, 2002.

[viii] http://www.usrds.org/2003/pdf/11_econ_03.pdf

[ix] Butler JA, Roderick P, Mullee M, et al. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplant 77(5):769-89, 2004.

[x] Schweizer RT, Rovelli M, Palmeri D, et al. Noncompliance in organ transplant recipients. Transplant 49(2):374-7, 1990.

[xi] Friedman A. Strategies to improve outcomes after renal transplantation (letter). N Engl J Med 346(26):2091, 2002.

[xii] Matthews JB. Ramos E. Bluestone JA. Clinical trials of **transplant tolerance**: slow but steady progress. *American Journal of **Transplant**ation. 3(7):794-803, 2003*

[xiii] Hricik DE. Knauss TC. Bodziak KA. Weigel K. Rodriguez V. Seaman D. Siegel C. Valente J. Schulak JA. Withdrawal of steroid therapy in African American **kidney transplant** recipients receiving sirolimus and tacrolimus. **Transplant**ation. 76(6):938-42, 2003

[xiv] Wuerzner K., Hassler C., Burnier M. Difficult blood pressure control: watch out for non-compliance! Nephrol Dial Transplant 18: 1969-1973, 2003.

[xv] Butler JA, Roderick P, Mullee M, et al. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplantation 77(5): 769-789, 2004.

[xvi] Meredith PA. Therapeutic implications of drug "holidays". European Heart Journal 17(S):21-4, 1996.

[xvii] Isaacs RB, Conners A, Nock S et al. Noncompliance in living-related donor renal transplantation: the United Network of Organ Sharing experience. Transplant Proc 31:19S-20S, 1999.

[xviii] Anonymous. Renal transplantation path saves $34K per patient. Hospital Case Management 7(1):5-8, 1999.

[xix] Johnson CP, Kush EM, Hariharan S, et al. Pre-transplant identification of risk factors that adversely affect length of stay and charges for renal transplantation. Clinical Transplant 13(2):168-75, 1999.
[xx] Yarnall KS. Pollak KI. Ostbye T. et al. Primary care: is there enough **time** for prevention?. American Journal of Public Health. 93(4):635-41, 2003 .
[xxi] Taylor SA, Galbraith SM, Mills RP. Causes of non-compliance with drug regimens in glaucoma patients: a qualitative study. J Ocular Pharm and Therap. 18(5):401-9, 2002.
[xxii] Winslow ER. Bowman MC. Klingensmith ME. Surgeon work**hours** in the era of limited **resident** work**hours**. Journal of the American College of Surgeons. 198(1):111-7, 2004
[xxiii] Barden CB. Specht MC. McCarter MD. Daly JM. Fahey TJ 3rd. Effects of limited work hours on surgical training. Journal of the American College of Surgeons. 195(4):531-8, 2002
[xxiv] Health Literacy: A Prescription to End Confusion. http://www.nap.edu.
[xxv] Wuerzner K, Hassler C, Burnier M. Difficult blood pressure control: watch out for non-compliance! Nephrol Dial Transplant 18:1969-1973, 2003.
[xxvi] Section IV: Long-term management of the transplant recipient. Nephrol Dial Transplant 17(S4):3-67, 2002.
[xxvii] Meyers KE, Thomson PD, Weiland H. Noncompliance in children and adolescents after renal transplantation. Transplant 62(2):186-9, 1996.