

Original Research Article

Variability of Cognitive Performance during Hemodialysis: Standardization of Cognitive Assessment

Susanne Tholen^a Christoph Schmaderer^a Ekatharina Kusmenkov^a
Stefan Chmielewski^d Hans Förstl^b Victoria Kehl^c Uwe Heemann^a
Marcus Baumann^a Timo Grimmer^b

^aDepartment of Nephrology, ^bDepartment of Psychiatry and Psychotherapy, and ^cInstitute for Medical Statistics and Epidemiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; ^dInstitute of Molecular Biology and Biotechnology, Faculty of Biology, Adam Mickiewicz University, Poznan, Poland

Key Words

Cognitive assessment · Dementia · Montreal Cognitive Assessment · End-stage renal disease · Hemodialysis

Abstract

Background/Aims: Up to 70% of hemodialysis patients over the age of 54 have relevant cognitive impairment. No standardized protocol for the evaluation and monitoring of this population is available today. We hypothesized that the dialysis procedure and the testing environment induce fluctuations of cognitive performance. **Methods:** 26 hemodialysis patients were randomly tested using the Montreal Cognitive Assessment (MoCA) before, during and after hemodialysis and inside the dialysis room or alone in a separate room. Tests were performed at weekly intervals using five test variations to prevent learning effects. The Mini-Mental State Examination (MMSE) was performed as a reference test. **Results:** MoCA scores significantly differed between the conditions: 'before hemodialysis' revealed the best MoCA score as compared to 'during hemodialysis' or 'after hemodialysis' ($p = 0.013$). During the combined condition 'before dialysis AND separate room', best performance was achieved ($p < 0.001$). The BP decline had no significant influence on cognitive performance, whereas the fluid shift showed a significant impact ($p = 0.008$). **Conclusion:** Cognitive performance in hemodialysis patients highly depends on the time point and testing environment. Therefore, we strongly suggest a standardization, using the MoCA before hemodialysis in a separate room, in order to make testing results of future research in this field comparable.

© 2014 S. Karger AG, Basel

S. Tholen and C. Schmaderer contributed equally to this work.

Susanne Tholen, MD
Department of Nephrology, Klinikum rechts der Isar
Technische Universität München, Ismaninger Strasse 22
DE–81675 Munich (Germany)
E-Mail susanne.tholen@tum.de

Introduction

Cognitive impairment and dementia are common among hemodialysis patients: up to 70% of them aged 55 years and older suffer from moderate to severe chronic cognitive impairment [1, 2]. Systematic cognitive assessment is important, as cognitive dysfunction may have adverse effects on the management and outcomes. Cognitive impairment interferes with informed decision making and the capacity for self-care and therefore may have potential effects on medical, fluid and dietary compliance [3, 4]. More advanced stages of dementia are associated with disability, hospitalization and an approximately 2-fold increased risk of both dialysis withdrawal and death [5–7]. Apart from these overt complications for the patients and their quality of life, the associated increase in care costs represents a growing socioeconomic burden [8].

Apart from chronic cognitive impairment, the hemodialysis procedure itself may induce an acute state of confusion affecting global cognition. Recurrent blood pressure (BP) fluctuations, large fluid shifts and hemoconcentration during dialysis are considered to cause reversible cerebral ischemia [9]. This is important for clinical practice as this state of altered consciousness may interfere with conversations concerning, for example, therapeutic strategies between the patient and his attending physician.

However, the factors influencing cognition have not been thoroughly considered in previous studies, and to our knowledge no cognitive screening instrument has been validated in hemodialysis patients so far, apart from one cross-sectional study including 374 hemodialysis patients by Murray et al. [1] in 2006. In this study the Modified Mini-Mental State Examination (3MS) detected 21% of those patients with severe chronic cognitive impairment, who were diagnosed on the basis of an algorithm including nine validated neuropsychological tests.

The Montreal Cognitive Assessment (MoCA) was used for the evaluation of cognitive function in this study [10]. The MoCA test evaluates the domains attention and concentration, memory, orientation, language, visuoconstructional skills, conceptual thinking, calculations and executive functions. The detection of impairment in executive functions is important for the assessment of hemodialysis patients, because apart from memory function, this skill seems to be impaired early in these patients [11, 12].

Thus, we aimed (a) to determine the feasibility of using the MoCA in detecting cognitive impairment in hemodialysis patients, (b) to determine the best test conditions for assessing cognitive function to establish a standard for future research, and (c) to identify factors associated with differences in cognitive performance, such as BP fluctuation and fluid shift.

Methods

Inclusion and Exclusion Criteria of Patients

During September and October 2011, patients were recruited from the KfH Kuratorium für Dialyse und Nierentransplantation e.V., Munich, Germany, and from the University Dialysis Unit at the Department of Nephrology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany. All study participants had to be older than 18 years and had to have been on hemodialysis treatment for at least 3 months. Patients were not included, if they had any motor impairment of the dominant hand, aphasia or amaurosis, which would impair test performance. Patients were recruited consecutively. 20% of eligible patients consented to participate.

The study protocol was approved by the local ethics committee. Written informed consent was obtained from all participants before any study-specific procedures were carried out. This study is part of the ISAR study, which was registered on ClinicalTrials.gov (identifier No.: NCT01152892). ISAR is an observational study to evaluate the use of noninvasive markers of autonomic function and micro- and macrocirculation to predict mortality and cardiovascular end points in end-stage renal disease patients.

Evaluation of Cognitive Function

The MoCA was used for the evaluation of cognitive function in this study [10]. In order to prevent learning effects caused by repetitive testing, four alternative variations of the original version were developed in collaboration with an experienced neuropsychologist.

The participants were evaluated at weekly intervals when they were randomly administered one of the five alternative test versions at five different testing conditions: (1) before hemodialysis in the group room, (2) before hemodialysis in a separate room, (3) during hemodialysis at the beginning of the 2nd hour, (4) immediately after hemodialysis in the group room, and (5) immediately after hemodialysis in a separate room.

In addition, every participant was tested using the Mini-Mental State Examination (MMSE) during the hemodialysis treatment subsequent to the first testing condition mentioned above. The MMSE was used as a reference test, as it is the best-known and most-studied screening instrument for cognitive function, and normative values for age and education level are available [13].

An a priori power analysis revealed that 20 patients would be sufficient to detect a significant difference between the testing conditions using a paired Student t test (power 80%, level of significance of 0.5).

BP Fluctuation and Fluid Shift

BP was measured at the beginning and the end of dialysis and the difference between the two time points was calculated ('BP fluctuation'). The extracted ultrafiltration volume was taken from the dialysis protocols ('fluid shift').

Statistical Analyses

The SPSS 21.0 software (www.spss.com) was used for all statistical analyses. Demographic and clinical characteristics were obtained by means of descriptive statistics.

Identification of Optimal Test Setting

Of primary interest was the identification of the test setting that leads to optimal performance of cognitive testing. In order to compare MoCA test scores of 'before' versus 'after dialysis', average scores of MoCA test scores of all test conditions before dialysis and after dialysis were calculated. Mean scores of these two time points were compared using the dependent t test for paired samples (variables were normally distributed).

In order to compare MoCA test scores of 'group room' versus 'separate room', an average score of MoCA test scores of all test conditions in the group room and in the separate room was calculated. Mean scores of these two setting conditions were compared using the dependent t test for paired samples (variables were normally distributed). To identify the condition with the best MoCA results, a dependent t test for paired samples was carried out. p values were corrected for multiple comparisons (Bonferroni).

Factors Associated with the Variability of Cognitive Performance

Of secondary interest was the identification of additional factors that explained test score variability. To investigate the potential effects of BP decline and fluid shift on cognitive performance, patients were divided into 2 subgroups on the basis of the median of the variables: i.e. -6 mm Hg for the BP difference and -2.7 liters for the fluid shift, respectively.

Then, average MoCA scores of the 'after' and 'before dialysis' conditions as well as MoCA differences between 'before' and 'after dialysis' conditions were calculated. For the between-group comparisons, the independent two-sample t test was used (variables normally distributed). As we obtained statistically significant between-group differences for the variable fluid shift, we carried out group comparisons of all MoCA subscores accordingly (visuospatial/executive function, naming, memory, attention, language, abstraction and orientation).

To explore a potential impact of the variable age on the mean MoCA total score, a Pearson correlation was calculated. In a second step, the study population was divided into 2 subgroups using the median of 64 years. Mean MoCA total scores and mean MoCA differences between 'before' and 'after dialysis' conditions were compared between both subgroups using an independent two-sample t test.

MoCA test scores were adjusted for education. To explore an effect of education, the patient sample was divided into 2 subgroups. One group consisted of patients with more than 12 years of education, the other one of those with 12 years or less. Mean MoCA total scores and mean differences between the testing conditions 'after' and 'before dialysis' were compared between the 2 subgroups using an independent two-sample t test.

Table 1. Demographic and clinical characteristics of the 26 patients

Age, years	65.81 ± 16.11 (28–87)
Sex, n (%)	
Male	17 (65.4)
Female	9 (34.6)
Education >12 years/≤12 years, n (%)	10 (38.5)/16 (61.5)
MoCA total score	23.88 ± 3.21 (15–30)
MMSE score	27.27 ± 1.85 (22–30)
Mean time on dialysis, months	45.08 ± 37.88 (3–128)

Values represent mean ± SD with the range in parentheses unless otherwise indicated.

Table 2. Five different testing conditions

Testing conditions	MoCA total score
Before dialysis, group room	23.27 ± 2.99 (18–28)
Before dialysis, separate room	24.35 ± 2.96 (18–29)
During dialysis	23.23 ± 3.36 (17–28)
After dialysis, group room	22.73 ± 3.62 (14–29)
After dialysis, separate room	22.77 ± 3.80 (15–29)

Values represent mean ± SD with the range in parentheses.

Results

Patients

26 patients were included in the study. The demographic data and the clinical characteristics of the sample are provided in table 1. The mean total score of the MoCA was 23.88 ± 3.21 points, a score which was abnormal according to the proposed cutoff of <26 points [10]. The mean total score of the MMSE was 27.27 ± 1.85 points, a score within the normal range of >25 points.

Evaluation of Cognitive Function

In table 2, the MoCA total scores of the five different testing conditions are given. The results of all the following setting analyses are shown in table 3. Firstly, the conditions ‘separate room’ against ‘group room’ were compared, resulting in no significant difference. Secondly, the conditions ‘before’ versus ‘after dialysis’ were compared, showing a significant difference with higher MoCA test scores ‘before dialysis’ (p = 0.013). Thirdly, the condition ‘before dialysis in a separate room’ revealed statistically significant (p < 0.001) higher MoCA scores as compared to other testing conditions (the individual differences are depicted in fig. 1).

Factors Associated with the Variability of Cognitive Performance

The between-group comparison of the mean MoCA scores of the less than –6 mm Hg versus more than –6 mm Hg BP decline for the ‘before’ and ‘after dialysis’ condition and for the difference of the testing results (‘after’ minus ‘before dialysis’) exhibited nonsignificant results. Thus, the BP decline was not significantly associated with a decline of MoCA scores after dialysis.

MoCA scores of the testing condition ‘before dialysis’ were significantly higher in the subgroup with a low fluid shift (<2.7 liters) as compared to the subgroup with a high fluid

Table 3. Analyses with regard to time point and setting

Testing conditions	MoCA total score	p value (t test)
Separate vs. group room	24.17 ± 3.1 vs. 23.69 ± 2.64	0.101
Before vs. after dialysis	24.42 ± 2.62 vs. 23.37 ± 3.33	0.013*
Before dialysis		
Separate vs. group room	23.27 ± 2.99 vs. 24.35 ± 2.95	0.012*, ^a
Separate room vs. other conditions	24.96 ± 2.84 vs. 23.62 ± 2.78	<0.001*, ^a

Values represent mean ± SD. Statistically significant: * p < 0.05.

^a Statistically significant after Bonferroni correction of multiple comparisons.

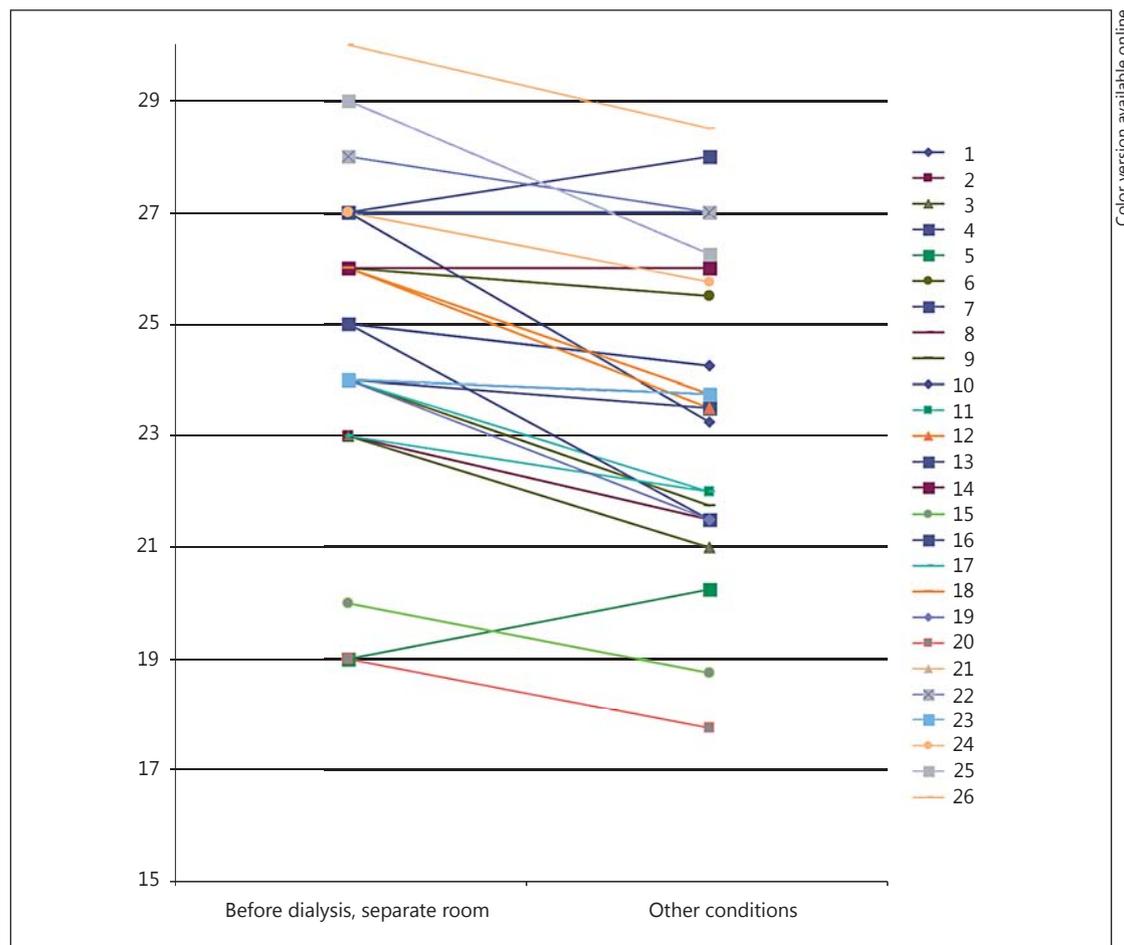


Fig. 1. Difference between 'before dialysis in a separate room' and all other testing conditions for all 26 patients. y-axis = Number of patients; x-axis = testing conditions.

Table 4. Subgroup analysis and fluid shift (MoCA total score)

Testing conditions	Fluid shift ≥ 2.7 liters	Fluid shift < 2.7 liters	p value (t test)
Before dialysis	23.15 \pm 2.13	25.58 \pm 2.59	0.017*
After dialysis	22.23 \pm 3.07	24.25 \pm 3.33	0.128
After dialysis – before dialysis (Δ)	-0.92 \pm 2.05	-1.33 \pm 2.08	0.624

Values represent mean \pm SD. Statistically significant: * p < 0.05.

shift (> 2.7 liters). The results of these between-group comparisons were not significant for the testing conditions ‘after dialysis’ and for the difference of the testing results ‘after’ and ‘before dialysis’. These results are given in table 4.

The group comparisons of the MoCA subscores between the ‘high’ versus the ‘low fluid shift’ subgroups revealed differences in memory function and language. Memory function differed significantly between the groups for the testing conditions ‘before’ and ‘after dialysis’ (p = 0.018 and p = 0.042, respectively). Language skills were significantly different at the conditions ‘before dialysis’ (p = 0.004) and ‘after dialysis’ (p = 0.031). The analyses of the other subtests did not reveal any statistically significant differences with regard to fluid shift.

There was no significant association between age and mean MoCA total score (p = 0.267). Neither MoCA total score nor MoCA differences were significantly different between patients older than 64 years and the younger subgroup (p = 0.923 and p = 0.420, respectively).

Patients with an education level of more than 12 years did not differ significantly from patients with 12 years or less of education on mean MoCA total score or MoCA differences (p = 0.632 and p = 0.988, respectively).

Discussion

The aim of the current study was to assess the variability of cognitive test scores associated with the time point and the setting of a dialysis treatment in order to establish a standard of testing conditions suitable as a basis for future research in the field of cognitive impairment in dialysis patients. For that purpose, we analyzed the variability of cognitive performance during hemodialysis using the MoCA in 26 patients, who had been on dialysis treatment for at least 3 months. Patients had an abnormal mean MoCA score of 23.88 ± 3.21 points and scored within the normal range of the MMSE.

The main strength of our study is the evaluation of differences in cognitive performance in hemodialysis patients according to the time point of testing and the surrounding conditions, which has not been a topic of scientific research so far. Studies dealing with cognitive function in hemodialysis patients did not focus on the test setting. In one study by Kurella et al. [2], including 80 patients on hemodialysis treatment, cognitive assessment took place during dialysis. Patients taking part in a study by Murray et al. [14] in 2007 were even tested at different testing conditions (1 h before or after dialysis or on the day between two dialysis sessions).

We could show that the test setting had a significant influence on the results of cognitive testing. Testing the patient alone, before dialysis yielded the best cognitive performance. Therefore, the testing situation, which should preferably be used for the evaluation of cognitive function in hemodialysis patients, is before dialysis in a separate room. This result is of major importance for the comparison of test results of different future studies. It is

consistent with the findings of one study by Smith and Winslow [15] in 1990 that revealed lower scores of the Number Connection Test during hemodialysis as compared to before in 29 hemodialysis patients.

The patients' mean MoCA scores differed on average by 1.34 points corresponding to 5% of the total score. The purpose of standardizing cognitive testing is to reduce the variability in cognitive assessments primarily in research settings. Unfortunately, no data on a direct correspondence between MoCA scores and scores or scales assessing activities of daily living exist, but such data would be of great interest to better understand the clinical relevance of a certain interval of MoCA.

The decline of cognitive performance after dialysis as compared to before could not be attributed to the BP decline in our study. This result is in line with several other studies, which also could not find a relationship between BP and cognitive function in hemodialysis patients [1, 11, 16, 17].

In our cohort, the cognitive performance of patients with an average fluid shift >2.7 liters differed significantly from those patients with a lower fluid shift. Interestingly, this difference was already present at the assessment before dialysis. We therefore assume that the difference of cognitive test scores is more likely due to a long-term effect of large fluid shifts, rather than to an acute state of confusion during dialysis. However, the underlying mechanisms still remain rather unclear and thus should be an objective of future studies. Furthermore, longitudinal assessment of hemodialysis patients is urgently warranted, as no studies have focused on the development of cognitive impairment over time so far.

Analyzing the MoCA subtests between the low- and high-fluid shift group, significant differences were obtained for the subtests 'memory' and 'language'. This result is in discrepancy with another study by Kurella Tamura et al. [11] that also included the ultrafiltration rate over the dialysis session as a potential determinant of cognitive performance. No significant impact of hemodynamic changes neither on global cognition nor on executive functions, measured by the 3MS and the Trail Making Test B, was shown. Different testing conditions may be causative for this controversial result, as cognitive assessment was not performed under standardized conditions.

There was no significant association between patients' age and their cognitive performance, despite the fact that age is considered the main risk factor for cognitive impairment in the general population. This may be explained by the wide range of age of the patients in our cohort. A higher education level, which is usually associated with greater brain reserve and more resilience against cognitive impairment, was not associated with better cognitive performance, but MoCA test scores are already adjusted for education.

The present study has one main limitation: the recruitment of patients might be biased. Patients, who had already noticed cognitive impairment themselves, might have refrained from participating in our study.

In conclusion, we found a significant influence of the test setting on cognitive performance in hemodialysis patients. The highest MoCA scores were achieved before dialysis in a separate room. Therefore, we strongly recommend this test setting as a standard for future studies. In addition, the extent of fluid shift was significantly associated with cognitive performance already in test settings before dialysis, which points to a long-term effect of large fluid shifts. On the basis of our results, we propose to include cognitive assessment in the regular screening examinations of dialysis patients, e.g. once before initiation of the treatment and at a 3-month interval thereafter, in order to increase our knowledge of dialysis-associated cognitive impairment.

References

- 1 Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, Smith GE, Hochhalter AK, Collins AJ, Kane RL: Cognitive impairment in hemodialysis patients is common. *Neurology* 2006;67:216–223.
- 2 Kurella M, Chertow GM, Luan J, Yaffe K: Cognitive impairment in chronic kidney disease. *J Am Geriatr Soc* 2004;52:1863–1869.
- 3 Carrasco FR, Moreno A, Ridaio N, Calvo N, Pérez-Flores I, Rodríguez A, Sánchez A, Marques M, Barrientos A: Kidney transplantation complications related to psychiatric or neurological disorders. *Transplant Proc* 2009;41:2430–2432.
- 4 Sugarman J, McCrory DC, Hubal RC: Getting meaningful informed consent from older adults: a structured literature review of empirical research. *J Am Geriatr Soc* 1998;46:517–524.
- 5 Kurella M, Mapes DL, Port FK, Chertow GM: Correlates and outcomes of dementia among dialysis patients: the Dialysis Outcomes and Practice Patterns study. *Nephrol Dial Transplant* 2006;21:2543–2548.
- 6 Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE: Functional status of elderly adults before and after initiation dialysis. *N Engl J Med* 2009;361:1539–1547.
- 7 Rakowski DA, Caillard S, Agodoa LY, Abbott KC: Dementia as a predictor of mortality in dialysis patients. *Clin J Am Soc Nephrol* 2006;1:1000–1005.
- 8 United States Renal Data System: *USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2005.
- 9 Stefanidis I, Bach R, Mertens PR, Liakopoulos V, Liapi G, Mann H, Heintz B: Influence of hemodialysis on the mean blood flow velocity in the middle cerebral artery. *Clin Nephrol* 2005;64:129–137.
- 10 Nasreddine ZS, Phillips NA, Bedirian V, Whitehead V, Collin I, Cummings JL, Chertkow H: The Montreal Cognitive Assessment (MoCA): a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–699.
- 11 Kurella Tamura M, Larive B, Unruh M, Stokes JB, Nissenson A, Mehta RL, Chertow GM: Prevalence and correlates of cognitive impairment in the frequent hemodialysis network (FHN) trial. *Clin J Am Soc Nephrol* 2010;8:1429–1438.
- 12 Pereira AA, Weiner DE, Scott T, Chandra P, Bluestein R, Griffith J, Sarnak MJ: Subcortical cognitive impairment in dialysis patients. *Hemodial Int* 2007;11:309–314.
- 13 Folstein MF, Folstein SE, McHugh PR: ‘Mini Mental State’. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
- 14 Murray AM, Pederson SL, Tupper DE, Hochhalter AK, Miller WA, Li Q, Zaun D, Collins AJ, Kane RL, Foley RN: Acute variation in cognitive function in hemodialysis patients: a cohort study with repeated measures. *Am J Kidney Dis* 2007;50:270–278.
- 15 Smith BC, Winslow EH: Cognitive changes in chronic renal patients during hemodialysis. *ANNA J* 1990;17:283–286.
- 16 Giang LM, Tighiouart H, Lou KV, Agganis B, Drew DA, Shaffi K, Scott T, Weiner DE, Sarnak MJ: Measures of blood pressure and cognition in dialysis patients. *Hemodial Int* 2013;17:24–31.
- 17 Sehgal AR, Grey SF, DeOreo PB, Whitehouse PJ: Prevalence, recognition, and implications of mental impairment among hemodialysis patients. *Am J Kidney Dis* 1997;30:41–49.