Conservative Management of Chronic Renal Failure

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Introduction

The prevalence of chronic kidney disease (CKD) in India is estimated at 7572 per million and end stage kidney disease at 757 per million population with a staggering financial and social burden [1]. To reduce this burden and improve patient outcome, CKD should be detected and treated before the onset of kidney failure through investigations and prompt treatment of CKD.

This article focuses on retarding the progression of renal failure, management of anaemia, coronary artery disease and hepatitis C virus infection in CKD, and initiation of renal replacement therapy.

Definition of Chronic Kidney Disease

Chronic kidney disease is defined as kidney damage for more than three months as evidenced by structural or functional abnormalities with or without decreased glomerular filtration rate (GFR) and manifested either as pathological abnormalities or kidney damage markers in blood or urine or in the imaging tests. A GFR of <60ml/min/1.73m² body surface area for greater than three months per se also indicates chronic kidney disease [2].

Stages of Chronic Kidney Disease

Chronic kidney disease can be divided into five stages [2] for early identification, planning of therapy and prognostication (Table 1).

Strategy for Reno Protection in CKD

To prevent progressive loss of renal function any prevailing primary damaging factor should be eliminated, like obstructive uropathy, hypertension and diabetes. In a large proportion of renal patients where no disease specific factor is accessible there are interventions to ameliorate non-disease specific, renal risk factors for preventing progressive renal loss.

Table 1

Stages of Chronic Kidney Disease

Stage	Description	GFR (ml/min/1.73m ²)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mild decreased GFR	60-89
3	Kidney damage with moderate decreased GFR	30-59
4	Kidney damage with severe decreased GFR	15-29
5	Kidney Failure	<15

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After the GFR declines to below half the normal value, a progressive loss of renal function ensues even in the absence of original disease activity. The deterioration is often attributed to systemic hypertension, proteinuria, hyperlipidaemia [3, 4], and intra glomerular hypertension [5]. Smoking, obesity and anaemia are considered other risk factors for progression of chronic kidney disease [6-8].

In response to decrease in renal mass and function there is an adaptive change in the remaining nephrons in the form of raised haemodynamic pressure within the glomerular capillaries and increased single nephron glomerular filtration rate. Such adaptive changes maintain the GFR in the short term, but over a period of time lead to progressive renal damage [3]. The raised glomerular hydraulic pressure is maintained by vasodilatation of the afferent arteriole to the glomerular capillaries which results in enhanced transmission of systemic pressures to the glomerular capillary bed and/or by angiotensin dependent mechanisms, which lead to vasoconstriction of efferent arterioles, in addition to elevation of systemic blood pressures [5]. Angiotensin converting enzyme inhibitors (ACEI's) reduce intra glomerular hypertension by relieving the efferent arteriole vasoconstriction.

Based on this hypothesis of hyperfiltration, the effect of ACEI's in retarding the progression of renal disease independent of its antihypertensive effect has been the subject of many studies [9-16]. The use of ACEI's is recommended in all type 1 and type 2 diabetic patients with microalbuminuria. Considering the association between type 2 diabetes and cardiovascular disease, the use of ACEI's is recommended in these patients to reduce cardiovascular risk. Even in non diabetic nephropathy, ACEI's have been shown to retard the progression of renal disease [13]. Preliminary data suggests that angiotensin receptor blockers (ARB's) are probably as effective as ACEI's. Combined ACEI's and ARB's have been shown to further reduce the rate of progression of renal disease [14]. At present, their use is recommended in patients who can not achieve the goal of proteinuria <0.5gms/day, rate of decline of renal function <2ml/mt/year and blood pressure of <130/80 mm/Hg [15].

It is widely accepted that high blood pressure is one of the most important factors in the progression of CKD and that lowering the blood pressure can slow or even halt the progression of CKD in both diabetics and non diabetics [16]. The blood pressure should be reduced to less than 130/80 mm/Hg, in patients with less than 1 gm proteinuria, and 125/75 mm/Hg in those with greater than 1 gm proteinuria. ACEI's and ARB's are recommended as part of the regimen [16].

There is a strong association between proteinuria and progression of CKD. Glomerular hypertension and damage to the glomerular barrier causes non selective proteinuria. This excess proteinuria is taken up by the proximal tubule cells by way of endocytosis, which in turn excites a host of inflammatory and cytokine response, ultimately resulting in fibrosis and scarring of the kidney and progression of CKD [17]. Reduction of proteinuria to a predetermined target of <0.5 gm/day is recommended [16]. The possibility of retarding the progression of CKD by restricting protein in the diet was one of the earliest suggested clinical interventions. It is postulated that a high protein diet hastens the progression of CKD by causing afferent arteriolar dilatation and increasing intra glomerular hypertension [18]. A meta analyses of randomized studies showed an overall beneficial effect of dietary protein restriction on the progression of CKD in both diabetic and non diabetic patients [19]. A dietary protein restriction to 0.6-0.8g/kg/day is recommended for patients with CKD [20].

Chronic renal failure is commonly associated with high very low density lipoprotein (VLDL), high low density lipoprotein (LDL) and low high density lipoprotein (HDL). The role of dyslipidemias in atherosclerotic cardiovascular disease is well known but its role in the progression of CKD is less well defined. At present it is recommended to use lipid lowering agents not only for their possible role in slowing CKD progression but also for their proved benefit in the management of atherosclerotic cardiovascular disease which continues to be the main cause of mortality in CKD patients [16]. The available data [6] suggests that smoking increases the risk of proteinuria and the rate of progression of CKD. There is some evidence that smoking cessation retards the progression of renal disease and all patients should be counselled in this regard.

It has been proposed that hypoxia of the renal tubules plays a role in the progression of CKD. Decreasing hypoxia by correcting anaemia may be beneficial in retarding the progression of CKD [8].

In a recent study of 30 overweight patients and various nephropathies, a mean weight loss of 4.1% in the diet group was associated with a 31.2% reduction in proteinuria [7].

To achieve complete long-term renoprotection an approach is suggested in Table 2 [3]. Treatment strategy for renal protection is preferably started in stage 2 of CKD.

Anaemia Guidelines in Chronic Kidney Disease

The anaemia of chronic kidney disease is a predictable and early complication of CKD, the severity of which is directly related to the severity of CKD. There

is also a strong association between anaemia and cardiovascular disease, which acts as an independent predictor of mortality. The anaemia of CKD is of a normochromic normocytic variety.

Much of the morbidity and mortality inherent to renal failure patients is attributed to secondary consequences of chronic anaemia like decreased oxygen delivery to tissues, left ventricular hypertrophy (LVH), angina and congestive cardiac failure. It causes decreased mental abilities, poor quality of life and decreased overall survival [21,22].

Haemoglobin (Hb) desired is 11-12gm/dl. Anaemia evaluation should include RBC indices, peripheral smear, serum iron, ferritin and transferrin saturation (TSAT) and blood folic acid and vitamin B12 levels. Stools should be tested for occult blood and parasites

Iron therapy should be started when serum ferritin is less than 100ng/ml and/ or TSAT is less than 20%. In pre dialysis patients oral iron can be used, 200mg/day, preferably on an empty stomach and definitely not along with phosphate binders. In dialysis patients the intravenous route is used. Iron sucrose or sodium ferric gluconate are preferred to iron dextran complex, in view of the increased incidence of adverse reactions with the latter. Total dose infusion can be given with iron dextran complex while other iron preparations should be given in divided dosages. Total infusion dose can be calculated using the formula: Hb deficit (gms) x body weight in kg x 3= dose of iron in mgs. Other iron preparations can be given 100 milligrams post dialysis for 10 consecutive injections. After giving the calculated dose, iron should be withheld for two weeks and Hb

and iron status should be rechecked. In case target iron stores are not achieved, parenteral iron therapy 100 mg per dose is to continue for another 10 injections. Discontinue iron when TSAT is >50% and ferritin is >800ng/ml. Iron stores should be reassessed after three months and if TSAT is <50% and ferritin is <800 ng/ml, restart iron 100mg every two weeks. Water soluble vitamins like folic acid and B complex should be supplemented [21].

The diagnostic value of serum ferritin as an estimate of body iron stores is limited as it also behaves as an acute phase reactant. Therefore, in patients on haemodialysis, ferritin values may be high even in the presence of iron deficiency. In patients on haemodialysis the test has a sensitivity of 41-54 % [23]. TSAT assesses the availability of circulating iron, though reasonably sensitive it has specificity in haemodialysis patients of 61-63%[23]. As a result, low values of transferrin saturation can not reliably make the diagnosis of iron deficiency. These limitations in the predictive value of serum ferritin and TSAT suggest that clinical judgement be used to correlate the results with patient's clinical status.

Treatment with Recombinant Human Erythropoietin

Recombinant Human Erythropoietin (Epo) should be started if patients Hb remains below 11gm% despite correcting the nutritional and iron deficiencies. The intravenous route is recommended in patients on haemodialysis while in others it can be used subcutaneously two to three times a week. Epo should be started in a dose of 120-180 units/kg/week in two to three divided doses [21]. Hb should be monitored once in two weeks till target Hb is achieved. Once target Hb is achieved, Hb should be monitored every month.

At the end of two weeks with Epo therapy the Hb should rise by 1 gm%. If the rise is less than 1 gm%, the dose of Epo should be increased by 50%, till the target Hb is achieved. If the rise in Hb% is more than 2 gm% at the end of two weeks then the dose of Epo can be reduced by 25%. Once the target Hb is reached or exceeded, then reduce the dose of Epo by 25%. The blood pressure should be checked with each dose and brought under control. Epo resistance should be suspected when the dose requirement exceeds 450 units/kg/week.

Coronary Artery Disease in Chronic Kidney Disease

Coronary artery disease accounts for nearly half the deaths in end stage renal failure and renal transplantation patients [24]. Silent myocardial ischemia is common and the incidence rises in diabetic patients and those with

Table 2
Treatment strategy for renal protection

Intervention	Therapeutic goal
Angiotensin converting enzyme inhibitor or Angiotensin receptor blocker (consider combination if goal not achieved with monotherapy)	Proteinuria less than 0.5gms/day GFR decline less than 2ml/mt/yr
Dietary protein restriction	0.6-0.8 gms/kg/day
Additional antihypertensive therapy	BP <130/80 mm of Hg
Dietary salt restriction (in presence of hypertension)	3-5 gms/day
Tight glycemic control	Hb A1c <6.5%
Reduce elevated calcium phosphate product	Normal values
Lipid lowering therapy	LDL-C less than 100 mgm/dl
Anti platelet therapy	Thrombosis prophylaxis
Correction of anaemia	Hb more $\geq$ 12 gms%
Smoking cessation	Abstinence
Weight control	Ideal body weight
Prevent urinary tract infection as in reflux nephropathy	

atherosclerosis. Coronary artery disease may manifest as hypotensive episodes, exertional angina, angina during dialysis, arrhythmias or exertional dyspnoea. The risk factors for coronary artery disease in end stage renal failure are hypertension, left ventricular hypertrophy, myocardial dysfunction, dyslipidemia, uncorrected anaemia, elevated homocysteine levels, smoking and vascular calcification.

Screening Program

Screening for risk factors for coronary artery disease may be done at stage 2 (GFR<90ml/min) of CKD, repeated at least once a year and before a renal transplant. The complete blood counts, fasting and post prandial blood sugar level, serum uric acid, calcium, phosphorous, lipid profile, electrocardiogram(ECG), echocardiography and chest radiograph should be the screening parameters.

The metabolic abnormalities in uraemia may themselves induce abnormalities in the ECG and stress thallium tests. Most patients with renal failure will not be able to perform the amount of exercise required for a treadmill test and therefore a dobutamine stress echocardiography is currently the procedure of choice to screen for coronary artery disease. Coronary angiography remains the gold standard for diagnosis of coronary artery disease. Asymptomatic patients at high risk should have a coronary angiography only if the screening tests reveal an abnormality. However symptomatic patients should undergo a coronary angiography without any screening tests. The estimation of serum enzymes may also have its pitfalls. Troponin T may be markedly elevated in patients on haemodialysis. A test may be considered positive if serum Troponin T is more than 0.8 ng/ml and creatinine kinase (CK) MB isoenzyme more than 5%, if the total CK is high. Troponin I is a more sensitive indicator of acute myocardial infarction. Regional wall motion abnormality detected by echocardiography has high sensitivity but does not differentiate old from new infarction. In all diabetics over the age of 45 years and symptomatic patients, a treadmill test and 2D echocardiography should be done. Coronary angiography is recommended if these tests are borderline or positive or even negative in symptomatic patients [24].

The targets to minimize cardiovascular disease risk in patients with CKD [24], include smoking cessation, blood pressure <130/80 mmHg, haemoglobin of 11-12 gm/dl, LDL cholesterol <100 mgm/dl, serum calcium 9-10 mg/dl, serum phosphate 2.5-5.5 mg/dl and intact para thyroid hormone (PTH) 100-200pg/mL, blood sugar fasting<126 mg/dl, postprandial <180mg/dl and serum albumin > 3.5gm/dl.

Therapy for established coronary artery disease

Aspirin, β -blockers, nitrates, platelet glycoprotein II_b and III_a inhibitors, heparin and thrombolytic agents can be used if there are no specific contraindications. Whenever anti coagulation is required, conventional heparin is preferred since its effect can be monitored by clotting time. Low molecular weight heparin should be avoided, and if used, the dose should be reduced by 50%. The safety profile of glycoprotein II_b and III_a inhibitors in dialysis patients is not well established. The dose should be reduced by 50% in case of tribofan and eptifibatide but not for abciximab. The indications for coronary artery bypass grafting and percutaneous transluminal angioplasty are similar in both uraemic and non-uraemic patients. These include significant left main vessel disease, reduced left ventricular function, triple vessel disease and unstable angina [25,26].

Renal Replacement Therapy (RRT)

Patient education on the need for transplant, dialysis and available modes of dialysis should preferably begin at stage 4 of CKD when the GFR is in the range of 15-29 ml/min. If haemodialysis is the selected mode of therapy then an arterio venous fistula may be constructed when the GFR falls below 20 ml/min [2]. For diabetics, a serum creatinine>6 mg/dl, creatinine clearance <15ml/min and for non diabetics a serum creatinine>8 mg/dl, creatinine clearance <10ml/min can be taken as indications to start dialysis. Dialysis can be started earlier, if there are uncorrectable signs of renal failure such as nausea, vomiting, weight loss, intractable congestive cardiac failure, hyperkalemia, asterexis, restless leg syndrome and a reversal of sleep wake cycle [27].

The basic choices are between haemodialysis and continuous peritoneal dialysis as shown in Table 3 [28].

Adequacy of Haemodialysis: The determination of the adequacy of dialysis therapy requires more than routine laboratory studies since malnourished and anorectic patients will make less urea and have a smaller muscle mass with deceptively low blood urea nitrogen and creatinine concentrations. Measurement of the “delivered dose” of dialysis is therefore focused on the removal of urea, an easily measured surrogate marker for uremic toxins [28]. The two most widely used measures of the adequacy of dialysis are calculated from the decrease in the blood urea nitrogen concentration during the treatment, the urea-reduction ratio, and KT/V. KT/V is a dimensionless index based on the urea clearance rate K, and the size of the urea pool represented as the urea-distribution volume, V. K the sum of clearance by the dialyser plus renal clearance, is multiplied by the time spent on dialysis T. Currently, a

Table 3**Dialysis mode decision guide**

Peritoneal Dialysis (PD) preferred	PD not preferred, but possible with added consideration	Contraindicated for CAPD (Continuous Ambulatory Peritoneal Dialysis)
Age 6-16 years		
Cardiovascular disease/hypertension	Large size (obesity)	Malnutrition
	History of diverticulitis	Multiple abdominal adhesions
Chronic disease like bleeding disorder, multiple myeloma, brittle diabetes, hepatitis B positive, travel demand for flexible diet	Severe low-back pain	Ostomies
	Hernias	Proteinuria >10g/day
	Multiple abdominal surgeries	Severe diabetic gastro paresis
	Impaired manual dexterity	Severe hypertriglyceridaemia
	Blindness	Advanced COPD
	Hiatus hernia with reflux esophagitis	Ascites
		Patient with patent Le Veen shunt
		Patient with ventriculo – peritoneal shunt
		Upper limb amputation
		Severe inflammatory bowel disease
		Acute active diverticulitis
		Active ischemic bowel disease
		Abdominal abscess
		Starting dialysis in the 3rd trimester of pregnancy
		Severe active psychotic disorder

urea-reduction ratio of 65 percent and a KT/V of 1.2 per treatment are minimal standards for adequacy, and lower levels of dialysis treatment are associated with increased morbidity and mortality. What constitutes an “optimal” dose of dialysis, above which no further improvement in survival or well-being can be achieved, is not known. Retrospective data show that survival rates do not rise as the urea-reduction ratio rises above 70 percent, or as KT/V rises above 1.3 [29,30].

Managing Hepatitis C virus Infection in Dialysis Patients

There are no clearly effective therapies for hepatitis C, that can be used safely in renal transplant recipients. In view of this limitation, there should be an increased focus on identification of and therapy for hepatitis C in patients with chronic kidney failure. The factors favouring HCV infection in CKD are time on dialysis, number of blood transfusions, mode of dialysis haemodialysis > peritoneal dialysis and existing prevalence of HCV infection in the dialysis unit. [32].

To prevent spread of HCV infection in dialysis units, CDC recommends routine serological testing and surveillance, and observing infection control practices for haemodialysis units. Where the prevalence remains unchanged despite application of CDC recommendations, additional measures to control nosocomial transmission include isolation of HCV positive patients, use of dedicated machines and a restriction on dialysers reuse for HCV infected patients [33,34].

Monitoring for HCV infection in Dialysis Patients

A base line testing should include serum alanine aminotransferase (ALT) levels and anti HCV antibody assays by third generation enzyme-linked immunosorbent assay (ELISA). In patients who are negative, monitor ALT levels monthly. If positive at any time then repeat HCV testing. Otherwise routine screening for anti HCV antibody should be done every six months. If ALT levels are persistently elevated despite negative anti HCV antibody, then testing for HCV RNA by polymerase chain reaction (PCR) is required [31]. Where cost is not a constraint, then HCV ribonucleic acid (RNA) may be used as a screening test.

Treatment and Monitoring Response

If HCV RNA is positive and a necro inflammatory/fibrosis (Knodell's) score on liver biopsy shows > stage 3 and grade 3, then give interferon 3 million IU, thrice weekly for 48 weeks. It can be stepped down to 1.5 million IU if side effects are bothersome. Monitor HCV RNA at 8-12 weeks of therapy. If it remains positive then chances of sustained virological response is unlikely. Pegalated interferon may be better because of the ease of administration and less side effects. In patients awaiting a renal transplant, surgery should be planned once HCV RNA is negative. At present the data is not enough, to recommend the use of ribavirine in end stage renal disease.

References

1. MK Mani. Prevention of Chronic Renal Failure at the

- Community Level. Medicine Update 2002; 12: 768-74.
2. National Kidney Foundation-DOQI clinical practice guidelines for chronic kidney disease evaluation, classification & stratification. *Am J Kidney Dis* 2002; 39 (Suppl):1S -266S.
 3. Brenner BM. Retarding the progression of renal disease. *Kidney Int* 2003; 64: 370-8.
 4. Hunsicker LG, Adler S, Caggiula A, et al. Predictors of the progression of renal disease in the Modification Of Diet In Renal Disease Study. *Kidney Int* 1997; 51:1908-19.
 5. Meyers BD, Deen WM, Brenner BM. Effects of nor epinephrine and angiotensin II on the determinants of glomerular ultra filtration and proximal tubule fluid absorption in the rat. *Circ Res* 1975; 37:101:10.
 6. Orth SR. Smoking and the kidney. *J Am Soc Nephro* 2002; 13:1663-72.
 7. Muntner P, Coresh J, Alikoski T, et al. Plasma Lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney Int* 2000; 58:293-301.
 8. Rousett J, Fouqueray B, Bofa JJ. Anemia management and the delay of chronic renal failure progression. *J Am Soc Nephrol* 2003; 14:173-7.
 9. Mathiesen ER, Hommel E, Hansen HP, et al. Randomised control trial of long term efficacy of captopril on preservation of kidney functions in normotensive patients with insulin dependent diabetes and microalbuminuria. *BMJ* 1999; 319:24-5.
 10. Kventy J, Gregersen G, Pedersen RS. Randomised placebo-control trial of perindopril in normotensive, normoalbuminuric patients with type I diabetes mellitus. *QJM* 2001; 94:89-94.
 11. Heart Outcomes Prevention Evaluation Study Investigators. Effect of Ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE study. *Lancet* 2000; 355:253-9.
 12. Jafar TH, Schmid CH, Landa M, et al. Angiotensin converting enzyme inhibitors and progression of non diabetic renal disease: a meta analysis of patient level data. *Ann Intern Med* 2001; 135:73-8.
 13. Viberti G, Wheeldon NM. Microalbuminuria reduction with Valsartan in patients with type 2 diabetes mellitus: a blood pressure independent effect. *Circulation* 2002; 106:672-8.
 14. Ruilope LM, Aldegier JC, Ponticelli C et al. Safety of the combination of valsartan and benazepril in patients with chronic renal disease. *J Hypertens* 2000; 18; 89-95.
 15. Ruggenenti P, Perna A, Remuzzi G. Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. *Kidney Int* 2003; 63:2254-61.
 16. Kambiz ZN, Brenner BM. Strategies to retard the progression of chronic kidney disease. *Med Clin N Am* 2005; 89:489-509.
 17. Klahr S, Levey AS, Beck GJ, et al. The effect of dietary protein restriction and the effect of blood pressure control on the progression of chronic renal failure. *Modification of Diet in Renal Disease study Group. N Engl J Med* 1994; 330:877-84.
 18. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. *N Engl J Med* 1998; 339:1448-56.
 19. Kasiski BL, Lakatua JD, Ma JZ, et al. A meta analysis of the effect of dietary protein restriction on the rate of decline of renal function. *Am J Kidney Dis* 1998; 31:954-61.
 20. Yu HT. Progression of chronic renal failure. *Arch Intern Med* 2003; 163:1417-29.
 21. National Kidney Foundation -DOQI clinical practice guidelines for the treatment of anaemia of chronic renal failure. *Am J Kidney Dis* 1997; 30 (3Suppl).192S-240S.
 22. Eschbach J, De Oreo P, Adamson J, et al. rHu EPO. Clinical practice guidelines for the treatment of anaemia in chronic renal failure. *Am J Kidney Dis* 1999; 30: 5192 – 240.
 23. Fishbane S, Kowalski EA, Imbriano LJ, Maesaka JK. The evaluation of iron status in haemodialysis patients. *J Am Soc Nephrol* 1996; 7:2654-7.
 24. Rostand SG, Rutsky EA. Ischemic heart disease in chronic renal failure: management considerations. *Semin Dial* 1989; 2:98-104.
 25. Sorrell VL. Diagnostic tools and management strategies for coronary artery disease in patients with end-stage renal disease. *Semin Nephrol* 2001; 21:13-24.
 26. Herzog CA. How to manage the renal patient with coronary heart disease: The agony & the ecstasy of opinion based medicine. *J Am Soc Nephrol (Indian Edition)* 2003; 2:1537-53.
 27. Shulman G, Himmelfarb J. Hemodialysis. In: Brenner BM, editors. *The Kidney*. 7thed. Philadelphia: W B Saunders, 2004; 2563-662.
 28. Shetty AK, Oreopoulos DG. Peritoneal Dialysis: Its indications and contraindications. *Dialysis & Transplant* 2000; 29: 71.
 29. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 1985; 28:526-34.
 30. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing haemodialysis. *N Engl J Med* 1993; 329:1001-6.
 31. Held PJ, Port FK, Wolfe RA, et al. The dose of haemodialysis and patient mortality. *Kidney Int* 1996; 50:550-6.
 32. Meyers MC, Seef LB, Stehman Breen CO, Hoofnagle JH. Hepatitis and renal Disease: An Update. *Am J Kidney Dis* 2003; 42: 631-7.
 33. Centre of disease control & prevention: Recommendations for preventing transmission of infections among chronic haemodialysis patients. *MWWR Recomm Rep* 2001; 50:1-43.
 34. Santos JP, Loureiro A, Cendrolo Neto M, Pereira BJ. Impact of dialysis room reuse strategies on the incidence of hepatitis C virus infection in haemodialysis unit. *Nephrol Dial Transplant* 1996; 11:2017-22.