Hepatitis C in dialysis units

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Patients with chronic renal insufficiency on renal replacement therapy (RRT) with hemodialysis have higher infection rates for Hepatitis C virus (HCV) than the general population. Rates in developed countries such as Holland (4%), the United Kingdom (4%), Germany (7%), Belgium (7%) and Sweden (10%) are low. However, prevalence is a little bit higher in the USA (14%), France (15%), Spain (22%) and Italy (22%). In developing countries prevalence is higher: in Brazil (18%), in Turkey (21%), in the Sudan (22%), in Tunisia (24%), in Saudi Arabia (45%), in Moldavia (74%), in Morocco (78%) and in Egypt (80%). Despite clearly indicated reductions in these rates related to the implementation of biosafety measures in recent years, Hepatitis C continues to be an important problem in these populations. (1, 2)

The main risk factor for acquisition of the Hepatitis C infection is the amount of time in a patient spends in hemodialysis units. Screening for antibodies in bags of blood and the use of erythropoietin have allowed for significant reductions in HCV transmission by blood derivatives. Nosocomial transmission between patients at present represents the most important path of infection. It is facilitated by failure to strictly adhere to universal recommendations for infection control. Among the most important measures to be considered are:

a. Medicine preparation in separated areas
b. Avoiding the use of the same vials for several patients (e.g. for heparin)
c. Disinfecting surfaces, equipment and circuits after use by or treatment of each patient
d. Washing hands and changing gloves between patients. It is not clear whether isolation of patients, use of independent machines or reusability of filters have any relation to prevention or to HCV transmission risk. (3, 4)

HCV diagnoses by 3rd generation Elisa tests using antibodies have a very low rate of false negatives (about 0.23%). Confirmation of infection by reverse transcription polymerase chain reaction (RT-PCR) allows detection of viral loads of less than 43 UI of. It is recommended that the blood sample for RT- PCR be taken before hemodialysis to avoid technical errors in administration of heparin, and to avoid the capture and destruction of viral particles on the internal surface of the hemodialyzer. This is caused by the hydraulic pressure exerted by the blood during the dialysis. Although levels of aminotransferases are lower in hemodialysis patients than in the general population, and patients with Hepatitis C tend to have higher levels, their levels do not exceed the upper

limit of normal range. This limits the utility of measuring levels of aminotransferases for diagnosis of the disease (5, 6, 7).

The natural history of HCV in patients with chronic renal insufficiency has been difficult to evaluate since different factors affect the prognosis of these patients. These include age and the presence of comorbidities including diabetes, vascular disease and HIV coinfection. A meta-analysis of 11,589 patients in a hemodialysis program confirmed that infection by HCV increases the relative risk (RR) of global mortality by a factor of 1.34 (95% confidence interval (CI), 1.13 to 1.59) while the RR of mortality from hepatic disease in these cases is 5.89 (95% CI, 1.93 to 17.99). Recently an association with cardiovascular mortality has also been found. Its RR is 1.8 (95% CI, 1.1 to 2.95). Survival rates of patients with Hepatitis C who have undergone renal transplant and survival rates of the implanted organ are shorter in the long term (10 years) than survival times for uninfected controls: 65% vs. 85% for patient survival and 49% vs. 69% for graft survival. This is related to higher incidences of de novo diabetes, arteriosclerotic disease and membranoproliferative glomerulonephritis in the graft (8, 9).

Contrary to the analysis above, a recent study of 13,384 patients did not show any proof of association between HCV and risk of developing a terminal renal disease when compared to uninfected controls (5.3% vs. 5.1%) (10).

Hepatic biopsies are indicated for patients with Hepatitis C in order to measure the level of inflammation and to stratify the fibrosis of the disease so that the need for antiviral treatment can be defined. Nevertheless, this procedure is not free from complications, mainly related to hemorrhaging. A patient with chronic renal insufficiency may suffer from platelet dysfunction related to medicines and uremia and from hepatocellular dysfunction associated with advanced hepatopathy. A point of interest related to biopsy is whether or not cirrhosis is present, since the patient may require a double liver-kidney transplant. The current recommendation is that the presence of compensated cirrhosis (Child A) does not automatically indicate a need for hepatic transplant, so the renal transplant alone may be performed. The role of the noninvasive studies of fibrosis such as Fibrotest and Fibroscan for chronic renal patients has yet to be decided (11).

HCV treatment is based on the use of the pegylated interferon (PEG-IFN) and Ribavirin. In patients with terminal renal insufficiency, glomerular filtration rate (GFR) is reduced which increases the half life of both antiviral drugs. This predisposes patients to a greater number of adverse events. A recent meta-analysis of 24 studies with conventional interferon treatment of a total of 429 hemodialysis patients showed sustained response in 39% of all patients with a adverse events causing discontinuance of treatment of 19% of all patients. This response is superior to that observed in patients in the general population where response was sustained in 7% of patients treated and discontinued for 16%. Perhaps this is related to smaller viral loads, increased interferon clearance time (half life of 9.6 hours in hemodialysis patients versus 5.3 hours in the general population), increased the endogenous release of interferon and increased production of hepatocyte growth factor (12).

Dialysis removes very little Ribavirin, so there is tendency to accumulation which predisposes to hemolysis in these patients. At present its extended use is not recommended except in protocols with low doses (200 mgs a day or three times per week), weekly hemoglobin monitoring, high doses of erythropoietin and maintenance of serum levels between 10 and 15 umol/L (these are only measured in specialized centers) (13).

Use of pegylation increases the half life of interferon allowing weekly application. The few studies done with these molecules have not demonstrated superiority of this method over conventional interferon. However, tolerance is good and adverse life threatening events such as sepsis and acute pancreatitis are rare. The majority of the studies have been done with PEG-IFN alpha 2a alone or in combination with low doses of Ribavirin. This combination seems to have a rate of a higher sustained response rate in some series (between 50% and 90%) but with mortality related to anemia (14, 15).

Treatment is not indicated for patients with renal transplants who have a high risk of graft rejection except in those unusual cases of cholestatic fibrosing hepatitis (16, 17).

The most important recommendations of the practical guides for prevention, diagnosis, evaluation and treatment of Hepatitis C in chronic renal patients (KDIGO) are summarized as follows:

1. All hemodialysis patients must have anti-HCV every six months.
2. Al patients with unexplained alanine aminotransferase (ALT) elevations must have anti-HCV.
3. All dialysis patients with HCV must be evaluated for antiviral therapy.
4. All patients with acute Hepatitis C must be treated without delay.
5. All patients on waiting lists for kidney transplants must receive antiviral drugs.
6. Patients with kidney transplants should not undergo dialysis due to rejection risk.
7. PEG-IFN is the medication of choice.
8. Ribavirin use should be avoided due to hemolysis risk.
9. Isolation of infected patients is not necessary.
10. Patients with compensated cirrhosis must be evaluated for kidney transplants.

The 999 patients studied in the report on the prevalence of antibodies in dialysis units in Cali, presented in this magazine, is probably the largest study of this type ever undertaken in our country. The low prevalence (2.9%) of infection in the dialysis units evaluated is important. It allows us to conclude that good bio-security practices for avoiding transmission of infections are being implemented. This rate is similar to the one found in a 2004 study of 99 patients of two dialysis units in Cartagena. In that study there were 2 positive cases for antibodies and PCR, a prevalence of rate 2.4% (unpublished data).

The rate of false positives (patients with positive antibodies and negative PCR) was low, but this rate is striking since spontaneous clearance of virus in these patients is not usual. There were no false negatives (patients with negative antibodies and positive PCR), although large population studies have reported rates of as high as 0.23% of patients studied. The PCR used in this study was the Cobas Amplicor HCV monitor test, version 2.0. This is the PCR that is most often employed in daily practice. It is superior to the homemade PCRs that were used in previous studies in our country. Length of stays in dialysis units was variable. 58% of the patients with HCV had no history of previous blood transfusions, increasing the probability of nosocomial transmission as the most likely source of infection. 34% of the patients had visited more than one dialysis unit, a factor adding to risk of exposure to infections by hepatitis virus.

No doubt, this study will be referenced on the international maps of prevalence of HCV infection in dialysis units.

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