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Isolation as a strategy for controlling the transmission of hepatitis C virus (HCV) infection in haemodialysis units (Review)

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[Intervention Review]

Isolation as a strategy for controlling the transmission of hepatitis C virus (HCV) infection in haemodialysis units

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ABSTRACT

Background

The hepatitis C virus (HCV) infection affects about 2% of the world's population and can cause chronic liver infection and persistent long-term sequelae such as cirrhosis and liver cancer.

The prevalence of HCV infection among people on haemodialysis is often higher than the general population. The virus is easily transmitted parenterally, and blood transfusions have previously played a significant role in transmission; however, erythropoietin therapy has reduced the need for transfusions, and coupled with improved screening of donated blood, has significantly decreased transmission by transfusion. Although control of hospital-acquired infection has improved with the advent of biosafety measures, stopping HCV transmission in haemodialysis units remains challenging.

Isolating people infected with HCV involves physical separation from others to limit direct or indirect transmission and includes a number of strategies during dialysis. The evidence for isolating people infected with HCV during haemodialysis is sparse with some inconsistencies.

Objectives

To evaluate the benefits and harms of isolation of HCV-infected patients during haemodialysis on the transmission of HCV to other patients.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 26 November 2015 through contact with the Information Specialist using search terms relevant to this review. We also searched the Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to 2015), Web of Science Conference Proceedings Citation Index-Science (CPCI-S, 1990 to 2015), ProQuest Dissertations & Theses Database (1990 to 2015), and Open Grey (1990 to 2015).

Selection criteria

We included randomised controlled trials (RCTs), quasi-RCTs and cluster RCTs evaluating the clinical benefits and harms of isolating HCV-infected patients during haemodialysis on the transmission of HCV to other patients. We considered incidence of dialysis-acquired HCV infection, all-cause mortality, and adverse effects associated with isolation as the primary outcomes.

Data collection and analysis

Summary estimates of effect were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) or standardised mean difference (SMD) and 95% CI for continuous outcomes.

Main results

Only one study, which included 12 centres was identified: four centres used dedicated haemodialysis machines for HCV-infected patients and eight centres used non-dedicated machines. The total number of patients enrolled was 593. One centre was excluded after randomisation. Random sequence generation was not described and allocation concealment was not performed. Participants and personnel were not blinded and blinding of outcome assessors was not reported. Only 74.5% of the patients were followed for 9 months; and 47.3% were followed for an additional 9 months. The authors only reported one outcome, measuring the difference in the incidence of HCV in both groups. The authors did not consider the exposure time, to determine the adjusted rate of seroconversion risk/patient-year.

The study reported that the incidence of HCV infection during the first follow-up period (9 months) was 1.6% in the dedicated group, and 4.7% in the non-dedicated one (446 patients analysed out of 593 randomised; RR 0.34, 95% CI 0.11 to 1.07). During the second follow-up period (18 months) the incidence was 1.3% in the dedicated group and 5.8% in the control (281 patients analysed out of 593 randomised; RR 0.22, 95% CI 0.05 to 1.02). Therefore, we found no differences in terms of the number of participants developing HCV infection when comparing the dedicated group with the usual care. Moreover, the evidence was of very low quality, which means that we have very little confidence in the effect estimate.

Authors' conclusions

The benefits and harms of isolation of HCV-infected patients during haemodialysis on the transmission of HCV to other patients are uncertain. Evidence from one short-duration cluster-randomised study with a high risk of bias did not find differences in terms of the number of participants developing HCV infection when comparing the use of dedicated haemodialysis machines for HCV infected patients with the use of non-dedicated machines.

PLAIN LANGUAGE SUMMARY

Isolation as a strategy for controlling the transmission of hepatitis C virus (HCV) infection in haemodialysis units

What is the issue?

The hepatitis C virus (HCV) is easily transmitted intravenously, such as blood transfusions and the use of haemodialysis. It can cause a persistent infection and chronic liver disease. The frequency of HCV is higher among people on haemodialysis than the general population; and is associated with increased risk of death from heart disease and liver. We wanted to find out if the isolation of people with HCV during haemodialysis (using a different room, machines or dedicated staff, a specific shift) was effective in limiting the direct or indirect transmission of the virus to non-infected patients.

What did we do?

We conducted an extensive literature search to November 26, 2015, but only found one study looking at isolation as a strategy for controlling the transmission of HCV infection.

What did we find?

This one study included 12 centres (593 patients). Four centres assigned HCV-infected patients to a dedicated haemodialysis machine and eight centres did not. This study reported the incidence of HCV in haemodialysis patients decreased with the use of dedicated machines; however it was not possible to determine the benefits and harms associated with isolation, cost, or mortality from the disease.

Conclusions

There is insufficient evidence, but additional studies would help clarify the role of isolation to reduce the transmission of HCV in haemodialysis patients.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Dialysis machine separation versus usual care

Should patients with HCV be isolated in haemodialysis units for controlling the transmission of HCV?

Patient or population: patients in haemodialysis
Setting: ambulatory

Intervention: isolation
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with usual care	Risk with isolation				
Incidence of HCV infection (9 months)	Study population		RR 0.34 (0.11 to 1.07)	446 (1)	⊕⊖⊖⊖ VERY LOW	Very low quality of evidence due to high risk of bias and imprecision
	47 per 1.000	16 per 1.000 (5 to 50)				
Incidence of HCV infection (18 months)	Study population		RR 0.22 (0.05 to 1.02)	281 (1)	⊕⊖⊖⊖ VERY LOW	Very low quality of evidence due to high risk of bias and imprecision
	58 per 1.000	13 per 1.000 (3 to 59)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

BACKGROUND

Description of the condition

Hepatitis C virus (HCV) infection affects approximately 3% of the global population, or about 170 million people (Lee 2014). HCV causes persistent infection and chronic liver disease; long-term sequelae include cirrhosis (30%) and liver cancer (1% to 5%) (Hsu 2015; Webster 2015).

Extrahepatic manifestations of chronic HCV infection are considered to be of immunologic origin and include cryoglobulinaemia, membranoproliferative glomerulonephritis, (Morales 2012) and porphyria cutanea tarda.

Prevalence of HCV infection in haemodialysis patients is usually higher than in the general population (Fabrizi 2012). The overall incidence rate of HCV infection is 1.47/100 patient-years; 4.44/100 patient-years in low- to middle-income countries, and 0.99/100 patient-years in high-income countries (Su 2013). Prevalence ranges from less than 5% in most Northern European countries (Fissell 2004; Schneeberger 2000) to over 70% in many parts of the world, including countries in Asia, Latin America and North Africa (Sun 2009; Vladutiu 2000). However, the prevalence of HCV in European dialysis centres declined sharply in the early 2000s. This was attributed to reduced risk of hospital-acquired infection and occupational HCV infection (Jadoul 2004), increased mortality rates, and stabilisation of the incidence of acute HCV infection (Espinosa 2004). Falling prevalence rates emphasise the importance of adhering to recommended infection control precautions and virological follow-up to detect anti-HCV antibodies using sensitive, specific new-generation serological tests (Saune 2011).

HCV-infected haemodialysis patients are at increased risk of liver or cardiovascular disease-related death compared with non-infected patients (Fabrizi 2012). HCV infection is associated with increased morbidity and mortality in kidney transplant recipients (Batty 2001; Butt 2007; Mahmoud 2004). Anti-HCV-positive patients on dialysis are at increased risk compared with anti-HCV-negative patients.

Description of the intervention

Isolating HCV-infected patients (or patients waiting HCV screening results) during haemodialysis is defined as physical segregation from others for the express purpose of limiting direct or indirect transmission of HCV. Isolation policies may include strategies for HCV-infected patients with different grades of intensity, such as use of a dedicated dialysis machine, personnel, room, or shift, or other barrier precautions (such as aprons, gowns, or gloves), by healthcare professionals attending these patients. These strategies may be implemented in combination.

How the intervention might work

HCV is easily transmitted parenterally and its control has therefore been a challenge in dialysis settings (Natov 2005; Su 2013). More recently erythropoietin therapy, which reduces requirements for transfusions, together with more sensitive tests to detect HCV in donated blood, have significantly reduced transmission via transfusion (Marwaha 2014). The post-transfusion risk has been calculated at around 0.0001% in the USA (i.e. 1 blood transfusion in 1 million units of blood), with similar dramatic improvements in the viral safety of blood in other western countries (Selvarajah 2012).

The WHO has estimated an overall prevalence of 3% for HCV infection in the global population, but there is a wide geographic variability: fewer than 5% of people in most northern European countries are infected, close to 10% in southern Europe and the USA, and estimates range from 10% to 50% and up to 70% in many low- to middle-income countries. HCV infection incidence has however decreased to less than 1.2% of people in high-income countries (Espinosa 2004; Finelli 2005; Jadoul 2012).

This reduction was initially attributed to decreased rates of post-transfusion infection (Djordjevic 2000; Valtuille 2002), but it was later ascribed to other infection control measures used to prevent hospital-acquired infection rates in dialysis units. Prevalence of HCV infection among people on haemodialysis is generally below 10% in most countries, but may be higher (> 20%) where social crisis, war, or economic downturn exist (Ali 2011; Selm 2010; Voiculescu 2010). In these situations, maintenance of chronic haemodialysis programs is highly challenging, and infection control programs are difficult to maintain.

In spite of reduced rates of infection, HCV transmission in haemodialysis units remains an unsolved problem. Despite advances in screening blood products for HCV people on haemodialysis it remains at a higher risk of infection than in the general population (Ozer Etik 2015)

HCV seroconversion (change from anti-HCV negative to anti-HCV positive) has been detected in patients who were never transfused (Agarwal 2011) therefore other mechanisms of transmission occur in dialysis units. Shared haemodialysis machines (Elamin 2011; Sartor 2004) and reprocessing of dialysers from people with HCV have been linked to HCV transmission (Bashiri 2013). Other factors include physical proximity to an infected person and sharing personal items (Al-Ghamdi 2004; Fabrizi 2008); breakdown in standard infection control practices, including improper handling and preparation of medications (Alter 2008; CDC 2009; Samandari 2005; Thompson 2009; Williams 2004); poor environmental cleaning (CDC 2009; Girou 2008; Kamili 2007; Patel 2010; Thompson 2009) and basic hygiene practices (Alfurayh 2000; Patel 2010); staff numbers and workload (Arenas 2005; CDC 2009; KDIGO 2008; Patel 2010; Shimokura 2011).

Why it is important to do this review

The evidence for or against the use of isolation of HCV-infected patients during haemodialysis is weak and certain inconsistencies exist regarding the recommendations for its use among different guidelines. The centres for Disease Control and Prevention (CDC 2001; Mbaeyi 2013) published guidelines to prevent the transmission of HCV and other infections among haemodialysis patients, but did not recommend the isolation of HCV-infected patients. KDIGO 2008 stated that haemodialysis units should ensure implementation of and adherence to strict infection-control procedures designed to prevent transmission of blood-borne pathogens, including HCV, but isolation of HCV-infected patients was not recommended as an alternative to strict infection-control procedures (unless in cases of continued hospital-acquired transmission, where a local isolation policy may be deemed necessary). The UK Renal association stated that patients with HCV patients do not need to be dialysed in a segregated area, however more experienced staff should be assigned. If nosocomial transmission continues to occur, despite reinforcement and audit

of the precautions, a local segregation policy may be deemed necessary (Geddes 2011)

The European Best Practice (ERBP) Work Group considers that implementation of universal hygienic measures should be the standard of care. Isolation of positive patients could be considered, but only if this practice does not have a negative impact on the implementation and reinforcement of basic hygienic measures in the unit as a whole (Covic 2009). Some investigators support isolating patients with HCV infection in a specific haemodialysis room (Fabrizi 2008), or suggest that the no isolation policy should not be generalised. Whether or not HCV-positive patients should be isolated is still debated, particularly since isolation policies to control HCV infection transmission in haemodialysis units involves significant logistic problems that should be considered.

OBJECTIVES

This review aimed to evaluate the benefits and harms of isolation of HCV-infected patients during haemodialysis on the transmission of HCV to other patients.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods), and cluster RCTs and cluster quasi-RCTs (where centres rather than individual patients were randomised), looking at isolation of HCV-infected patients during haemodialysis were eligible for inclusion.

Types of participants

All patients (adults and children) undergoing maintenance haemodialysis and dialysed in a haemodialysis centre (e.g. hospital unit, outpatient clinic) were eligible for inclusion.

Types of interventions

Intervention group

Any strategy targeting the isolation during haemodialysis of HCV-infected patients or patients waiting HCV screening results was eligible. Isolation was defined as the physical segregation of these patients from others with the express purpose of limiting direct or indirect transmission of HCV to other patients. Isolation policies could include a number of strategies with different grades of intensity, such as the use of a dedicated dialysis machine, personnel, room or dialysis shift.

Control group

We considered any control group that enabled comparison to determine the relative effect of the isolation strategy as eligible for inclusion. Studies comparing two types of isolation strategies were also eligible.

Types of outcome measures

Primary outcomes

- Incidence of dialysis-acquired HCV infection
- All-cause mortality
- Adverse effects associated to the isolation strategy (such as negative effects on patient mental well-being, or adverse effects related to supportive care failures).

Secondary outcomes

- Incidence of dialysis-acquired non-HCV infections
- Patient satisfaction with treatment, measured with a validated tool
- Isolation costs.

Search methods for identification of studies

Electronic searches

We searched Cochrane Kidney and Transplant's Specialised Register to 26 November 2015 through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on Cochrane Kidney and Transplant scope. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

We searched the following electronic databases.

1. Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to 2015)
2. Web of Science Conference Proceedings Citation Index-Science (CPCI-S, 1990 to 2015) (accessed via ISI Web of Science)
3. ProQuest Dissertations & Theses Database (1990 to 2015)
4. Open Grey (1990 to 2015).

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles and relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. Titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however, studies and reviews thought to include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts, and if necessary the full text, of these studies to determine which satisfied the inclusion criteria.

Data extraction and management

Data extraction was to be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were to be translated before assessment. Where more than one publication of one study existed, reports were to be grouped together and the publication with the most complete data used in analyses. Where relevant outcomes were only published in earlier versions these data were to be used. Any discrepancy between published versions was to be highlighted.

Assessment of risk of bias in included studies

The following items were to be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011a) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was recruitment bias adequately prevented?
- Were baseline imbalances (in terms of either the clusters or the individuals) adequately addressed?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?
- Was the study analysed by correct statistical methods (i.e. taking the clustering into account)?

Measures of treatment effect

For dichotomous data and for counts of rare events and rates (dialysis-acquired HCV infections, dialysis-acquired non-HCV infections, mortality due to dialysis-acquired infections, all-cause mortality, adverse effects) we planned to report risk ratios (RR); for continuous data (patient satisfaction with treatment) we planned to use the mean difference (MD) with 95% CI. Where different scales were used to measure continuous outcomes, we planned to calculate a standardised mean difference (SMD).

Unit of analysis issues

We planned to include cluster RCTs, and when possible, extract effect measures and standard error rates from an analysis taking clustering into account. If that was not possible, we planned to extract the number of clusters and estimate the intra-cluster correlation coefficient to inform a reliable analysis. If this was not possible, we planned to disregard the clustering and investigate the effect of this in a sensitivity analysis (Deeks 2011).

Dealing with missing data

We planned to extract data for intention-to-treat analyses (ITT) and contact authors if required information was missing. Where ITT analysis was not possible, we planned to extract data from an available case analysis and assess the risk of bias from attrition.

Assessment of heterogeneity

We planned to analyse heterogeneity using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance, and the I^2 statistic.

Assessment of reporting biases

We did not expect that a sufficient number of studies would be identified to create a useful funnel plot. Assessing reporting bias is difficult, but we planned to note whether outcomes that we considered important were reported. We planned to contact authors about possible unpublished outcomes.

Data synthesis

We planned to use a random-effects model and to express the results as both relative risks and number-needed-to-screen to achieve the relevant outcomes, both beneficial and harmful.

Subgroup analysis and investigation of heterogeneity

We planned to perform the subgroup analyses

1. Mean duration of the haemodialysis treatment
2. The degree of missing primary outcome data
   a. High prevalence of HCV in the haemodialysis unit: studies implemented in a context of high HCV prevalence (< 5%) versus non-high HCV prevalence (≥ 5%)
3. Outbreak situation: studies implemented when healthcare associated infection (any pathogen) were noted to be increasing or to exceed a recognised benchmark versus non outbreak situation
4. Types of isolation.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors on effect size.

- Repeating the meta-analysis to assess the effect of excluding studies with high risk of bias
- Exploring the impact of the assumptions taken in the available case analysis by performing a sensitivity analysis with imputation of missing data
- Assessing the effect of the statistical model chosen for meta-analysis (fixed-effect model versus random-effects model)
- Repeating the meta-analysis to assess the effect of including only studies with allocation to interventions at the group level (cluster designs) (Ukoumunne 1999).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

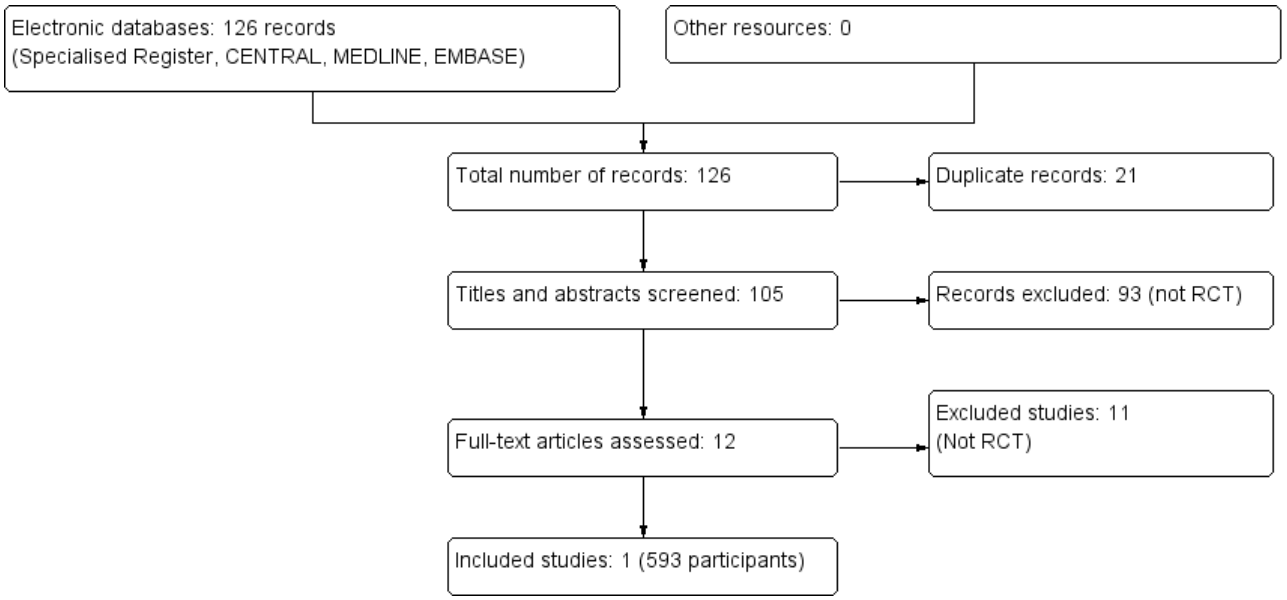
Results of the search

The combined search of MEDLINE, EMBASE and CENTRAL identified a total of 126 articles, of which 125 were excluded.

1. Twenty one records were duplicates
2. After reviewing the abstracts, 93 records were excluded because they did not meet our inclusion criteria
3. After full text review an additional 11 records, which were not RCTs, were excluded.

We therefore included one study enrolling 593 patients (Shamshirsaz 2004). A flow chart of the study selection process is shown in Figure 1

Figure 1.



Included studies

Shamshirsaz 2004 was a prospective RCT evaluating the effect of dialysis machine separation in reducing HCV transmission to haemodialysis patients. Selected centres were randomly divided into dedicated and non-dedicated haemodialysis machine groups. Positive cases were confirmed by RT-PCR. Information regarding age, sex, occupation (health care personnel, surgeons and dentists), HCV-infected relatives, previous peritoneal dialysis, surgery during last 2 months, duration of haemodialysis, number of blood product transfusions, history of organ transplantation, and the causes of ESRD was collected. Outcomes included incidence of HCV infection in both groups.

Patients were dialyzed for 4 to 4.5 hours, 2 or 3 times/week, using standard haemodialysis techniques. All included haemodialysis patients were HIV and hepatitis B surface antigen (HBsAg) negative. Dialysis membranes were low pressure and used only once and haemodialysis machines were bleached and rinsed between dialysis sessions according to the manufacturers' instruction. All machines were located in dialysis wards and not in separate rooms for both groups. Patient to staff ratio in the dedicated and non-dedicated groups was not statistically different (3.1 and 3.4 respectively) and all staff members were negative for anti-HCV. Education courses hygiene guidelines the CDC were conducted for all personnel involved in patient care, a checklist of the practice was used. In all centres the patients had specific dialysis place. It was specified how often the tests were performed HCV patients during the study or whether this was routinely carried out.

The patients were followed for 9 months (first follow-up population) and 281 patients who remained within the study were followed for an additional 9 months (second follow-up population). See Characteristics of included studies.

Excluded studies

Eleven studies were not RCTs (Agarwal 2009; Barril 2003; Gallego 2006; Garcia-Valdecasas 1994; Huang 1995; Mohamed 2010; Ross 2009; Saxena 2003; Shebeb 2006; Valtuille 1998; Yang 2003)

Risk of bias in included studies

See risk of bias in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across one included study.

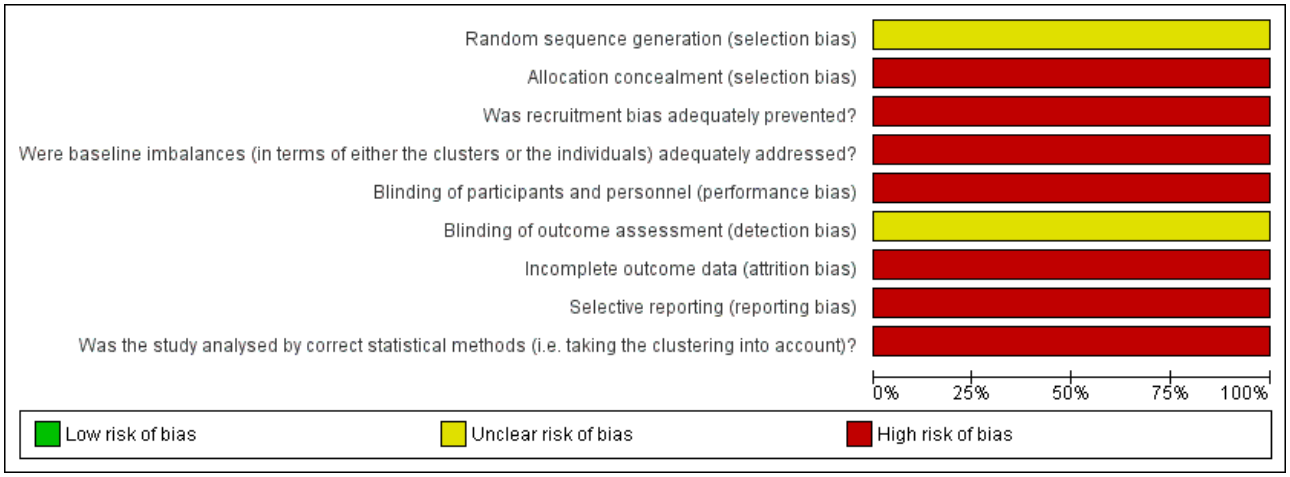
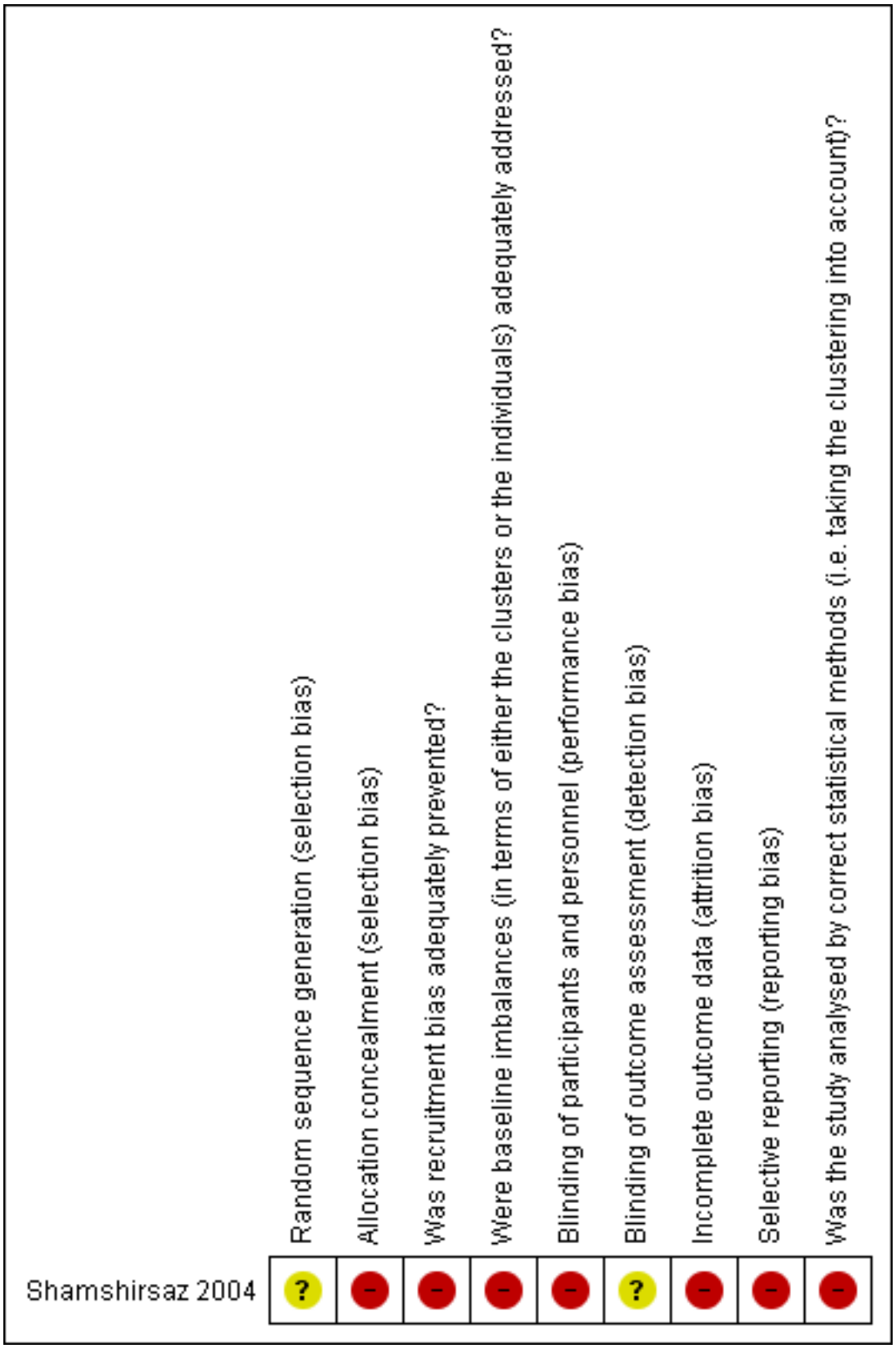


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for one included study.



Allocation

This study did not describe the use of a random number table to generate the allocation sequence. Allocation concealment was not performed

Randomisation was performed by dialysis centre. It was a cluster RCT, which included four centres (dedicated) compared with eight centres (non-dedicated).

Blinding

Participants (patients and investigators) were not blinded. Blinding of outcome assessors was not reported.

Incomplete outcome data

Only 74.5% (446/593) of the patients were followed for 9 months, and 47.3% (281/593) were followed for an additional 9 months.

One centre was excluded after randomisation causing a deviation from protocol.

Selective reporting

The authors only reported one outcome, measuring the difference in the incidence of HCV in both groups. No secondary outcomes were reported.

The authors did not consider the exposure time, to determine the adjusted rate of seroconversion risk/patient-year.

Other potential sources of bias

The assessments of the risk of bias domains relative to cluster designs are detailed in the risk of bias table (see Characteristics of included studies).

Effects of interventions

See: **Summary of findings for the main comparison** Dialysis machine separation versus usual care

Incidence of dialysis-acquired HCV infection

Shamshirsaz 2004 reported the incidence of HCV infection was 1.6% in the dedicated group and 4.7% in the non-dedicated one (Analysis 1.1 (1 study 446 participants): RR 0.34, 95% CI 0.11 to 1.07) during the first follow-up period (9 months). During the second follow-up period (18 months), the incidence was 1.3% in the dedicated group and 5.8% in the non-dedicated group (Analysis 1.2 (1 study, 281 participants): RR 0.22, 95% CI 0.05 to 1.02). Therefore, we found no differences in terms of the number of participants developing HCV infection when comparing the dedicated group with the usual care. Moreover, the evidence was of very low quality, which means that we have very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect.

All-cause mortality

Mortality was not reported.

Adverse effects

Adverse effects associated with the isolation strategy were not reported.

Incidence of dialysis-acquired non-HCV infections

Incidence of dialysis-acquired non-HCV infections were not reported.

Patient satisfaction with treatment

Patient satisfaction with treatment was not reported.

Isolation costs

Isolation costs were not reported.

DISCUSSION

Summary of main results

Only one study meeting our inclusion criteria was identified (Shamshirsaz 2004). This study selected haemodialysis centres, one by one to reach a total number of 593 patients (12 centres). Selected centres were randomly divided in to dedicated and non-dedicated haemodialysis machine groups, including 297 patients in the dedicated group (4 centres) and 296 patients in the non-dedicated group (8 centres). This study found that the use of dialysis machines dedicated for HCV infected individuals, as compared with the use of non-dedicated dialysis machines, made no difference in terms of reducing the incidence incidence of HCV infection during the first (9 months) or second (18 months) follow-up periods. The quality of the evidence was very low (see Summary of findings for the main comparison).

This study did not report any of our other primary outcomes of interest (all-cause mortality, adverse effects associated with the strategy of isolation).

Overall completeness and applicability of evidence

We planned to include patients (adults and children) undergoing maintenance haemodialysis and dialysed in a haemodialysis centre and assess whether strategies isolation machine, room, staff or dialysis shift influence the transmission of hepatitis C. Our search just found one study where the separation of machines is evaluated as a form of isolation.

Consideration should also be given to both the prevalence of hepatitis C and the geographical region as this may influence the possibility of seroconversion. Regions with high prevalence may require isolation combined strategies: room, machine, and personnel. No costs are included for the isolation strategy.

Methods of randomisation were unclear, participants and patients were not blinded, so that the results of this study must be considered with some caution. Confirmatory research is required. Any further studies conducted in this area must be well designed RCTs assessing these primary outcomes.

Quality of the evidence

This review is based on the evidence of one RCT (Shamshirsaz 2004) that included a total of 12 haemodialysis centres (593 patients) divided into a group of dedicated dialysis machines involving four centres: 297 patients, 267 negative and 30 positive for HCV and a group of centres with non-dedicated machines: 8 centres: 296 patients, 275 negative and 21 positive for HCV.

The authors did not disclose the details of the method of randomisation, participants and patients were not blinded, and blinding of outcome assessors was not reported. The authors decided to exclude, after randomisation, one of dialysis centres in the non-dedicated group due to non-adherence to CDC hygienic guidelines early in the study. There was a high risk of bias due to incomplete outcome data: only 74.5% of patients were followed for 9 months, and 47.3% were followed for an additional 9 months. In addition, the estimation of the effect of the intervention was imprecise. This makes the quality of evidence very low (see Summary of findings for the main comparison).

Potential biases in the review process

We followed the Cochrane Collaboration guidelines for conducting this systematic review and meta-analysis. Strengths of our review include the searching of several databases. Study selection, assessment of risk of bias, and data extraction were performed by two authors, which reduced the risk of error and bias. Although efforts were made to collect relevant data, the possibility of missing data cannot be excluded. Publication bias remains a possible source of important bias. Meanwhile, interpretation of the result should be done with extreme caution.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic review on this topic; many authors have reported some reduction (but not full prevention) of HCV transmission in haemodialysis, and after the adoption of an isolation policy, most of the studies have compared their results with their own historical control (before-and-after). Thus, it is unclear whether the reported improvement resulted from the adoption of an isolation policy or rather from the simultaneous raising of awareness and reinforcement of the application of hygienic precautions. These isolation policies include: implementing the isolation of a room (Agarwal 2009; Barril 2003); using exclusive machines (Garcia-Valdecasas 1994); and isolating machines, room and staff (Gallego 2006; Huang 1995; Saxena 2003); and Mohamed 2010, Ross 2009 and Shebeb 2006, compared isolation versus universal precautions. In all cases isolation was found to decrease the rate of seroconversion. In addition, Yang 2003 conducted a study with three sets of patients: one set without isolation, a second set with a dedicated area and a dedicated machine in the same room and a third set of patients isolated in a separate room, and showed that isolation in a different room was better than dedicated machines.

In contrast, a DOPPS multicentre study concluded that isolation does not protect against transmission of HCV in haemodialysis patients (Fissell 2004). A prospective observational study by Jadoul 1998 showed a reduction from 1.4% to 0% of the annual incidence of HCV seroconversion. They have reported a reduction of HCV transmission after the reinforcement of basic hygienic precautions, without any isolation measures.

AUTHORS' CONCLUSIONS

Implications for practice

Data from robust RCTs are not available to allow conclusions to be drawn about the relative effectiveness of isolation as a strategy to control HCV transmission in haemodialysis units. Therefore, the benefits and harms of isolation remain unknown.

Implications for research

Large, multicentre long-term RCTs of good quality are required to answer the questions concerning the benefits and harms of isolation of HCV-infected patients during haemodialysis. These studies should evaluate mortality, costs and complications associated with isolation. These studies should ensure the physical separation of either the centre or room; these programs should have strict isolation strategies in place that include staff as well as machines dedicated to HCV-infected haemodialysis patients.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Shamshirsaz 2004

Methods	• Study design: cluster RCT; they randomly selected centres one by one to reach a total number of 593 patients (12 centres) • Study duration: 2 years • Duration of follow-up: 442 patients (254 cases in the treatment group and 192 in the control group) were followed for 9 months. 281 patients (160 in the treatment group and 121 in the control group) were followed for an additional 9 months
Participants	• Setting: multi-centre • Country: Iran • ELISA III checked all patients for HCV antibody detection before enrolling in the study, positive cases were confirmed by RT-PCR • Number: 593 enrolled * ◦ Treatment group: 297; 267 negatives and 30 positives by HCV * ◦ Control group: 296; 275 negatives and 21 positives by HCV • Mean age ± SE (years): treatment group (48.1 ± 0.9); control group (50.6 ± 1.0)

Shamshirsaz 2004 *(Continued)*

- Sex (% male): treatment group (59.9); control group (54.2)
- Exclusion criteria: not reported

Interventions	Treatment group • Centres with dedicated HD machines • Dialysis membranes were low pressure and used only once and HD machines were bleached and rinsed between dialysis sessions according to the manufacturers' instruction. All machines were located in dialysis wards and not in separate rooms in both groups. Control group • Centres with no dedicated HD machines
Outcomes	• Incidence of HCV infection in both groups, to evaluate the effect of dialysis machine separation on the spread of HCV infection
Notes	• To prevent HCV transmission, educational courses were held for the staff to re-emphasize the CDC hygienic guidelines • Patients were dialyzed for 4 or 4.5 hours, 2 or 3 times/week, using standard HD techniques, patient to staff ratio in the groups wasn't statistically different (3.1 and 3.4 respectively) and all staff members were negative for anti-HCV

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process Randomisation was performed by dialysis centre, it was a cluster randomised trial which included four centres (intervention) compared with eight centres (control)
Allocation concealment (selection bias)	High risk	Allocation concealment was not performed
Was recruitment bias adequately prevented?	High risk	Individuals were recruited to the trial after the clusters had been randomised (the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited).
Were baseline imbalances (in terms of either the clusters or the individuals) adequately addressed?	High risk	There were baseline imbalances between the randomised groups, but finally they were not controlled for at the design or analysis stage of the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis was not performed. There was an "available case analysis" done with substantial departure of the intervention received from that assigned at randomisation. Only 74.5% of the patients were followed for 9 months and 47.3% were followed for an additional 9 months

Shamshirsaz 2004 *(Continued)*

		They lost > 10% of their population One centre was excluded after randomisation, causing a deviation from protocol
Selective reporting (reporting bias)	High risk	The authors only reported one result, measuring the difference in the incidence of HCV in both groups, based on that issued its findings, did not have secondary outcomes. The authors did not consider the exposure time (i.e. years patients at risk) in determining the rate of seroconversion
Was the study analysed by correct statistical methods (i.e. taking the clustering into account)?	High risk	"Comparisons between groups were made by the chi square test method for categorical variables and by the t test for quantitative variables." The cluster-randomised trial was analysed by incorrect statistical methods, not taking the clustering into account

CDC - Centers for Disease Control and Prevention; HCV - hepatitis C virus; HD - haemodialysis; SE - standard error

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agarwal 2009	Cohort study 2003 to 2006, room isolation, HCV seroconversion from 42% in 1995 to 1998 (without isolation) to 4% in 2003 to 2006 (with isolation)
Barril 2003	Cohort, multicentre study: 44 centres, room isolation, evaluate prevalence of hepatitis C and time, it divide its population in 4 quartiles according prevalence of hepatitis C, after isolation they observe decrease of seroconversion in all quartiles
Gallego 2006	Analytic study, comparing two periods of 1993 to 1995 in which isolation of machines for patients with hepatitis C is applied, and where are 2 seroconversions and second period 1996 to 2003 applied isolation room and staff, which do not show any seroconversion. Progressive decline observed prevalence of hepatitis C in its population 30.5% vs 6.8%
Garcia-Valdecasas 1994	Analytic study, three rooms of dialysis: Room A: 27 patients and 6 HCV (+), Room B: 28 patients; 7 HCV (+), Room C: 25 patients, 14 with HCV (+); No isolation: 1990, 1991 to 1992 isolation of machine only in rooms A and B, isolation
Huang 1995	Prospective study, from April 1992, 32 patients negative for HCV, isolated machine and room, after 14.2 + 3 months, a patient seroconverted, apparently associated with blood transfusion, seroconversion rate 14.6% versus 3.1% prior to isolation (historical data)
Mohamed 2010	Prospective study was conducted on 36 seronegative HD patients. All patients were managed with strict application of infection control guidelines as well as isolation of HCV-positive patients. After five years of follow-up, They found that the incidence of HCV seroconversion was zero.
Ross 2009	Large prospective multicentre study was conducted. In the first and second rounds, 150 (5.2%) of 2909 and 114 (5.4%) of 2100 patients were anti-HCV positive, respectively, and 4% of individuals were viraemic. 20% of these patients no nosocomial Hepatitis C transmission occurred during the observational period suggests that the lack of HCV seroconversions was not only attributable to the isolation of HCV-infected patients but also to the strict adherence universal hygienic precautions
Saxena 2003	Retrospective study, In the first phase, 189 patients who were receiving maintenance HD from 1995 to 2000 were studied about prevalence of HCV. Phase II involved stringent isolation of anti-HCV

Study	Reason for exclusion
	positive patients detected during phase, with dedicated space, dialysis equipment, and nursing staff from December 2000 to December 2001. Prevalence rate of 43.9% (83/189) and an annual HCV seroconversion rate of 6.8% were identified in this cohort. Only 2 new HCV seroconversions (1.01% (2/198)) were identified after isolation.
Shebeb 2006	This study compared strict adherence to the universal precautions and anti HCV seropositive patient isolation. Three units: A: education intervention program, 30 patients and 12 staff personal, B: none of the preventive measures were applied, 66 patients nursed by 16 staff C: had 67 patients nursed by 27 staff. The incidence rate of anti HCV seroconversion decreased in unit A from (10% to 0%), and in unit C from (24.4% to 10%), 6 months of the follow. It increased in unit B, where no measure was taken, from 10.5% to 16.7%.
Valtuille 1998	Study applying extreme conditions of permeability to the dialysis membrane and avoiding the use of heparin and dialysis bath. They obtained samples from the ultrafiltrate at the beginning of 18 HD sessions carried out in 6 HCV RNA-positive patients. HCV RNA was detected by PCR in 3 (16.7%) ultrafiltrate samples belonging to 1 of the patients. HCV genotype was the same as that found in positive ultrafiltrate samples and in the serum corresponding to this patient.
Yang 2003	Retrospective study, 325 HD patients from1993 to 2000 were included, isolation started after 1997. Patients positive for either hepatitis B or C were clustered in 1 area. Anti-HCV-negative and HBsAg - negative patients were assigned either to a segregated zone (Area 2) in the same room or to a separate independent room (Area 3). Forty months after the implementation of the isolation policy, there was significant reduction in the total prevalence (49.7 vs 31.7%) and incidence (9.1 vs 2.9 % patient-years) of HCV infection.

HBsAg - hepatitis B surface antigen; HCV - hepatitis C virus; HD - haemodialysis

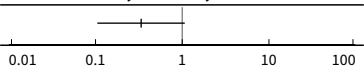
DATA AND ANALYSES

Comparison 1. Dialysis machine separation vs Usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HCV infection: 9 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Incidence of HCV infection: 18 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Dialysis machine separation vs Usual care, Outcome 1 Incidence of HCV infection: 9 months.

Study or subgroup	Isolation n/N	Usual care n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Shamshirsaz 2004	4/254	9/192		0.34[0.11,1.07]



Analysis 1.2. Comparison 1 Dialysis machine separation vs Usual care, Outcome 2 Incidence of HCV infection: 18 months.

Study or subgroup	Isolation n/N	Usual care n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Shamshirsaz 2004	2/160	7/121		0.22[0.05,1.02]

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Renal Dialysis] this term only 2. MeSH descriptor: [Hemofiltration] explode all trees 3. dialysis or hemodialysis or haemodialysis in Trials 4. hemofiltration or haemofiltration in Trials 5. hemodiafiltration or haemodiafiltration in Trials 6. #1 or #2 or #3 or #4 or #5 7. MeSH descriptor: [Hemodialysis Units, Hospital] this term only 8. ((hemodialysis or haemodialysis or dialysis) and (centre* or centre* or unit* or department* or hospital* or facilit* or clinic*)) in Trials 9. MeSH descriptor: [Outpatient Clinics, Hospital] explode all trees 10.MeSH descriptor: [Ambulatory Care Facilities] explode all trees 11.#7 or #8 or #9 or #10 12.MeSH descriptor: [Hepatitis C] explode all trees 13.MeSH descriptor: [Hepacivirus] this term only 14."hepatitis c" in Trials 15.hcv in Trials 16.#12 or #13 or #14 or #15 17.MeSH descriptor: [Cross Infection] explode all trees 18.MeSH descriptor: [Infection Control] explode all trees 19.MeSH descriptor: [Universal Precautions] explode all trees 20.infection control* in Trials 21.isolat* in Trials 22.#17 or #18 or #19 or #20 or #21 23.#6 and #11 and #16 and #22
MEDLINE	1. Renal Dialysis/ 2. exp Hemofiltration/ 3. dialysis.tw. 4. (hemodialysis or haemodialysis).tw. 5. (hemofiltration or haemofiltration).tw. 6. (hemodiafiltration or haemodiafiltration).tw. 7. or/1-6 8. Hemodialysis Units, Hospital/ 9. ((hemodialysis$ or haemodialysis$ or dialysis$) and (centre$ or centre$ or unit$ or department$ or hospital$ or facilit$ or clinic$)).tw.

(Continued)

	10.ambulatory care facilities/ or outpatient clinics, hospital/ 11.or/8-10 12.exp Hepatitis C/ 13."hepatitis c".tw. 14.HCV.tw. 15.Hepacivirus/ 16.or/12-15 17.Cross Infection/ 18.exp Infection Control/ 19.infection control$.tw. 20.isolat$.tw. 21.Universal Precautions/ 22.or/17-21 23.7 and 11 and 16 and 22
EMBASE	1. hemodialysis/ 2. ((hemodialysis$ or haemodialysis$ or dialysis$) and (centre$ or centre$ or unit$ or department$ or hospital$ or facilit$ or clinic$)).tw. 3. outpatient department/ 4. or/1-3 5. hepatitis C/ 6. Hepatitis C virus/ 7. "hepatitis c".tw. 8. HCV.tw. 9. or/5-8 10.infection control/ 11.infection control$.tw. 12.patient care/ 13.isolat$.tw. 14.or/10-13 15.4 and 9 and 14

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequential-

(Continued)

inadequate concealment of allocations prior to assignment	ly numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse

(Continued)

	effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement

Appendix 3. Risk of bias assessment tool for cluster randomised studies

Potential source of bias	Assessment criteria
Was recruitment bias adequately prevented?	*Low risk of bias:* Individuals were not recruited to the trial after the clusters had been randomised.
	High risk of bias: Individuals were recruited to the trial after the clusters had been randomised (the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited).
	Unclear risk of bias: Insufficient information to permit judgement.
Were baseline imbalances (in terms of either the clusters or the individuals) adequately addressed?	*Low risk of bias:* The randomised groups were similar at baseline; or the randomised groups were imbalanced at baseline but finally controlled for at the design (such as using stratified or pair matched randomisation of clusters) or analysis stage of the study.
	High risk of bias: There were baseline imbalances between the randomised groups, but finally they were not controlled for at the design or analysis stage of the study.
	Unclear risk of bias: Insufficient information to permit judgement.
Were loss of clusters and participants adequately addressed?	See Appendix 2: "Incomplete outcome data" for criteria of how we will assess this domain.
Was the study analysed by correct statistical methods (i.e. taking the clustering into account)?	*Low risk of bias:* The cluster-randomised trial was analysed by correct statistical methods, taking the clustering into account. Ways to avoid unit-of-analysis errors in cluster-randomised trials are (see Cochrane Handbook 16.3.3, Higgins 2011b): to conduct the analysis at the same level as the allocation; to conduct the analysis at the level of the individual while accounting for the clustering in the data. Such an analysis might be based on a 'multilevel model', a 'variance components analysis' or a 'generalized estimating equations (GEEs)', among other techniques.
	High risk of bias: The cluster-randomised trial was analysed by incorrect statistical methods, not taking the clustering into account. Such analyses tend to create a 'unit of analysis error' and produce over-precise results (the standard error of the estimated intervention effect is too small) and P values that are too small. Although they do not lead to biased estimates of effect, if they remain uncorrected, they will receive too much weight in a meta-analysis.
	Unclear risk of bias: insufficient information to permit judgement.

CONTRIBUTIONS OF AUTHORS

Writing of protocol and review: JB, CLM, JLA
Screening of titles and abstracts: JB, CLM, JLA
Assessment for inclusion: JB, CLM, JLA
Quality assessment: JB, CLM, JLA
Data extraction: JB, CLM

Data entry into RevMan: JB, CLM
Data analysis: JB, CLM, JLA

DECLARATIONS OF INTEREST

- Jessica I Bravo Zuñiga: none known
- César Loza Munárriz: none known
- Jesús López-Alcalde: none known

SOURCES OF SUPPORT

Internal sources

- None known, Peru.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Additional risk of bias assessments have been added due to the inclusion of cluster RCTs.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hepacivirus; *Patient Isolation; *Renal Dialysis [instrumentation]; Hepatitis C [epidemiology] [*prevention & control] [transmission]; Incidence; Randomized Controlled Trials as Topic

MeSH check words

Humans