

Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) hepatitis C guidelines: a European Renal Best Practice (ERBP) position statement

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Introduction

Recently the Kidney Disease Improving Global Outcomes (KDIGO) initiative published ‘the first product of what has been an unprecedented undertaking of the renal community’ [1]: the first set of global nephrological guidelines devoted to prevention, diagnosis and treatment in hepatitis C [1]. Previously, the KDIGO Board had defined non-duplication of existing guidelines and priority to topics of worldwide interest as its primary goals. Ultimately, a major infectious disease hepatitis C (HCV) was considered as the first topic to be dealt with because ‘(i) of the larger number of available studies on the subject; (ii) HCV is an infection that can detrimentally affect patients throughout the spectrum of chronic kidney disease (CKD) and can itself cause kidney disease; and (iii) HCV is a problem of worldwide clinical relevance in developed and developing countries’ [2].

A group of experts was commissioned to develop a rigorous and consistent approach for the development and grading of the evidence considered for, and recommendations established by KDIGO guidelines, based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (table 1) [3]. This approach was followed by the interdisciplinary, international and independent Work Group charged with developing the guideline. The guidelines were subjected to a three-step review process. Initially, the KDIGO Board reviewed all questions to

be addressed (in December 2005). In the second phase, a first draft of the final guidelines was reviewed by the Board and representatives of Caring for Australians with Renal Impairment (CARI), United Kingdom Renal Association (UK-RA), Canadian Society of Nephrology (CSN), Kidney Disease Outcomes Quality Initiative (KDOQI) and European Best Practice Guidelines (EBPG) (in December 2006). Finally, the draft guidelines were submitted for public review and comment by any interested individual or party. All comments received by the Work Group were considered, discussed and, if relevant, included in the final document. It is thus clear that prominent European experts were also actively participating in this process of global guideline elaboration.

Most recently, European Renal Association–European Dialysis and Transplantation Association (ERA-EDTA) analysed its 10-year-long history of commitment to producing guidelines in nephrology in light of the new perspectives offered by recent KDIGO, UK National Institute for Health and Clinical Excellence (NICE), KDOQI and CARI documents and the clear trends in (i) selecting therapies based on the most objective evidence available and (ii) financial policies based on performance indicators. Originally, it was thought that KDIGO would cover the whole guideline spectrum, producing new and updated nephrology guidelines on any theme considered suitable. In 2006, the KDIGO Board of Directors decided, however, to concentrate on selected topics only. This left a new opening for existing guideline bodies as more room was created for a more active participation of European as well as of other more local guideline initiatives. ERA-EDTA joined the KDIGO project of producing global guidelines from the very beginning, the general philosophy of KDIGO being to globalize the evidence and to localize the implementation. Nevertheless, the collaboration with KDIGO should be continued without neglecting our own European identity.

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A new ERA-EDTA initiative, European Renal Best Practice (ERBP), was established to cover all aspects related to European nephrological guidelines [4], replacing the previous European Best Practice Guidelines (EBPG), aiming at (i) producing new guidelines in areas not covered by other initiatives, (ii) endorsing and fine-tuning guidelines produced by other bodies to European conditions and (iii) highlighting still controversial areas where consensus-driven expert advice might be useful for daily practice. The current document addresses the second of these aims—namely endorsing and fine-tuning guidelines produced by other bodies to European conditions.

An *ad hoc* Work Group was commissioned by the ERBP Advisory Board to recommend endorsement of the hepatitis C KDIGO guidelines, with possible comments, amendments or caveats applying to the local European conditions, if needed. An important point to be answered was why it is appropriate to adapt guidelines for regional circumstances. Epidemiology, dialysis practice and reimbursement are significantly different across the world. With the notable exception of parts from Eastern Europe, hepatitis C incidence and prevalence are low. A capitation system with a fixed price per dialysis is more widely present; strict protocols are required on a large scale by state or private operators, based on an optimum compromise between evidence-derived efficiency and costs. Significant new evidence has emerged in the area of hepatitis C treatment, after the publishing of KDIGO guidelines (see below).

Thus, evidence was reviewed from the particular perspective of European experience and current nephrology practice. In the following publication, if appropriate, statements approved by the ERBP Work Group will be given in general and as per guideline. The same GRADE approach as applied by KDIGO was maintained.

Guideline review, analysis and endorsement

General

Table 1 summarizes the interpretation of the guidance statements used in the KDIGO hepatitis C guidelines as this differs from the GRADE approach [3]. There are three levels of recommendation, 'strong', 'moderate' and 'weak', based on the strength of the underlying evidence. Each statement uses specific wording and formatting according to the strength of the recommendation. As in many cases in nephrology, there are few randomized controlled trials evaluating this specific area; therefore, the majority of statements are weak recommendations. In agreement with the introductory background laid down by the KDIGO co-chairs, the ERBP Work Group underlines the fact that 'statements specified as "Weak" refer to consensus-based recommendations where the evidence is low, very low, or absent, with the expectation that consideration would be given to follow the suggested judgment-based recommendation on an individual basis'. The decision to follow any guideline statement, dependent on the level of its supporting evidence, must be made individually for each patient.

Guideline 1: detection and evaluation of HCV in CKD

Guideline 1.1: determining which CKD patients should be tested for HCV

1.1.1 It is suggested that CKD patients be tested for HCV. (Weak)

1.1.2 Testing for HCV should be performed in patients on maintenance haemodialysis (CKD stage 5D) and kidney transplant candidates. (Strong)

Guideline 1.2: HCV testing for patients on maintenance haemodialysis

1.2.1 Patients on haemodialysis should be tested when they first start haemodialysis or when they transfer from another haemodialysis facility. (Strong)

- In haemodialysis units with a low prevalence of HCV, initial testing with EIA (if positive, followed by NAT) should be considered (see Algorithm 1). (Moderate)
- In haemodialysis units with a high prevalence of HCV, initial testing with NAT should be considered (see Algorithm 1). (Moderate)

1.2.2 For patients on haemodialysis who test negative for HCV, retesting every 6–12 months with EIA should be considered. (Moderate)

1.2.3 Testing for HCV with NAT should be performed for haemodialysis patients with unexplained abnormal aminotransferase(s) levels. (Strong)

1.2.4 If a new HCV infection in a haemodialysis unit is suspected to be nosocomial, testing with NAT should be performed in all patients who may have been exposed. (Strong)

- Repeat testing with NAT is suggested within 2–12 weeks in initially NAT-negative patients. (Weak)

The following issue was identified by the ERBP Work Group.

What is the best overall strategy for HCV testing?

In the 2002 EBPG-HD, the enzyme immunoassay (EIA) test was advised for screening and the recombinant immunoblot assay (RIBA) test for confirmation [5]. Nucleic acid testing (NAT) was only considered for patients with consistently positive ALT who are HCV negative. Hence, as compared to EBPG 2002, KDIGO 2008 broadens the candidate population to be tested by NAT.

Detection of HCV RNA by PCR assay is acknowledged by the ERBP Work Group to be the best strategy because of false negative results in patients tested by EIA. A significant proportion of false negatives with EIA are seen also in a European setting [6]. Furthermore, a window period during incubation is seen when EIA is used. It is thus recognized that PCR is excellent but expensive while ELISA is cheaper but less accurate. There is a potential conflict of interest

between 'treating as well as possible' and 'doing as much as possible' with the same amount of funds, particularly in a bundled reimbursement system. Units with the highest prevalence of HCV are usually located in regions where dialysis reimbursement is low. However, ERBP considered it difficult to set a limit discriminating high versus low HCV, in order to establish cut-off values to distinguish between EIA and NAT—as preferred choice for primary testing. In addition, such figures may differ from region to region.

- The ERBP Work Group considers that every nephrologist should decide in function of this knowledge and that no strong recommendation can be issued.
- The ERBP Work Group considers that it is up to the medical and managing team of the unit to find a balance between 'individual patient best practice' and 'health organizational point of view best practice' when setting the HCV retesting frequency ceiling for a particular HD centre. Further European research is encouraged.

Guideline 2: treatment of HCV infection in patients with CKD

Guideline 2.1: evaluation of HCV-infected CKD patients for antiviral treatment

2.1.1 It is suggested that CKD patients with HCV infection be evaluated for antiviral treatment. (Weak)

2.1.2 It is suggested that the decision to treat be based on the potential benefits and risks of therapy, including life expectancy, candidacy for kidney transplantation and comorbidities. (Weak)

2.1.3 It is suggested that in CKD patients—except kidney transplant recipients—who develop an acute HCV infection, a waiting period beyond 12 weeks to observe spontaneous clearance (by NAT) is not justified, and that antiviral treatment should be started. (Weak)

2.1.4 It is suggested that HCV-infected patients accepted for kidney transplantation be treated (see Guideline 4). (Weak)

2.1.5 It is suggested that treatment of HCV-infected kidney transplant recipients be considered only when the benefits of treatment clearly outweigh the risk of allograft rejection due to IFN-based therapy (for example, fibrosing cholestatic hepatitis, life-threatening vasculitis). (Weak)

2.1.6 It is suggested that antiviral therapy be considered for patients with HCV-related GN (see Guideline 5.3). (Weak)

The following issue was identified by the ERBP Work Group.

Which patients should be treated?

Regarding the treatment of transplant candidates on dialysis, the potential conflict of interest is between treating and potentially wasting time for transplantation, being aware

of the fact that the overall outcome of transplantation is better than that of dialysis in similarly conditioned populations. However, only a few studies analysed the claim that HCV-infected patients who remain on dialysis do less well than patients who are transplanted and generally only short-term data (<5 years) are available [7–9]. The focus on treating transplant candidates (usually younger dialysis patients with fewer comorbidities) is fuelled by fairly large studies from several countries, showing that the long-term outcome is worse with HCV than without HCV after transplantation. Indeed, the risk of losing the graft and the risk of death are about 1.5- to 2-fold higher in the HCV-positive group [10]. Proteinuria is significantly more common in HCV-infected kidney transplant recipients and increases the risk for premature graft loss [11]. Apart from worsening the liver disease, there is a risk of *de novo* HCV GN and an increased risk for newly onset diabetes after transplantation (NODAT), especially in the tacrolimus-treated patients [12,13]. Two studies have compared HCV patients who have cleared the virus with untreated ones and found no *de novo* HCV GN and a significantly lower risk for diabetes in the treated arm [14,15]. Finally, with a negative HCV RNA prior to transplantation, the viral response is generally sustained even with extended follow-up [15].

- The ERBP Work Group agrees with the suggestion to try to clear HCV in transplant candidates by appropriate treatment.

The issue of HCV treatment in the transplant population will be discussed further in conjunction with Guideline 4.

The decision to treat HCV-positive patients not on the transplant list is more difficult. All candidates should meet dedicated infectiologists or hepatologists and undergo a thorough evaluation of (a) liver disease severity, (b) viral genotypes and (c) comorbidities. A liver biopsy is generally preferred with the exception for most cases of viral genotype 2 or 3. Although the fibroscan was suggested as a non-invasive alternative to liver biopsy in populations with normal renal function, it unfortunately has never been validated in CKD patients. Similarly, the 'normal' reference range for liver enzymes considered pathological in haemodialysis patients is still debatable, as aminotransferase values are in general lower in these patients compared to the standard population. Comorbidity burden and age (as well as stage of liver disease) are important factors in the decision to treat: if the patient is older, has mild changes on biopsy and the aetiology of the primary kidney disease is not HCV related, the benefit of therapy might be lacking. If the patient in addition is infected with HCV genotype 1 with a high viral titre, caution is generally recommended, since chances to clear the virus are lower with implications for treatment toxicity [16]. Interferon therapy is fairly frequently associated with poor tolerance in particular in CKD 5. The prevalence of side effects and patient non-compliance tend to be higher in non-experienced centres [17].

- The ERBP Work Group considers that treatment should be mainly considered for younger patients, without major comorbidities and that the decision to treat should be thoroughly discussed with the patient, particularly if patients are infected with genotype 1.

Guideline 2.2: basing HCV treatment on CKD stages

2.2.1 For HCV-infected patients with CKD stages 1 and 2, combined antiviral treatment using pegylated IFN and ribavirin is suggested, as in the general population. (Weak)

- It is suggested that ribavirin dose be titrated according to patient tolerance. (Weak)

2.2.2 For HCV-infected patients with CKD stages 3, 4 and 5 not yet on dialysis, monotherapy with pegylated IFN with doses adjusted to the level of kidney function is suggested. (Weak)

2.2.3 For HCV-infected patients with CKD stage 5D on maintenance haemodialysis, monotherapy with standard IFN that is dose adjusted for a GFR of 15 ml/min/1.73 m² is suggested. (Weak)

2.2.4 For HCV-infected kidney transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks (see Guideline 2.1.5), monotherapy with standard IFN is suggested. (Weak)

The following issues were identified by the ERBP Work Group.

Standard IFN versus pegylated IFN?

There are only a few published studies using pegylated interferon in CKD 5D. The ERBP group also reviewed several papers published by the end of 2007 or early 2008, not yet available for review and inclusion in the KDIGO clinical practice guidelines, most of them being small and uncontrolled trials. Thus, the clinical information on standard IFN use in dialysis patients remains currently better (there are a higher number of clinical trials with superior quality).

Peg-IFN-alfa-2a would be more attractive for its pharmacokinetic profile as it is dosed once weekly compared with three times weekly for interferon- α . More recent studies use a weekly reduced dose peg-IFN-alfa-2a of 135 μ g in CKD 5D. ERBP considers that it is difficult to recommend standard interferon in CKD 5D solely, since it will most likely be outdated in the near future. In the KDIGO guidelines, there was a concern that pegylated interferon had not been proven superior to standard interferon with regard to outcome and tolerability in CKD 5. However, recent papers (again from experienced, dedicated single centres) have used peg-IFN-alfa-2a with fair tolerance. The Rendina study [18] with peg-IFN-alfa-2a 135 μ g and low-dose ribavirin in 35 HD patients showed impressive results with a 97% sustained viral response (SVR) and good tolerance. However, it is important to underline that the characteristics of the study patients (young subjects without significant comorbidities—see also the discussion above on decision to treat HCV-positive patients) could have had an impact on treatment results. A very recent head-to-head randomized study compared standard-IFN and peg-IFN-alfa-2a 135 μ g in HD patients [19] showing a lower treatment-related withdrawal rate (0 versus 20%) and a better outcome with peg-IFN versus standard IFN by multivariate analysis.

In contrast to these highly positive results, a recent survey auditing all cases from multiple, non-reference centres (nevertheless combining the largest series to date of HCV+ HD patients treated with peg-IFN alfa-2a 135 μ g s.c. weekly in monotherapy) described a high prevalence of non-compliance (32%) and of adverse events (83%); the incidence rate of serious adverse events was 0.19/patient-year (median time to event 20.5 weeks), and incidence of deaths was 0.11/patient-year. Furthermore, compared with previously published historical data using non-peg-IFN, a low compliance rate and an unsatisfactory overall safety profile were seen, not supporting the superiority of peg-IFN monotherapy [17]. The concern on safety of peg-IFN use in the dialysis population has been already emphasized by prior authors [20]. Some other recent studies have highlighted the side effects related to peg-IFN use in CKD patients [21]. These conflicting results reported in the medical literature up to this point (efficacy and safety of standard versus pegylated IFN in dialysis patients) are related also to the heterogeneity of patient monitoring during antiviral therapy. Close monitoring of study patients is crucial with IFN monotherapy and combined antiviral (IFN plus ribavirin) treatment.

- The ERBP Work Group considers that antiviral treatment with careful selection of patients before therapy and rigorous monitoring during IFN treatment should be encouraged.
- Peg-IFN could be a treatment option in dialysis patients alongside standard interferon in experienced centres or in close collaboration with such centres. A rigorous selection of treatment candidates considering transplantability, age, full evaluation of liver function, genotype and comorbidity burden is mandatory regardless of the type of antiviral therapy.

Treatment with IFN + ribavirin?

Treatment of difficult cases with IFN + ribavirin should be recommended to take place only at dedicated experienced centres, preferably where ribavirin plasma levels can be controlled [22].

- In the opinion of the ERBP Work Group, ribavirin (for dosing suggestions related to GFR—see KDIGO Table 6) in combination with (peg)-IFN and high-dose erythropoiesis stimulating agents (ESAs) may be considered as the preferred approach, even in CKD 3–5, but this should only be done in dedicated centres.

Guideline 2.3: monitoring the response to HCV treatment in CKD patients

2.3.1 SVR, defined as HCV RNA clearance 6 months after completion of antiviral treatment, is suggested for assessing response to antiviral treatment. (Weak)

2.3.2 If SVR is achieved, it is suggested that testing with NAT be performed annually to ensure that the patient remains nonviraemic. (Weak)

- For patients on maintenance haemodialysis, repeat testing with NAT every 6 months is suggested. (Weak)

2.3.3 All patients with HCV infection, regardless of treatment or treatment response, should be followed for HCV-associated comorbidities. (Strong)

- Patients who have evidence of clinical or histologic cirrhosis should have follow-up every 6 months. (Strong)
- Annual follow-up for patients without cirrhosis is suggested. (Weak)
- The ERBP Work Group agrees with the recommendations and suggestions in Guideline 2.3.

Guideline 3: preventing HCV transmission in haemodialysis units

Guideline 3.1: haemodialysis units should ensure implementation of, and adherence to, strict infection-control procedures designed to prevent transmission of blood-borne pathogens, including HCV. (Strong)

- Isolation of HCV-infected patients is not recommended as an alternative to strict infection-control procedures for preventing transmission of blood-borne pathogens. (Weak)
- The use of dedicated dialysis machines for HCV-infected patients is not recommended. (Moderate)
- Where dialyzer reuse is unavoidable, it is suggested that the dialyzers of HCV-infected patients can be reused provided there is implementation of, and adherence to, strict infection-control procedures. (Weak)

Guideline 3.2: infection-control procedures should include hygienic precautions (tables 18 and 19) that effectively prevent the transfer of blood—or fluids contaminated with blood—between patients, either directly or via contaminated equipment or surfaces. (Strong)

- It is suggested to integrate regular observational audits of infection-control procedures in performance reviews of haemodialysis units. (Weak)

The following issues were identified by the ERBP Work Group.

Lack of KDIGO guidelines for peritoneal dialysis patients

Specific recommendations for PD patients

Although the KDIGO hepatitis C recommendations, besides haemodialysis, also cover CKD and transplanted patients, no recommendations are found for PD.

- The ERBP Work Group considers that the practice suggestions related to the management of hepatitis C in PD patients detailed in Appendix I could be added.

Isolation of HCV-positive HD patients

The 2002 EBPB recommended that in addition to universal precautions, which are the most efficacious preventive measures, treatment of anti-HCV patients in separate areas with dedicated staff is recommended in units with a high prevalence of HCV infection [5]. Considering that hygienic measures presented in detail by the KDIGO guidelines [1] are really implemented, the KDIGO workgroup concluded that ‘the isolation of HCV infected patients is not recommended as an alternative to strict infection control procedures for preventing transmission of blood borne pathogens (weak) and the use of dedicated dialysis machines for HCV infected patients is not recommended (moderate)’. However, the ERBP Work Group underlines that there is no trial comparing head-to-head hygienic measures only versus these measures coupled to isolation in a situation where the risk of spreading the infection is high.

- The 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; isolation might be only considered as an additional optional measure in those centres with a high HCV prevalence (same considerations for setting a ceiling as above for HCV testing).

Guideline 4: management of HCV-infected patients before and after kidney transplantation

Guideline 4.1: evaluation and management of kidney transplant candidates regarding HCV infection

4.1.1 All kidney transplant candidates should be evaluated for HCV infection (see Algorithm 2). (Strong)

- In low-prevalence settings, initial testing with EIA and follow-up of positive EIA with NAT should be considered. (Moderate)
- In high-prevalence settings, initial testing with NAT should be considered. (Moderate)

4.1.2 HCV infection should not be considered a contraindication for kidney transplantation. (Moderate)

4.1.3 It is suggested that HCV-infected kidney transplant candidates undergo a liver biopsy before transplantation. (Weak)

4.1.4 It is suggested that HCV-infected patients with cirrhosis confirmed by liver biopsy, but clinically compensated liver disease, be considered for kidney transplantation only in an investigational setting. (Weak)

4.1.5 It is suggested that HCV-infected kidney transplant candidates be considered for treatment with standard IFN before transplantation (see Algorithm 2). (Weak)

4.1.6 It is suggested that patients on a kidney transplant waiting list be evaluated for HCV infection (see Algorithm 3). (Weak)

- For patients who have never been tested for HCV, it is suggested that testing be performed with EIA in low-prevalence settings (with follow-up of positive results by NAT) and NAT in high-prevalence settings (see Guideline 1.1.1). (Weak)
- It is suggested that HCV-infected patients not previously known to be viraemic be placed on hold status pending full evaluation of the severity of their liver disease. (Weak)
- It is suggested that patients who had received antiviral treatment before listing and had SVR have testing with NAT repeated at least annually (see Guideline 2.3.2) (Weak); if NAT becomes positive, it is suggested that the patient be put on hold status and have full evaluation of their liver disease. (Weak)
- It is suggested that HCV-infected patients who had prior evaluation with liver biopsy, but either failed or refused antiviral treatment, have a repeat liver biopsy every 3–5 years while on the transplant waiting list, depending on their histologic stage. (Weak)

Guideline 4.2: use of kidneys from HCV-infected donors

4.2.1 All kidney donors should be tested for HCV infection. (Strong)

- Testing with both EIA and NAT (if NAT is available) is suggested. (Weak)

4.2.2 It is suggested that transplantation of kidneys from donors infected with HCV be restricted to recipients with positive NAT. (Weak)

Guideline 4.3: use of maintenance immunosuppressive regimens

4.3 All conventional current maintenance immunosuppressive regimens can be considered for use in HCV-infected kidney transplant recipients. (Weak)

Guideline 4.4: management of HCV-related complications in kidney transplant recipients

4.4.1 It is suggested that HCV-infected kidney transplant recipients more than 6 months after transplant have their liver disease evaluated at least annually. (Weak)

4.4.2 For HCV-infected kidney transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks (see Guidelines 2.1.5 and 2.2.4), monotherapy with standard IFN is suggested. (Weak)

4.4.3 It is suggested that HCV-infected kidney transplant recipients be screened for the development of hyperglycaemia after transplantation. (Weak)

4.4.4 It is suggested that HCV-infected kidney transplant recipients be tested at least every 3–6 months for proteinuria. (Weak)

- It is suggested that patients who develop new onset proteinuria (either urine protein/creatinine ratio >41 or 24-h urine protein > 1 g on two or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis. (Weak)

4.4.5 Because of the risk of rejection, it is suggested that kidney transplant recipients with HCV-associated glomerulopathy not receive IFN-based therapy, unless it is determined that the benefits of therapy outweigh the risks of treatment. (Weak)

The following issues were identified by the ERBP Work Group.

Should all HCV-infected kidney transplant candidates be considered for treatment with IFN before transplantation?

The issue of IFN therapy can be summarized as follows: (a) HCV-infected patients as well as any stage 5 CKD patient [23] enjoy better survival after transplantation than on dialysis; (b) transplanted HCV patients experience, in the long run, lower graft and patient survival, as well as increased incidence of proteinuric glomerulonephritis and NODAT, than HCV-free patients. This, together with small, retrospective studies showing that HCV clearance during HD resulted in possible improvement in NODAT and in post-transplant recurrence of HCV-associated GN [14,15], sets the rationale for trying to eradicate HCV before transplantation. However, one should acknowledge that this interventionalistic strategy may be paved with several pitfalls, such as high costs and possible complications consecutive to liver biopsy, IFN treatment *per se* (which is far from innocuous in the dialysis setting—see above) and leaving patients ‘on hold’ on the waiting list for periods that may vary between 6 months (optimal scenario) to >1 year (in the case of a patient infected with a type 1 genotype).

- The ERBP Work Group considers it of the utmost importance that nephrologists receive confirmation from their national/supranational organ allocation organizations that patients ‘on hold’ still continue to accrue waiting time points, and that after completion of either failed or successful IFN therapy, patients be restored to an active status on the waiting list immediately.
- The ERBP Work Group suggests that patients be properly informed about the ‘pros’ and ‘cons’ of IFN therapy, and that they should be given the opportunity to participate in the decision of either being treated or not with IFN. This was also the conclusion of the KDIGO guidelines.

Finally, the ‘interventionalistic’ strategy involves costs, manpower and time, and may not be appropriate for countries with restricted resources (where the prevalence of HCV is higher).

- The ERBP Work Group agrees with the research recommendation for randomized controlled trials to examine the effectiveness of pre-transplant IFN therapy. Ideally, the trial would compare immediate listing of suitable HCV-infected dialysis patients for a transplant (without IFN treatment) with anti-HCV (IFN \pm ribavirin) therapy during which the patient has an ‘on hold’ status on the transplant waiting list. All participating patients should undergo a liver biopsy, as liver histology at trial inclusion obviously would be taken into account when interpreting outcome, even after many years. Main outcomes should be long-term patient and graft survival.

Should all HCV-infected kidney transplant candidates undergo a liver biopsy before transplantation?

The second point that deserves some clarification is whether all HCV-infected kidney transplant candidates should undergo a liver biopsy before transplantation. This issue is a matter of debate in the general population, and at present a liver biopsy is *generally* recommended only for patients infected with type 1 and 4 genotypes in order to guide therapy [24,25].

- As the main indication to biopsy is to exclude clinically and biologically silent cirrhosis, a situation that has indeed been reported in \sim 15% of HCV-infected dialysis patients [26–29], the ERBP Work Group agrees with the suggestion to perform a liver biopsy in all transplant candidates.

What is the optimal strategy for IFN therapy for HCV-infected transplant candidates who return to dialysis with a failed allograft?

The optimal strategy for IFN therapy for HCV-infected transplant candidates who return to dialysis with a failed allograft is not discussed in the KDIGO guidelines. It is fair to say that the optimal strategy for unselected patients returning to dialysis with a failed allograft—either leaving the graft in place, with minimal or no immunosuppression versus explantation and discontinuation of immunosuppression—remains unsettled, amongst others because of the scarcity of data on this important issue [30,31]. Leaving the failed allograft in place helps to preserve residual kidney graft function and diuresis, with sometimes only minimal immunosuppression, while graft nephrectomy may be associated with significant complications and morbidity [32]. In addition, graft nephrectomy may trigger an increase in anti-HLA antibody titres, which might be detrimental for the forthcoming graft [33]. On the other hand, the retained graft together with continued immunosuppression may increase the risk of complications

such as infection, chronic inflammation with vascular lesions, anaemia and bone disease [34]. Therefore, any guidance on this issue would be only ‘opinion-based’ and none has been provided to date.

IFN therapy, both standard and pegylated, has the potential to trigger ‘acute on chronic’ rejection of the failed allograft, mandating urgent nephrectomy [35–37]. Although the exact incidence of IFN-triggered acute rejection is not known, the above-mentioned studies suggest that such an evolution is not exceptional. Therefore, the question is: Would the benefit gained by avoiding rejection instigated by IFN- α in this specific subset of patients outweigh the risk of an additional surgical intervention to remove the non-functioning graft? No clear answer can be given to this question.

- The ERBP Work Group suggests that clinicians be well aware of these issues; although the frequency of IFN-triggered acute rejection is not known, it remains a serious side effect of IFN therapy.

Guideline 5: diagnosis and management of kidney diseases associated with HCV infection

Guideline 5.1: it is suggested that HCV-infected patients be tested at least annually for proteinuria, haematuria and estimated GFR to detect possible HCV-associated kidney disease. (Weak)

Guideline 5.2: it is suggested that a kidney biopsy be performed in HCV-infected patients with clinical evidence of GN. (Weak)

Guideline 5.3: it is suggested that for patients with HCV-associated glomerular diseases, particularly MPGN, antiviral treatment as per Guideline 2.2 be considered. (Weak)

- It is suggested that immunosuppressive agents be considered for patients with cryoglobulinaemic kidney diseases. (Weak)
- The ERBP Work Group agrees with the suggestions in Guideline 5.

Future research areas relevant to the European perspective

ERBP considers that the following research areas are particularly relevant in the European context:

- (1) Describing through Registries the current trends in HCV epidemiology in CKD in Europe.
- (2) Defining the limit between ‘low-prevalence’ and ‘high-prevalence’ for HCV in order to select the optimum testing programme, defining the optimum retesting strategy for HD centres.
- (3) Validation of fibroscan in CKD patients and defining its role versus liver biopsy.
- (4) Evaluation of the effectiveness (short term and/or long term) of pre-transplant IFN therapy, i.e. comparing patients ‘on hold’ because of starting treatment with IFN \pm ribavirin versus wait-listing and immediately

transplanting when an organ becomes available without prior antiviral therapy.

- (5) Auditing the current experience from dedicated treatment centres regarding post-transplant outcomes (*de novo* GN, vasculitis, graft function, death and so on) in HCV-positive patients.
- (6) Evaluation of future therapies for HCV, as this field is evolving quickly with new molecules in Phase I and II clinical trials, specifically polymerase and protease inhibitors used in combination with pegylated interferon and in many cases ribavirin.

European hepatitis C guideline implementation

(1) *Strengths*: ERA-EDTA is strong in the following fields of implementation: presentation of guidelines at its own general meetings; extensive publication (NDT) and availability of guidelines on websites. All these aspects should be maintained and even improved.

(2) *Weaknesses*: ERA-EDTA is weak in the following fields: presentation of guidelines at other general meetings (e.g. ASN); presentation of guidelines at specific meetings; presentation of guidelines at small interactive CME programs (recommended in the literature as one of the most effective tools); concise publications; CD-ROMs and e-mail distribution once published. All these aspects can be improved.

A guideline session will be automatically included at the future joined ERA-EDTA and ISN Congress in Milano meeting. CD-ROMs and e-mail blasts will be provided throughout Europe to improve dissemination. Diffusion throughout the websites of NDT-educational and via Oxford journals is excellent, and will be continued. A link to the guidelines on the website of ERA-EDTA will be a direct one from the homepage. Other CME sessions/videoconferences are planned in conjunction with European National Societies.

Appendix 1. Hepatitis C in peritoneal dialysis: practice suggestions from the ERBP Work Group

A.1. Testing for hepatitis C in PD patients

- It is suggested that HCV testing (using similar strategies as for HD patients) be performed in PD patients who are transplant candidates, suffer acute technique failure of PD and temporarily are to be transferred to HD.

A.2. Place of PD in hepatitis C negative patients

- It is suggested that for dialysis candidates who (1) are on the waiting list for transplantation or (2) from centres where the hepatitis C prevalence is high, treating physicians do their utmost best to convince HCV-positive patients to start on peritoneal dialysis or home haemodialysis, to avoid the possibility of nosocomial infection during centred-based haemodialysis. Of course, if a patient is not a good candidate for PD or home HD, he should not be advised to undergo PD or home HD

just to protect other patients from hepatitis C contamination. Furthermore, considering the policy to start HCV+ patients on PD or home HD to avoid seroconversion by contamination of HCV–patients from the regular HD unit does not exempt the responsibility of hospital haemodialysis units to apply the necessary hygienic measures, as depicted in the KDIGO guidelines.

A.3. Handling of spent peritoneal dialysate

Transmission of HCV is primarily via the percutaneous exposure to infected blood or body fluids. HCV can remain viable in the environment for at least 16 h. The presence of HCV-RNA has been demonstrated in PD effluent [38]. Based on the general principles of infection control, the following hygienic precautions should be taken when handling spent dialysate and other waste material.

- During all manipulation of materials potentially contaminated with spent dialysate, gloves should be worn; in addition, hand washing should be performed before and after as well.
- All necessary precautions should be made to avoid spillage of spent dialysate to the environment.
- Spent dialysate should be discarded using a separate drain (e.g. a toilet) when possible. The use of drains connected to surfaces used for preparation of foods or for regular hygienic purposes (e.g. a sink or a basin) should be avoided.
- All surfaces contaminated with spent dialysate during the drainage procedure should be decontaminated with a 1/100 household bleach solution (or 500 ppm hypochlorite).
- Where spent dialysate is collected in a closed system (drainage bags), which can be used to transport the spent dialysate to the drain, adding household bleach to the bag seems unwarranted.
- For APD patients, if the spent dialysate is collected in a larger open container, it is suggested that hypochlorite should be added to the waste PD fluid to obtain a final concentration of 500 ppm.
- Other waste material from both CAPD and APD should be kept in a closed and clearly identified container. The materials should be handled and destroyed by incineration by a suitably qualified organization.

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References

1. KDIGO. Clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int* 2008; 73(Suppl 109): S1–S2
2. Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. *Semin Liver Dis* 2000; 20: 1–16
3. Uhlig K, Macleod A, Craig J *et al*. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 70: 2058–2065
4. Zoccali C, Abramowicz D, Cannata-Andia JB *et al*. European Best Practice quo vadis? From European Best Practice Guidelines (EBPG) to European Renal Best Practice (ERBP). *Nephrol Dial Transplant*. 2008; 23: 2162–6
5. European Best Practice Guidelines. *Nephrol Dial Transplant* 2002; 17(Suppl. 7): 78–81
6. Hinrichsen H *et al*. Prevalence and risk factors of HCV infection in haemodialysis patients: a multicentre study in 2796 patients. *Gut* 2002; 51: 429–433
7. Knoll GA, Tankersley MR, Lee JY *et al*. The impact of renal transplantation on survival in hepatitis C-positive end-stage renal disease patients. *Am J Kidney Dis* 1997; 29: 608–614
8. Pereira BJ, Natov SN, Bouthot BA *et al*. The New England Organ Bank Hepatitis C Study Group. Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. *Kidney Int* 1998; 53: 1374–1381
9. Maluf DG, Fisher RA, King AL *et al*. Hepatitis C virus infection and kidney transplantation: predictors of patient and graft survival. *Transplantation* 2007; 83: 853–857
10. Fabrizi F, Martin P, Dixit V. Hepatitis C virus antibody status and survival after renal transplantation: meta-analysis of observational studies. *Am J Transplant* 2005; 5: 1452–1461
11. Cruzado JM, Carrera M, Torras J *et al*. Hepatitis C virus infection and *de novo* glomerular lesions in renal allografts. *Am J Transplant* 2001; 1: 171–178
12. Shah T, Kasravi A, Huang E *et al*. Risk factors for development of new-onset diabetes mellitus after kidney transplantation. *Transplantation* 2006; 82: 1673–1676
13. Bloom RD, Rao V, Weng F *et al*. Association of hepatitis C with posttransplant diabetes in renal transplant patients on tacrolimus. *J Am Soc Nephrol* 2002; 13: 1374–1380
14. Cruzado JM, Casanovas-Taltavull T, Torras J *et al*. Pretransplant interferon prevents hepatitis C virus-associated glomerulonephritis in renal allografts by HCV-RNA clearance. *Am J Transplant* 2003; 3: 357–360
15. Kamar N, Toupance O, Buchler M *et al*. Evidence that clearance of hepatitis C virus RNA after alpha-interferon therapy in dialysis patients is sustained after renal transplantation. *J Am Soc Nephrol* 2003; 14: 2092–2098
16. Gordon CE, Uhlig K, Lau J *et al*. Interferon treatment in hemodialysis patients with chronic hepatitis C virus infection: a systematic review of the literature and meta-analysis of treatment efficacy and harms. *Am J Kidney Dis* 2008; 51: 263–277
17. Covic A, Maftei ID, Mardare NG *et al*. Analysis of safety and efficacy of pegylated-interferon alpha-2a in hepatitis C virus positive hemodialysis patients: results from a large, multicenter audit. *J Nephrol* 2006; 19: 794–801
18. Rendina M, Schena A, Castellana NM *et al*. The treatment of chronic hepatitis C with peg-interferon alfa-2a (40 kDa) plus ribavirin in haemodialysed patients awaiting renal transplant. *J Hepatol* 2007; 46: 768–767
19. Liu CH, Liang CC, Lin JW *et al*. Pegylated interferon alpha-2a versus standard interferon alpha-2a for treatment-naive dialysis patients with chronic hepatitis C: a randomised study. *Gut* 2008; 57: 525–530
20. Russo MW, Ghalib R, Sigal S *et al*. Randomized trial of pegylated interferon alpha-2b monotherapy in haemodialysis patients with chronic hepatitis C. *Nephrol Dial Transplant* 2006; 21: 437–443
21. Ayaz C, Celen MK, Yuce UN *et al*. Efficacy and safety of pegylated-interferon alpha-2a in hemodialysis patients with chronic hepatitis C. *World J Gastroenterol* 2008; 14: 255–259
22. Bruchfeld A, Lindahl K, Schvarcz R *et al*. Dosage of ribavirin in patients with hepatitis C should be based on renal function: a population pharmacokinetic analysis. *Ther Drug Monit* 2002; 24: 701–708
23. Martin P, Carter D. Histopathological features of hepatitis C in renal transplant candidates. *Transplantation* 2000; 69: 1479–1484
24. <http://www.consensus.nih.gov/2002/2002HepatitisC2002116main.htm>
25. Strader DB, Wright T, Thomas DL *et al*. AASLD Practice Guideline: diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004; 39: 1147–1171
26. Caramelo C, Ortiz A. Liver disease patterns in hemodialysis patients with antibodies to hepatitis C virus. *Am J Kidney Dis* 1993; 22: 822–828
27. Cotler SJ, Diaz G. Characteristics of hepatitis C in renal transplant candidates. *J Clin Gastroenterol* 2002; 35: 191–195
28. Sterling RK, Sanyal AJ, Lukevic VA *et al*. Chronic hepatitis C infection in patients with end-stage renal disease: characterization of liver histology and viral load in patients awaiting renal transplantation. *Am J Gastroenterol* 1999; 94: 3576–3582
29. Pol S, Romeo R. Hepatitis C virus RNA in anti-HCV positive hemodialyzed patients: significance and therapeutic implications. *Kidney Int* 1993; 44: 1097–1100
30. Bennett WM. The failed renal transplant: in or out? *Semin Dial* 2005; 18: 188–189
31. Kendrick EA, Davis CL. Managing the failing allograft. *Semin Dial* 2005; 18: 529–539
32. Secin FP, Rovigno A. Cumulative incidence, indications, morbidity and mortality of transplant nephrectomy and the most appropriate time for graft removal: only nonfunctioning transplants that cause intractable complications should be excised. *Urology* 2003; 169: 1242–1246
33. Johnston O, Rose C. Nephrectomy after transplant failure: current practice and outcomes. *Am J Transplant* 2007; 7: 1961–1967
34. Smak Gregoor PJ. Immunosuppression should be stopped in patients with renal allograft failure. *Clin Transplant* 2001; 15: 397–401
35. Hanrotel C, Toupance O. Virological and histological responses to one-year alpha-interferon-2a in hemodialyzed patients with chronic hepatitis C. *Nephron* 2001; 88: 120–126
36. Rivera M, Gentil MA. Treatment of hepatitis C virus with interferon in hemodialysis patients awaiting kidney transplant. *Transplant Proc* 2005; 37: 1424–1425
37. Carbognin SJ, Solomon NM. Acute renal allograft rejection following pegylated IFN-alpha treatment for chronic HCV in a repeat allograft recipient on hemodialysis: a case report. *Am J Transplant* 2006; 6: 1746–1751
38. Cusumano AM, Poratto F, del Pino N *et al*. Identification of hepatitis C virus RNA in peritoneal dialysis fluid of patients with viremia. *Perit Dial Int* 2005; 25: 478–482

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