European Renal Best Practice (ERBP)

A Paper for Patients

1. General Introduction.

The prime function of ERBP is to provide evidenced based information for: nephrologists, physicians and other health care professionals to enhance the care of patients with kidney disease. The ERBP advisory board gathers the evidence from published clinical trials and, using the expertise of specialists in the relevant subject areas, produces recommendations on what to do in certain clinical situations and makes judgements on grading the quality of evidence that these recommendations are based on.

This process inevitably influences those physicians who follow ERBP guidance appropriately and as a consequence, impacts on the treatment of the patients they care for. On this basis alone, there is an obvious relevance to patients and for this reason ERBP has decided to edit their published work and present it in a form accessible to patients.

2. The history of kidney disease guidelines development

“In 1997, the National Kidney Foundation (NKF) in the USA established the Dialysis Outcome Quality initiative (DOQI) which produced clinical practice guidelines in four areas: haemodialysis adequacy, peritoneal dialysis adequacy, vascular access and the management of anemia. Subsequently, guideline development was extended to the management of non-dialysis-dependent kidney disease, and the name of the program was changed to the Kidney Disease Outcomes Quality Initiative (KDOQI).

In 1999, the European Renal Association and European Dialysis and Transplant Association (ERA-EDTA) initiated the European Best Practice Guidelines (EBPG) and most National Nephrology Associations also produced guidelines for best practice. [http://www.era-edta.org/page-8-38-0-38-erbpeuropeanrenalbestpractice.html](http://www.era-edta.org/page-8-38-0-38-erbpeuropeanrenalbestpractice.html).

KDIGO (Kidney Disease Improving Global Outcomes) was founded in 2003 to establish global nephrology guidelines on a worldwide basis and coordinate the development of the clinical practice guidelines of different international organizations in the field of kidney disease. However the number of topics and necessary updates were too large to be dealt with by KDIGO alone. In 2006 KDIGO decided to concentrate on selected topics only. [http://www.kdigo.org/pdf/Eckardt_NatRev_2009.pdf](http://www.kdigo.org/pdf/Eckardt_NatRev_2009.pdf) This presented an opportunity for European and other bodies to take a more active role in the formulation of nephrology recommendations.

3. Can patients use ERBP guidelines to improve their understanding of their treatment?

The format of advice promulgated by the ERBP advisory board is intended for use in circumstances that require professional training and judgement. But this should not be used as an excuse for restricting the information on which such advice is based to the professionals alone. To judge whether an individual patient should be treated in a particular way will depend
on many factors and a myriad of variations. A treatment plan is ultimately agreed by the interaction of the physician and patient in the context of a consultation, taking into account not only the scientific/medical reasoning but also quality of life issues. Although the arguments that underpin guidance may be complex, its conclusions should be clear and accessible to patients in language that members of the general public will find easy to understand so that they can evaluate the impact of certain decisions on their life in a holistic way. This paper is ERBP’s attempt to fulfil that requirement. Fully informed patients are more likely to become willing partners in the management of their illnesses.

**4. Patients will expect their nephrologist or physician to take heed of guidelines and guidance published by internationally recognised bodies such as KDIGO and ERBP.**

Patients believe that their doctors, nurses and health care professionals will have the knowledge, skills, attitudes and ethical standards expected of those professions. This guarantee is provided, primarily by the registration of professional qualifications and the issuing of licences to practice by the relevant statutory authorities in each country or state. Patients will also want to know if the statutory authorities expect their professional members to be cognisant of the most up to date guidance relevant to their stated specialty. But to demand that physicians slavishly follow guidance misunderstands the nature of clinical practice. Guidance is to inform and not to direct. Clinical practice involves judgements that enable the choices and decisions that doctors take, in conjunction with patients, to be based on verifiable evidence and modified according to individual circumstances.

**5. The Pitfalls of Guideline development**

The aim of guideline development is to improve patient care and outcomes by:

i) Reviewing the results of clinical research in order to derive recommendations for diagnosis and therapy

ii) Identifying gaps in knowledge in order to prioritize which research questions will generate new knowledge.

However patients should be aware of the pitfalls that can occur in producing guidelines.

i) **Professional medical societies** have frequently considered guideline development as one of their tasks, but they have not always established robust methodologies, transparent rules and policies, nor provided sufficient resources for their development.

ii) **Industry** has promoted guideline development in areas related to their products, which can result in ‘guideline publication bias’, by producing many clinical practice guidelines in commercially attractive areas but few in other areas that, although equally or even more important from a clinical perspective, are less commercially attractive.

iii) **The objectivity of any guidelines** may be questioned if there is any association by members of guideline work groups with industry
iv) **Inappropriate performance measures** can be developed if insurance or health authorities derive these measures from clinical guidelines that have themselves been based on weak or limited evidence.

### 6. How are topics selected?

The selection of topics for guideline development is a critical component of the process. **KDIGO** has held conferences to this end on a wide range of subjects since 2004. **ERBP** has decided to focus on literature reviews and the development of position statements rather than clinical practice guidelines, in order to complement the work of KDIGO.

The ERBP Board’s priority is to update existing ‘guidelines’ rather than create new recommendations. Maintaining outdated ‘ghost guidelines’ is not desirable. KDIGO’s role is more concerned with the coordination and generation of traditional guidelines and less with issuing position statements.

### 7. ERBP’s current statements and guidance

#### A. General Statements

ERBP has issued 2 general statements about the nature of its work:

i) It is the intention for European Guidelines to be issued only when evidence has been searched for by a structured, in depth and transparent process, otherwise they will be termed ‘recommendations’ or ‘position statements’ and published in a different format from Guidelines. As high levels of evidence are often lacking in nephrology, it was decided to change the name of the responsible body from: (EBPG) **European Best Practice Guidelines** to (ERBP) **European Renal Best Practice**. [http://ndt.oxfordjournals.org/content/23/7/2162.full](http://ndt.oxfordjournals.org/content/23/7/2162.full)

ii) The second general statement answered the question ‘Is there still a place for an institution generating European Nephrology Guidance?’ [http://ndtplus.oxfordjournals.org/content/2/3/213.full](http://ndtplus.oxfordjournals.org/content/2/3/213.full)

**Appendix A:** How do I know if a recommendation is really well-established? I don’t want to agree to something and then find it is not the best treatment.

#### B. Specific Statements

ERBP has addressed a number of ‘specific clinical’ topics by issuing ‘position statements’ and ‘clinical advice’. The appendices listed in this section contain the edited versions of the original ERBP papers and links to the original full statements. To facilitate a patient’s search for information relevant to a particular clinical problem, each appendix has a title in the form of a question that may be commonly asked:

**Appendix i)** What should my Hemoglobin be? [http://ndt.oxfordjournals.org/cgi/content/full/24/2/348](http://ndt.oxfordjournals.org/cgi/content/full/24/2/348)
Appendix ii) What does Hepatitis C mean to me as a CKD patient?  
http://ndt.oxfordjournals.org/cgi/content/short/gfn608v1

Appendix iii) Are High Flux dialysers better for me than Low Flux ones?  
http://ndt.oxfordjournals.org/cgi/content/full/gfp626v1

Appendix iv) Are venous catheters safe in terms of Blood Stream Infection? What should I know?  
http://ndtplus.oxfordjournals.org/cgi/content/full/3/3/234 and  
http://ndt.oxfordjournals.org/cgi/content/full/gfq205v2

Appendix v) Why is it important to regularly test the function of my Peritoneal Membrane if I am on PD?  
http://ndt.oxfordjournals.org/cgi/content/full/gfq100v1

Appendix vi) What sort of dialysis should I choose?  
http://ndtplus.oxfordjournals.org/cgi/content/full/3/3/225

8. Other matters of concern to patients affecting outcomes of care:

The aim of Best Practice for health care professionals (HCPs) must be to improve patient outcomes in clinical practice. However there are aspects of service provision that may not be wholly dependent on the clinical actions of doctors and HCPs. European Renal Best Practice could legitimately seek evidence to express opinions on such non-clinical matters.

8 i) Access to Care

The importance of early diagnosis of renal impairment is well documented. Good public health information will raise awareness in the general population. Most professional bodies and National Health Service providers have published evidence on this topic,  
http://www.cks.nhs.uk/patient_information_leaflet/kidney_disease_chronic. Screening programmes can identify affected individuals although there is a debate regarding the cost-effectiveness of so doing.  
http://www.evidence.nhs.uk/search.aspx?t=kidney+disease&am=%5B%7B%22ain%22%3A%5B%22%22%5D%7D%5D

Access to high quality primary care services will facilitate early detection. Access to specialist services for diagnosis and management is dependent on the number and distribution of these secondary care services in the health care systems of each EU member state. Such access will be impeded by a scarcity of specialists and long distances between the specialist unit and the patient’s home. This is directly related to the financing of the services whether by the state, health insurance companies, or individual patients.

8 ii) Range and Choice of Services

Specialist nephrology services, in addition to providing a diagnostic facility will monitor patients and offer interventions where appropriate. Choice is of prime importance if patients are to receive optimal care. The choice may be between: the modality of dialysis (haemodialysis and PD); the location for dialysis (Hospital; satellite and home dialysis); the scheduling of dialysis (to
fit in with work, educational, social and holiday requirements); or between dialysis and Active Supportive Care (formerly referred to as conservative or palliative care). For many the treatment of choice is Transplantation but this is dependent upon the supply of donor kidneys as well as the suitability of the recipient. A choice can be made to remain on a waiting list for a deceased donor kidney or to seek a live donation from a relative or friend, or even to participate in a paired or pooled donation scheme. There may be a choice between accepting a less than optimum functioning kidney and staying on the waiting list for a better kidney.

To help patients make such choices, sound evidence on the pros, cons and outcomes of each option must be provided.

8 iii) Information on the quality of services

Information about the process and outcome of renal services is important to patients. For example, the renal National Service Framework (UK) 2004, sets out (in figure 5, Chapter 2 Page 17), 5 standards and 30 markers of good practice for the providers of renal services to aim for and against which commissioners (the funders of NHS services) can measure performance.

The UK Renal Registry publishes detailed information about each renal unit in the UK [http://www.renalreg.com/index.html](http://www.renalreg.com/index.html) This is of interest to patients and enables them to know how their own renal unit is performing [http://www.kidney.org.uk/Medical-Info/your-renal-unit.html](http://www.kidney.org.uk/Medical-Info/your-renal-unit.html)

9. Conclusion

The information promulgated by European Renal Best Practice is as important to patients and their carers as it is to the HCPs who advise them. However professional guidance is often couched in terms that require professional training and knowledge for it to be understood and applied. To ensure that the information itself is more widely known, the conclusions and advice of European Renal Best Practice Advisory Board, as summarised in this paper, are presented in language that the general reader will find acceptable.
Appendix A:

Strength of recommendations

How do I know if a recommendation is really well-established? I don’t want to agree to something and then find it is not the best treatment.

The people who produce guidelines should always provide an indication of the quality of the evidence on which the recommendations are based. They normally use a system of numbers and/or letters to grade the strength of the recommendations.

- For example, guidelines produced by KDIGO (Kidney Disease Improving Global Outcomes) are now graded between 1A and 2D.
- Guidelines produced by the ERA (European Renal Association) used to be graded as A, B or C, or as I to IV, but are now moving to the 1A to 2D system preferred by KDIGO.

Strong recommendations will have the highest grade. They are usually supported by high quality evidence, such as the results of large, well-conducted studies.

- If, for example, the recommendation is about whether to use treatment X or treatment Y, the ideal study would take a group of patients and randomly assign them to either X or Y (preferably without telling the patient or their physician which treatment they received). This type of study is called a ‘randomised controlled trial’ (an RCT). If many more patients got better with treatment X, the recommendation to use it would be strong.
- High quality recommendations can also come from undisputed facts, even if they have not been proven through controlled studies. There has never been a randomised trial to provide strong evidence of the benefit of using a parachute when jumping from a plane, but the effects of falling from a great height without one are not disputed!
- Don’t be surprised to find that there are very few strong recommendations in the guidelines for the care of people with kidney disease. RCTs are very expensive to carry out and it is often necessary to follow patients for many years to see if one treatment really is better than another.

If the supporting evidence is good but could be challenged, the recommendation will have an intermediate grade.

- Taking the example above, if the evidence on whether to use treatment X or treatment Y comes from observing groups of patients who happened to have been given treatment
X or Y or from small studies comparing just a few patients, it may seem very convincing now but it could be refuted in future by a large well-conducted RCT.

When there is little or no supporting evidence for a recommendation, it will have a low grade. It may be called a weak recommendation and will often be phrased as a suggestion.

- Lack of supporting evidence may be because there are studies that disagree with each other, or because no-one has carried out the necessary studies. There can be lots of reasons for not carrying out a study, including the ethical problem of randomly assigning patients not to receive a treatment that most people already think is helpful.

For important issues which cannot be tested in studies for one reason or another, the guidance has to be based on a consensus of the opinions of experts. This may appear as a statement labelled ‘ungraded’ or ‘opinion’.

Most doctors would be expected to advise you to follow a strong recommendation, if the intervention is available and appropriate for you. If the recommendation is intermediate or weak, your doctor is expected to give more consideration to your individual circumstances and to discuss the alternatives with you.
Appendix i.

What should my Haemoglobin be?

Clinical Practice Guidelines for Anaemia management in patients with chronic kidney disease.

Introduction.

Haemoglobin (Hb) is a protein molecule containing iron that gives red blood cells their colour and is responsible for carrying oxygen from the lungs to the tissues as the blood is pumped around the body by the heart. If the amount of Hb is less than normal (known as anaemia), the organs of the body are starved of oxygen reducing their ability to function properly and causing tiredness, weakness, and breathlessness. The red blood cells are manufactured in the bone marrow requiring iron and a hormone produced by the kidneys called Erythropoietin (EPO). If the kidneys fail, EPO production is impaired and the patient becomes anaemic. This can be counteracted by administering (by injection) ESAs (Erythropoietin Stimulating Agents). Oral or intravenous injections of iron may also be required to correct the anaemia. Hb is measured by estimating its concentration in the blood and the units of measurement are in grams per 100ml (i.e. grams per decilitre). Iron is normally absorbed from food via the gut (intestines). A protein called ferritin is produced in the liver to store any iron absorbed by the gut that is not immediately required by the bone marrow to make new Hb. Thus iron levels in the blood are estimated by measuring the serum ferritin. The concentration of ferritin is measured in nanograms per millilitre (ng/ml) or micrograms per litre (µg/L). It may be helpful to know that 1 gram = 1000 milligrams = 1,000,000 micrograms = 1,000,000,000 (1 billion) nanograms). In order for iron to be transported to the bone marrow it is incorporated into a protein called transferrin which is made by the liver and then carried to the bone marrow, where it is converted under the influence of EPO to haemoglobin.

Diagnosing the cause of iron deficiency in CKD patients may be difficult if other conditions such as infection are present, as inflammation prevents the iron from being mobilised from the body’s iron stores. However the inflammation also causes a rise in serum ferritin. As serum ferritin is used to as a proxy to estimate the patient’s iron levels, the raised levels will give the impression of iron overload. To avoid this error, further tests may be necessary. One such test is the TSAT (transferrin saturation test) which is the ratio of serum iron to the total iron-binding capacity of the blood expressed as a percentage and indicates how much serum iron is actually bound to transferrin. (A TSAT of 15% means that 15% of free iron is being carried by transferrin). The total iron-binding capacity (TIBC) measures the blood’s capacity to bind iron with transferrin. In inflammatory conditions, as explained above, the serum ferritin levels are raised, and the TIBC will appear reduced giving the conflicting impression of iron deficiency, so called functional iron deficiency. Other more sophisticated (and expensive) tests may
clarify the diagnostic conundrum.

The TSAT is expressed as a percentage because this show how much carrying capacity is available

**This appendix discusses three issues:**

i) **what optimal levels of haemoglobin should be aimed for**

ii) **how they should be achieved**

iii) **what are the associated problems and risks in treatment.**

In normal individuals, depending upon age and gender, haemoglobin levels range between 13 and 15 grams per dl that is: per 100ml (decilitre). 1997, the DOQI guidelines on the treatment of anaemia in CKD patients, recommended a target range for Haemoglobin (Hb) of between 11 and 12 g/dl. Similar recommendations were made in 2006 by KDOQI and EBPG although no upper limit was defined for all stages of CKD by ERPG in 2004. For patients who also had diabetes or cardiovascular disease, it was generally not recommended to aim for these ‘higher’ target levels.

In patients whose anaemia was being treated with ESAs (Erythropoietin Stimulating Agents), the updated 2006 NKF-KDOQI guidelines recommended that the (lower limit) of the haemoglobin range should be ≥11.0 g/dl but there was insufficient evidence to routinely maintain an upper limit of ≥13.0 g/dl. At this time the evidence showed that although quality of life may be improved by complete correction of the anaemia, there was none to support other measures of benefit, such as improved mortality.

In March 2007, the US Food and Drug Administration (FDA) changed the labelling for erythropoiesis stimulating agents (ESAs) and added a boxed warning stating that Hb targets of >12 g/dl should be avoided because of the increased risk of death and serious cardiac events. They also noted that ESAs should be used to increase haemoglobin but only to the lowest level necessary to avoid transfusion and thus to a level where patients become asymptomatic.

These recommendations created considerable confusion and concern. The new evidence from the CREATE and CHOIR studies was sufficient to justify updating the statements of the NKF-KDOQI guideline working group concerned with Hb targets. An Evidence Review Team analysed all data from 6 randomized controlled trials of anaemia management in CKD. On the basis of these results, the NKF-KDOQI working group recommended: the Hb target in patients receiving ESAs should generally be 11–12 g/dl and not >13 g/dl because ‘the possibility of causing harm is greater than the potential of improving the quality of life and for decreasing the need for blood transfusions’.

In October 2007, KDIGO responded to the NKF-KDOQI updated recommendation by issuing a position statement with 3 conclusions:

i) Haemoglobin levels of >13 g/ dl may be associated with harm in subjects treated with ESA

ii) Haemoglobin Levels of 9.5–11.5 g/dl are associated with better outcomes than those of >13 g/dl.
iii) There was no evidence either way for intermediate levels (11.5–13 g/dl)

Limitations of the current knowledge of CKD-related anaemia were identified and deemed worthy of future research.

**The position of ERBP is as follows:**

i) **Haemoglobin target**

In 2004, EBPG suggested an Hb target ≥11 g/dl; values of >14 g/dl were considered undesirable in general, and the limit for patients with diseases of the heart and/or blood vessels was set at 12 g/dl. Caution of not exceeding Hb concentrations ≥12 g/dl was also recommended for patients with diabetes, especially if they had concurrent peripheral vascular disease. Since 2007, when the KDOQI Hb target update was published, no further data from new clinical trials have been published.

- In the opinion of the ERBP Work Group, it appears reasonable to maintain the lower limit of the target, although the actual evidence for choosing this value is also very limited. On the basis of new evidence, Hb values of 11–12 g/dl should be generally sought in the CKD population without aiming to exceed 13 g/dl.

Although harm is possible when aiming at higher Hb targets, it is likely that this applies mostly to selected populations such as patients with diabetes and/or clinically significant diseases of the heart and/or blood vessels. However, current evidence shows no benefit for higher targets in any subgroup and there is the additional consideration of the increased cost of higher ESA doses.

- The ERBP Work Group believes that there is a need for better understanding as to whether any harm may be associated with attempts to reach higher Hb values in patients with comorbidities or those who are hypo-responsive to ESAs. Physicians need to accept that patients may be below or above the target for a given period of time.

- The ERBP Work Group agrees with the recent position of KDIGO that the quality-of-life data that are currently available vary in quality and are often inconclusive. As more reliable methods of assessing patient-related outcomes and functional status have now become available, there is room for new studies which will test the effect of correcting anaemia on the quality of life.

ii) **Anaemia evaluation**

In 2004, EBPG defined anaemia in CKD patients on the basis of their gender and age. In patients living below an altitude of 1500 m, Hb values were considered below normal if they were <11.5 g/dl in women and <13.5 g/dl in men (<12 g/dl in those aged >70 years), and it was recommended that ‘an anaemia work-up’ be started when Hb levels fall below these limits. (‘An anaemia work-up’ is a series of investigations into the cause of the anaemia)

In 2006, KDOQI modified this definition by giving a single criterion for diagnosing anaemia in adult males (Hb <13.5 g/dl, regardless of age) because a decrease in Hb among males aged >60
years is often attributable to other concurrent diseases and requires investigation in its own right.

- The ERBP Work Group agrees with this new definition.

**iii) Targets for iron therapy**

The most widely used tests for iron levels are serum ferritin and transferrin saturation (TSAT) levels. In 2004 EBPG recommended lower limits of ferritin levels as 100 ng/ml and TSAT as 20%, with target ranges of 200–500 ng/ml (ferritin) and 30–50% (TSAT). Because of patient safety considerations, in 2006 KDOQI defined the lower ferritin limit on the basis of a patient’s CKD status: (100 ng/ml in non-HD-CKD and 200 ng/ml in HD-CKD); if serum ferritin levels are >500 ng/ml, iron administration should be discouraged.

- The ERBP Work Group agrees with the recommendations of the KDOQI guidelines.

**iv) New ESAs**

In 2004 (EBPG) and 2006 (KDOQI) recommendations were made concerning the use of the three ESAs available at that time: epoetin alpha, epoetin beta and darbe poetin alpha. Since then, two more have been introduced: epoetin delta and CERA (continuous erythropoiesis receptor activator).

- In the opinion of the ERBP Work Group, epoetin delta should be administered similarly to epoetin alpha but (CERA), has a considerably longer half-life than the other licensed ESAs (∼130 h) and should be administered once every 2 weeks for correcting the anaemia and once every 4 weeks to maintain the target level of haemoglobin. Its safety and tolerability is similar to that of other ESAs.

**v) Biosimilars**

When a drug company’s patent on one of their products expires (generally after 20 years although less so in Europe) other manufacturers can make an equivalent but cheaper version. They are known as ‘Biosimilars’.

In Europe, the patent on epoetin alpha expired in December 2004 and that of epoetin beta, in 2005. HX575, a biosimilar of epoetin alpha, received marketing authorization throughout the European Union in August 2007 and is marketed by three companies under three different brand names. In December 2007, epoetin zeta, another biosimilar of epoetin alpha, also received EMEA (European Medicines Agency) marketing authorization.

Whilst biosimilars may be more affordable, their safety record is shorter than the original ESAs. In view of the delicate production process of these complex molecules, different brands cannot be considered equivalent, even if they have the same formula, as was demonstrated by the PRCA epidemic. The production process of biosimilars necessitates stringent pharmaco-vigilance monitoring as do all ESAs. It should be mandatory that biosimilars are not substituted for other r- HuEPOs (Recombinant human erythropoietins) without a physician’s prior approval. It is also
noteworthy that ESA biosimilars are currently only approved for intravenous administration (direct injection into a vein) in CKD patients making them de facto, unsuitable for non-haemodialysis patients, although epoetin zeta has recently been approved for subcutaneous injection.

vi) Pure red cell aplasia (PRCA)

Antibody-mediated (allergy-like) pure red cell aplasia (PRCA) is a rare but serious adverse event related to ESA therapy. There was an upsurge in the number of PRCA cases since 1998, mainly associated with the subcutaneous use of Eprex\textsuperscript{R}. Eprex\textsuperscript{R} is the epoetin alpha produced outside the United States. The breaking of the cold chain is potentially an important factor. Cold chain failure occurs when vaccines or other temperature sensitive products are exposed to temperatures outside the recommended range of storage. The subcutaneous use of Eprex\textsuperscript{R} in CKD patients had been contraindicated in Europe by regulatory authorities since December 2002, and was strongly discouraged in Canada and Australia. The number of reported cases of PRCA has decreased sharply since 2003, with no more cases were reported in 2007. This may be due to: a change in the route of administration; the reinforcing the importance of not breaking the cold chain; and eliminating uncoated rubber syringe stoppers. The regulatory authorities consider the latter as the most significant factor and have recently re-authorised the subcutaneous use of Eprex\textsuperscript{R} when vascular access is not available as long as there is an extensive pharmaco-vigilance plan in place.

• The ERBP Work Group considers it essential that suspected PRCA cases are carefully worked up and confirmed cases are closely monitored.

• With the data available, the ERBP Work Group considers that recommencement of treatment with ESA can be considered in patients with a history of PRCA, if anti-EPO antibodies are no longer detectable.

It has recently been reported that hematide, (a non-peptide erythropoietin receptor agonist which is currently under clinical development) corrects the anaemia induced by anti-erythropoietin antibodies as previously shown in a rat PRCA model. In 2010 this was also demonstrated in men (NEJM).

vii) Safety concerns in CKD patients with cancer

No direct relationship has yet been established between the presence of EPO\textsubscript{R} (Erythropoietin Receptor) on tumour cells and tumour proliferation in response to administering exogenous EPO. However the use of ESAs may increase the risk of venous thrombo-embolism in cancer patients.

ESA therapy is approved in patients with non-myeloid malignancies who have developed chemotherapy-associated anaemia in order to decrease transfusion requirements. But since 2004, there have been safety concerns in cancer patients, particularly in relation to off-label indications such as: anaemia not secondary to chemotherapy; or an Hb target of >12 g/dl.

In May 2007, the Oncologic Drugs Advisory Committee of the Food and Drug Administration
(FDA) reassessed the ESA-related risks of: venous thrombo-embolism; poorer cancer outcomes; and cardiovascular disease in cancer patients receiving chemotherapy. They subsequently ordered that boxed warnings be added to the labels of the ESAs recommending that the lowest ESA dose be used to increase Hb to a level high enough to avoid red blood cell transfusions. According to FDA indications, an Hb target of >12 g/dl should be avoided.

• In the opinion of the ERBP Work Group, ESA therapy should be cautiously used in patients with CKD and malignancies as no information is available concerning the risk of mortality and tumour growth in this subset of patients.
Appendix ii

What does Hepatitis C mean to me as a CKD Patient?

Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in CKD

Introduction

Worldwide, about 170 million people are infected by the hepatitis C virus (HCV). Infection is much more common in patients with chronic kidney disease (CKD) than in the general population. One reason for this is that infection with HCV can cause kidney disease. Another reason is that the virus is transmitted through contact with blood and can be passed between patients in dialysis units if the correct hygienic precautions are not followed. Before it was possible to screen for HCV, many CKD patients were infected through blood transfusions.

Hepatitis C is one of a family of viruses that cause inflammation of the liver. Initial infection with HCV is usually so mild that people affected do not seek medical attention. Some people are able to completely clear the virus from their blood, but more than half of those infected with HCV become chronic carriers of the disease. The main long-term complications of chronic infection with HCV are liver failure caused by scarring (fibrosis or cirrhosis) and liver cancer.

The guidance on how to diagnose, prevent and manage HCV in CKD patients was the first global guideline in nephrology. It was prepared by an international working group with a range of expertise with the help of a team based at Tufts University (Boston, USA) who specialise in searching through medical publications for evidence on which guidelines can be based. The draft guidelines were reviewed by interested organisations and individuals before being finalised and published in 2008.

The complete KDIGO guideline in English can be downloaded free-of-charge from the KDIGO website (www.kdigo.org). Summaries are also available in Arabic, Chinese, French, Italian, Japanese, Russian, Spanish, and Turkish. The European Best Practice (ERBP) Advisory Board endorsed and commented on the KDIGO guideline in 2009 and you can access their full report at http://ndt.oxfordjournals.org/content/24/3/719.full

Strength of recommendations

The nature and history of guidelines are explained in the opening paragraphs of the introduction to this paper and the implications for the strength of the recommendation are discussed in Appendix A.

In the guideline on hepatitis C, the recommendations were graded as strong, moderate, or weak. The wording of the recommendation used gives an indication of the strength.

- A strong recommendation will say that something should be done. In most cases this is how you would like to be treated.
- A moderately strong recommendation will say that an action should be considered. You can think of this recommendation as being suitable for most patients, but circumstances may make you choose other options.
- When a recommendation only suggests doing something, it is weak. In this case other options can be just as valid.

Most doctors would be expected to advise you to follow a strong recommendation, if the intervention is available and appropriate for you. If the recommendation is moderate or weak, your doctor is expected to give more consideration to your individual circumstances and discuss alternatives with you.

1. Detection and evaluation of HCV in CKD

Guideline 1 suggests that all CKD patients are tested for HCV. This is because HCV has been associated with some types of kidney disease and also allows early treatment to be considered. Doctors may decide not to test for HCV in new patients if they have been diagnosed with a kidney disease that is not linked to HCV.

The guideline goes on to say that patients should be tested for HCV if they are candidates for a kidney transplant or if they are receiving haemodialysis (HD). It is essential to know if a patient who may receive a transplant is HCV-infected because it affects the way that donated kidneys are allocated. If the patient is to be given treatment to clear HCV, this is best carried out before the transplant takes place so this is another reason for testing these patients.

Patients should be tested when they start HD or when they transfer from another HD unit. This should form part of the dialysis unit’s infection control procedures. If your unit follows the recommendations in guideline 3 (below), there should be no cross-infection between patients. If a patient is found to be HCV-infected, the staff need to know if the infection occurred before or after the patient started HD in your unit so they can take appropriate action.

There are two types of test for HCV. The simpler ‘EIA’ test (Enzyme-linked Immunosorbant Assay) looks for antibodies that the body produces to fight off the virus while ‘NAT’ (Nucleic Acid Test) looks for the virus itself. NAT is more complicated and expensive but it is more accurate and it gives information about how infectious the patient is. The guideline recommends that units where there are few or no HCV-infected patients should consider using the EIA test routinely and only test with NAT if the EIA test is positive. Units where HCV infection is more common should consider using NAT as the first test for new patients. NAT is also the most appropriate test for new patients with a high risk of HCV infection such as drug users who may have shared needles. This strategy is intended to minimise the number of false-positive and false-negative tests.

- The ERBP Advisory Board agreed that NAT is a more accurate test than EIA, but it is expensive and units where HCV infection is more common are usually in regions where funding for dialysis is low. They suggest that doctors in these units decide which test to use for new patients based on their understanding of the tests and their resources.
The guideline says that units should consider routinely testing HD patients who are HCV-negative every 6–12 months with the simpler EIA test, even if there is nothing to suggest that the patient has been infected. However, any patient with an abnormally high level of a liver enzyme called ALT (Alanine transaminase) which can be a sign of infection should be tested at once with NAT. Testing with NAT should also be carried out for all potentially affected patients if cross-infection is found to have occurred within a dialysis unit.

2. Treatment of HCV infection in patients with CKD

Evaluation of HCV-infected patients for antiviral treatment: Guideline 2.1 suggests that doctors should evaluate all CKD patients with HCV infection to see if they will benefit from antiviral treatment. The current treatment does have side effects and it is not always successful, especially in HCV with ‘genotype’ 1 and 4. (A genotype is the genetic make-up of a cell, organism or individual). If you are being assessed for treatment, you may have to have a biopsy in which a small piece of your liver is removed to see how much scar tissue it contains.

The complications of HCV usually take decades to appear. Together with the potential risks of treatment, this means that you are most likely to benefit from treatment if you are hoping, and are suitable, for a kidney transplant; or if you are young and expecting to spend many years on dialysis.

Antiviral therapy reduces the risk for developing diabetes or HCV-related kidney disease after transplantation. It should be carried out before the transplant as antiviral therapy carried out after transplantation frequently leads to rejection of the transplanted kidney. The guideline suggests that therapy is initiated after transplantation, only where the consequences of not treating the HCV are life-threatening and where the patient accepts that they may have to go back onto dialysis should the transplanted kidney be rejected.

If you are infected with HCV and anti-viral treatment is considered to be in your best interest, the guideline suggests that it can be started as early as 12 weeks after the initial infection if you have not been able to clear the virus. NAT is used to see if you have been able to fight off the infection in which case you won’t need anti-viral treatment.

- The ERBP Advisory Board agreed that treatment should be mainly considered for younger patients. They emphasise the need for doctors to discuss the treatment and side effects carefully with the patient, particularly if they are infected with genotype 1 which is more difficult to clear.

Basing HCV treatment on CKD Stage: The severity of CKD is measured using the ‘glomerular filtration rate’ (GFR). This is the volume of fluid filtered by the kidney every minute with a correction for body size. A young person with healthy kidneys will have a GFR of around 120 ml/min/1.73m².

Guideline 2.2 suggests that patients with CKD Stages 1 and 2 (GFR > 60 ml/min/1.73m²) who are suitable for treatment should receive the same antiviral drugs as the general population. This is currently a combination of ‘pegylated’ interferon and ribavirin for 6 to 12 months.
Interferons (IFNs) are naturally-occurring proteins that activate the immune system and interfere with the reproduction (replication) of viruses. Pegylated IFN has a polymer attached that enables it to stay in the body for longer by reducing the normal excretion via the kidneys. Ribavirin also interferes with viral replication. The mechanism by which ribavirin works is not known, but it has been shown to make IFN treatment more effective. One of the side-effects of ribavirin is anaemia caused by damage to red blood cells, so the guideline suggests adjusting the dose while monitoring and treating the patient for anaemia.

For patients with CKD Stages 3 and 4 (GFR 15 to 60 ml/min/1.73m²) who are suitable for antiviral treatment, the guideline suggests using pegylated IFN alone as the side effects of combined therapy are expected to get worse as renal function declines. Anaemia caused by ribavirin can be particularly dangerous so it has to be used with caution and only if ribavirin levels in the blood can be monitored and any resultant anaemia can be treated. Lower doses of pegylated IFN are recommended for patients with CKD Stage 3 and 4.

Patients with CKD Stage 5 (GFR < 15 ml/min/1.73m²) who are not yet on dialysis can also be treated with pegylated IFN as described for patients with CKD Stages 3 and 4. For those who have started dialysis, the guideline suggests using standard IFN at a reduced dose because excretion via the kidneys is reduced. Ribavirin is not recommended for use in dialysis patients, but if a decision is made to use ribavirin, it should be with the same caution as for Stage 3 and 4 patients.

In the absence of evidence, the guideline suggests using the treatment recommended for dialysis patients in patients with transplants for whom the benefits of antiviral treatment outweigh the risks.

- The ERBP Advisory Board agree with the recommended treatment agents but point out treatment is best carried out in collaboration with dedicated, experienced centres and with very close monitoring.

**Monitoring the response to HCV treatment in CKD patients:** Guideline 2.3 suggests using SVR, the ‘sustained viral response’, to see if the antiviral treatment has worked. SVR is achieved if testing with NAT six months after completing treatment shows the virus has been completely cleared from the blood.

If you have been treated for HCV, the guideline suggests that your unit checks if you are free of the virus once a year using NAT (or every 6 months if you are on HD). It is especially important to check for relapse if you are hoping for a transplant in case you need another course of treatment before transplantation. The higher frequency recommended for HD patients is for reasons of infection control. The guideline recommends treating patients who have relapsed for at least a year.

Whether or not they have responded to treatment, the guideline says that all patients with HCV should be followed for complications associated with HCV. A 6-monthly follow-up is suggested for patients with evidence of cirrhosis, and an annual follow-up for those without cirrhosis.
3. Preventing HCV transmission in haemodialysis units

Guideline 3 says that HD units should ensure their staff apply the strict infection control procedures necessary to prevent of blood-borne viruses (including HCV) being transferred from one patient to another. These procedures should include hygienic precautions that effectively prevent the transfer of blood between patients, either directly or via contaminated equipment or surfaces.

These procedures are not complicated or expensive. Staff must wash their hands or use an antiseptic alcohol gel rub before and after contact with a patient or equipment at the dialysis station. Gloves that have been worn when caring for a patient, or touching equipment that may be contaminated with blood, must be removed before leaving the dialysis station. Patients should also clean their hands when arriving at or leaving their dialysis station if they are able to.

Items that are used more than once, such as tourniquets or blood pressure cuffs, should be disinfected between patients or dedicated to a single patient. After each session, all surfaces at the dialysis station from the dialysis machine to the TV controller, should be wiped with a disinfectant. Any visible blood should be cleaned up with bleach or an equivalent disinfectant.

- The ERBP Advisory Board noted that the KDIGO guideline on hygienic precautions did not cover peritoneal dialysis. ERBP AB recommends that hands should be washed before and after, and gloves worn during, any manipulation of material contaminated with spent dialysate. Contaminated surfaces should be cleaned with a 1% bleach solution. Spent fluid should be kept in closed drainage bags or in open contained dosed with bleach and, when possible, disposed of in a drain (e.g. a toilet) that is not connected to surfaces used for food or washing (i.e. not a sink).

If the infection control procedures are strictly followed, cross-infection can be prevented without the need to segregate (‘isolate’) patients. Units where infection with hepatitis C is quite common often have separate rooms for HCV-infected and HCV-negative patients. The guideline suggests that even when HCV-infected patients are isolated, the infection control procedures still need to be enforced to protect patients from undetected viral or bacterial infections.

In units where very few patients are HCV-infected, isolation can mean that patients have to dialyse in locations or on shifts that are not convenient for them. This should not be necessary if the infection control procedures described above are properly enforced.

A common practice in units with few HCV-infected patients has been to dialyse infected patients with dedicated ‘HCV’ machines. Guideline 3 does not recommend this practice as the evidence indicates that the main route of transmission is via the staff (e.g. through poor hand washing). If dialysis units have to introduce isolation because they are unable to enforce infection control procedures, they need to ensure the staff do not move between HCV-infected and uninfected patients.

- The ERBP Advisory Board noted agrees that staff should apply strict hygienic precautions at all times. If HCV-infected patients are isolated as an additional measure to prevent
transmission in units where HCV is common, this should not lead to the staff being less vigilant.

The guideline suggests using regular audits where someone observes the staff while they work to ensure that the recommended infection control procedures are being followed. Staff should not object if a dialysis patient or their carer asks if they have washed their hands.

4. Management of HCV infected patients before and after kidney transplantation

Evaluation and management of kidney transplant candidates: Guideline 4.1 says that all patients who are candidates for a kidney transplant should be tested for HCV infection using EIA or NAT (as described in guideline 1). Most patients who are HCV-infected can still be listed for a transplant as, like other patients, they are expected to live longer with a transplant than on dialysis.

The immunosuppressive therapy required after a transplant can allow the virus to replicate more rapidly which could accelerate liver damage. The guideline suggests that HCV-infected patients undergo a liver biopsy before they have a transplant. The biopsy is to identify patients who may have problems after transplantation as well as those who really need a combined liver and kidney transplant.

The guideline suggests that HCV-infected kidney transplant candidates are considered for treatment with standard IFN before transplantation (see guideline 2). As IFN works by stimulating the immune system, the transplant should not be done until at least 28 days after therapy to allow the IFN to be cleared from the body.

Guideline 1 recommends testing HCV-negative patients for new infection every 6-12 months. If a patient on the transplant list is found to be newly infected, guideline 4.1 suggests that they are suspended until their liver disease has been evaluated. The same advice is given for patients who relapse after having had antiviral therapy to clear the virus. For patients who have failed or refused antiviral treatment, guideline 4.1 suggests repeated the liver biopsy every 3 to 5 years while they are on the transplant list.

4.2 Use of kidneys from HCV-infected donors: As HCV can be transmitted from an infected donor to an uninfected recipient, guideline 4.2 says that all kidney donors should be tested for HCV infection using both EIA and NAT (if NAT is available). It suggests that kidneys from HCV-infected donors are only transplanted into HCV-infected recipients who have active infection (measured using NAT).

In practice, living donors who are HCV-infected will not be accepted because of the risk to the donor. To keep waiting times down, the kidneys of HCV-infected deceased donors are used for HCV-infected recipients and it has been shown that the recipients of these kidneys live longer than they would have done on dialysis.

4.3 Use of maintenance immunosuppressive regimens: As the most appropriate regime of immunosuppressive drugs for HCV-infected kidney transplant recipients has not been identified, guideline 4.3 suggests that all the currently available regimes can be considered. Most
immunosuppressive agents will increase replication of the virus so the lowest possible doses should be used and the patient should be checked for complications as described in guideline 4.4.

4.4 Management of HCV-related complications in kidney transplant recipients: HCV infected kidney transplant patients are at risk of worsening liver disease as well as developing ‘NODAT’ (new onset diabetes after transplantation) and glomerular disease (see guideline 5) in the new kidney. To ensure that these problems are picked up quickly, guideline 4.4 suggests checking liver enzyme levels (monthly for 6 months and then quarterly), fasting blood sugar (weekly for 3 months, fortnightly for months 4-6, monthly for months 6-12 then annually) and protein in the urine (every 3 to 6 months).

An annual ultrasound to check for liver cancer is recommended for patients whose liver biopsy showed cirrhosis, but there is no reason for patients to undergo liver biopsies after the transplant unless there is evidence that they have worsening liver disease. Antiviral treatment is not recommended unless the benefit (preventing liver failure) outweighs the risk of losing the transplanted kidney.

If significant levels of protein are found in the urine on two occasions, guideline 4.4 suggests carrying out a biopsy of the new kidney to look for glomerular disease. However, the IFN-based treatment that would be considered for glomerular disease associated with HCV infection (see guideline 5) is not recommended after transplantation.

5. Diagnosis and management of kidney diseases associated with HCV infection

Guideline 5 suggests that patients infected with HCV who are not on dialysis should be tested at least once a year for blood and protein in the urine and for changes in GFR. This is to check for ‘glomerulo-nephritis’ (GN) associated with HCV infection. GN is inflammation of the kidney caused by damage to the tiny structures (called ‘glomeruli’) that filter fluid containing toxins from the blood. The fluid is concentrated to make urine.

In HCV-associated GN, the body’s immune system attacks the glomeruli and disrupts the filtration so that red blood cells and proteins, which are normally held back, can pass into the urine. There are several types of GN associated with HCV, the most common one being membranoproliferative glomerulonephritis (MPGN). The guideline suggests that HCV-infected patients with clinical evidence of GN (e.g. significant amounts of protein in the urine) undergo a kidney biopsy to identify which type of GN they have.

HCV infection is also associated with ‘cryoglobulins’ in the blood. Cryoglobulins are ‘immunoglobulins’ (antibodies) produced by the immune system to fight disease. They clump together in the cold and dissolve again on warming. Cryoglobulins can cause clots and ‘vasculitis’ (inflammation of blood vessels) which can lead to damage in the organs receiving blood from the affected vessels, such as the skin or kidneys.

The guideline suggests considering using antiviral treatment for patients with HCV-associated glomerular diseases, particularly MPGN, as described in guideline 2.2, and immunosuppressive agents for patients with diseases caused by cryoglobulins.
Appendix iii

Are High Flux Dialysers better for me than low Flux ones?

High-flux or low-flux dialysis: a position statement (edited for patients and caregivers) following publication of the Membrane Permeability Outcome study.

Introduction

The term ‘flux’ refers to the permeability of the membrane in the dialyser (artificial kidney) across which accumulated toxins and excess fluid pass during haemodialysis. In the past, this membrane was made from natural cellulose which has relatively small pores. The ‘low-flux’ cellulosic dialysers could easily remove the smaller toxins such as urea and creatinine, but larger molecules that are normally removed by normal kidneys were unable to fit through the pores. Modern dialyser membranes are made from synthetic polymers or chemically modified cellulose. The manufacturers of dialysers with synthetic membranes can engineer the size of the pores to be the same size as a cellulosic dialyser or much larger.

A ‘high-flux’ dialyser has a membrane that allows middle-sized molecules to pass through but prevents the accidental removal of protein from the blood. One example of a ‘middle-molecule’ is beta 2 microglobulin (B2M) which can cause amyloidosis (see explanation at the end of this appendix). If plasma is filtered through a high-flux membrane at least 70% of the B2M will pass through with the plasma water (in the specifications this will appear as a ‘sieving coefficient of 0.7).

The more permeable membrane of a high flux dialyser also allows much faster removal of fluid. In haemodiafiltration, rapid removal (and replacement) of fluid is essential so high-flux dialysers are always used for this type of treatment. There are concerns that the easier passage of water through a high-flux could also make it easier for water borne contaminants, particularly endotoxins, to pass from the dialysis fluid back into the blood. Endotoxins are fragments of bacteria that can be small enough to pass through the dialyser membrane. If endotoxin gets into the blood, either through the dialyser membrane or though damage to the lining of the intestines, it can provoke an inflammatory response from the body’s immune system. Fortunately most synthetic membranes adsorb (trap) endotoxin which keeps it from entering the blood stream. But to minimise the risk of exposure, the machine can be fitted with an extra filter through which the dialysis fluid is passed to ensure that it is ‘ultrapure’.

The current guidelines for adequacy of dialysis are all based on the removal of urea and the recommended dose (in units of ‘Kt/V’) can be achieved with both low and high flux dialysers. Failure to achieve the minimum Kt/V, especially in patients who have no residual kidney function, has an impact on well-being and survival relatively quickly. The problems associated with inadequate removal of the larger toxins tend to be long term which makes it much harder to study the benefit of more efficient removal.

Current guideline
A summary of the current European guideline relating to dialyser membrane permeability or flux is contained in the EBPG guideline on dialysis strategies, published in 2007 and states:

**Guideline 2.1:** The use of synthetic high-flux membranes should be considered in order to delay long-term complications of dialysis-related amyloidosis (See explanation at the end of this appendix); improving control of hyperphosphataemia (See explanation at the end of this appendix); reducing cardiovascular risk; and improving the control of anaemia.

When this guideline was published, there was insufficient evidence to link membrane permeability with survival. The guideline cited the haemodialysis study (HEMO) as the only randomized clinical trial (RCT) then available that directly addressed the influence of high-flux dialysis on survival. Although this study found no difference in survival between high- and low-flux dialysis in the study group as a whole, a further analysis suggested that high-flux dialysis decreased cardiac death in the entire cohort and decreased all-cause mortality in patients who had been on long-term dialysis. This analysis was suggestive of a possible benefit but insufficient on its own to make the recommendation in the guideline stronger. It should be noted here that the HEMO study was performed in the USA where large for-profit dialysis chains have a financial benefit in proving that low-flux dialysis is as good as the more expensive high-flux dialysis.

**The MPO study**

A second RCT is now available, namely the MPO study, which was published in December 2008. This study compared survival in 647 patients randomized between high and low flux. It was designed be more sensitive to the influence of treatment, compared to the HEMO study, by selecting patients with relatively greater mortality risk. This was achieved by studying incident patients i.e. those who are started fresh on dialysis) with a serum albumin ≤ 40 g/l whereas the HEMO study enrolled prevalent patients (which includes those who have newly started on dialysis but also others who have been on dialysis for a longer time with the overall average length of time on dialysis being 3.7 years. This meant that the HEMO study had potentially selected fitter patients. Effectively they had selected a group of survivors, a large number of whom had previously been treated by high flux. By enrolling only incident patients the MPO study avoided any confounding or hangover effects related to the membrane type used prior to the start of the study.

The MPO study found no significant difference in survival between high- and low-flux groups when all patients were included in the analysis. However, when considering only patients with serum albumin ≤ 40 g/l on enrolment, there was a significant 37% reduction in mortality risk in patients treated by high flux. Further analysis also demonstrated a significantly improved survival in patients with diabetes when treated by high flux. In addition there was a significant improvement in serum beta-2-microglobulin (See Amyloidosis explanation at the end of this appendix) levels in patients treated by high-, compared to low-flux membranes for the whole group.

**Interpretation and evidence level.** The MPO study provides high grade evidence that survival is improved by the use of high-flux membranes in high-risk patients (as identified by serum albumin ≤ 40 g/l). The evidence is also very strong for the effect of flux on reducing levels of serum beta-2-microglobulin. However the study only provides moderate or low grade evidence.
that high flux improves survival in diabetics and did not provide evidence that it improved survival in other groups of patients or in the group as a whole.

In clinical practice the choice of low as opposed to high flux may be based on financial constraints of which the cost of ultrapure water is a component. Ultrapure water is required when using high flux dialysis. Therefore high flux dialysis should be recommended for patients at high risk and the only factor hampering the use of high flux in all patients is the small difference in cost between high- and low-flux filters in a limited group of patients and the cost of ensuring a supply of ultrapure water. As such, it makes sense to recommend using high flux in all patients, even if the evidence to support the use of high flux in patients with low risk is lacking.

Guidance and conclusion. The existing Guideline 2.1 should thus be replaced by: Synthetic high-flux membranes should be used to delay long-term complications of haemodialysis therapy in patients at high risk (serum albumin <40 g/l) In view of underlying practical considerations, and the observation of a reduction of an intermediate marker (beta-2-microglobulin), synthetic high-flux membranes should be recommended even in low-risk patients.

**Explanation of terms used in this appendix**

**Amyloidosis** is a group of diseases in which a protein, called amyloid, builds up in the organs and tissues. The build-up may happen in a single organ (localized) or throughout the body (systemically). Amyloid deposits can affect any organ or tissue.

There are three major types of systemic amyloidosis:

- **Primary amyloidosis** the most common form, occurs when bone marrow produces too much of certain fragments of antibody proteins, which build up in the bloodstream and may be deposited in body tissues.
- **Familial (hereditary) amyloidosis** is a genetic form passed down in families that often affects nerves and kidneys.
- **Secondary amyloidosis** develops along with a chronic infections or inflammatory disease, such as tuberculosis or rheumatoid arthritis.

Localized amyloidosis is associated with aging, as the body seems to naturally make amyloid as it ages. Two common conditions associated with localized amyloidosis are type 2 diabetes (where protein builds up in the pancreas) and Alzheimer’s disease (where protein builds up in the brain). **Beta2-microglobulin amyloidosis occurs in people with kidney failure who have been on dialysis for a long time (beta2-microglobulin is a protein that can build up in the blood as a result of kidney failure).**

**Hyperphosphataemia** means having too much phosphate in the blood. Often, calcium levels are lowered (hypocalcaemia) due to the combination of phosphate with the calcium which is then precipitated as calcium phosphate in tissues. There are 3 causes:
• **Hypoparathyroidism:** In this situation, there are low levels of Parathyroid hormone (PTH). PTH normally inhibits renal reabsorption of phosphate, and so without enough PTH there is more reabsorption of the phosphate.

• **Chronic renal failure:** When the kidneys aren't working well, there will be increased phosphate retention.

• **Osteomalacia,** which may be caused by the insufficient content of vitamin D in the diet, the lack of sunlight, malabsorption or renal disorders.
Appendix iv.

Are venous catheters safe in terms of bloodstream infection? What should I know?

DIAGNOSIS, PREVENTION AND TREATMENT OF HAEMODIALYSIS CATHETER-RELATED BLOOD STREAM INFECTIONS (CRBSI): A POSITION STATEMENT OF EUROPEAN RENAL BEST PRACTICE (ERBP) for patients and caregivers.

Introduction.

Haemodialysis is only possible if blood can be removed from, and returned to, the body at 200 ml/min or more. The ‘gold standard’ for gaining access to the blood in haemodialysis is the ‘arterio-venous’ fistula (AVF). This is a vein that has been surgically joined to an artery. If the vein cannot be directly joined to the artery, an ‘artificial’ graft, often made of Teflon, may be used. This is referred to as an AVG (Arterio-Venous Graft). Following the connection, the high pressure in the artery expands the vein so that it becomes easy to insert the needles required for dialysis.

Alternatively a catheter can be used for haemodialysis. It can be inserted directly through the skin into a large central vein. This type of catheter is generally used in patients who are not expected to need dialysis for more than a few weeks. If the patient is expected to require long-term dialysis, a tunnel will be made to allow the catheter to pass from the vein, under the skin and out of the body. Tunnelling the catheter under the skin provides a barrier to infection.

In patients on long term maintenance haemodialysis, permanent tunneled central vein catheters are generally considered as the last resort for vascular access. One of the major reasons for discouraging the use of tunneled as well as non-tunneled catheters as an access for haemodialysis, is the risk of infection. They are a source of morbidity (illness) and mortality, by inducing malnutrition, inflammation, cardio-vascular damage, septic complications and metastatic infectious disease. Metastatic infectious disease means that the infection has spread to distant parts of the body from its originating source via the blood stream and settled in these distant sites. Non-tunneled temporary catheters should be avoided as much as possible, since the risk of infection as compared to tunneled catheters is even higher. Although the use of permanent catheters in long term dialysis is generally discouraged, the proportion of patients treated with them continues to grow as they are a life saving option in a substantial number of people who have run out of ‘native vascular access’ (and AVF) possibilities. The presumption is that their high prevalence, especially in the Western World, is due to the increased frequency of dialysis in patients of older age with cardio-vascular disease and/or with diabetes mellitus, in whom the creation or repair of a native fistula is technically challenging, risky or impossible.

When and where should a Central Venous Catheter be placed?

Haemodialysis catheters are required either due to need for urgent dialysis or because patients refuse to have an AVF created. If catheter related complications occur, the
options for alternative access, such as an AVF or peritoneal dialysis should be re-evaluated.

ERBP recommends the following:

Catheter insertion should be performed under strict aseptic circumstances.

Catheters inserted in the femoral position (in the groin) are prone to a higher risk of infection and bacteraemia than if the internal jugular vein (in the neck) is used and should therefore be avoided as much as possible. Of the remaining positions, the subclavian is discouraged for reasons other than infectious risk (i.e. stenotic complications i.e. narrowing of the vein with consequential partial obstruction to the flow of blood from the dialysis machine). Among the internal jugular positions, the right one is the more convenient.

![Diagram of central venous catheter insertion sites](image)

**How should a Central Venous Catheter be managed?**

Strict hygienic precautions using sterile and disposable material (drapes, gloves) must be applied by caregivers whenever a central vein catheter is manipulated, connected or disconnected. The patient should at least wear a mask. Two trained staff members (one nurse focusing on the catheter and one helper to manage the dialysis machine and assist the nurse) are needed to enable the connection and disconnection. The most important principle for preventing infection is to adopt a meticulous approach to the handling of catheters in a reliable and sterile fashion, when connection and disconnection are performed or at any other time.

**Preventive antimicrobial catheter locks and catheter surface treatment**

After dialysis the catheter lumens are filled with a solution which is called the ‘lock’. There is increasing evidence that antimicrobial locks are effective in preventing catheter related blood stream infections.
Some locks may have extra antimicrobial or biofilm removing properties (A biofilm is an aggregate of microorganisms that adhere to each other or to a surface). Adding antibiotics, either to heparin or to citrate solutions used for locking catheters, has an extra beneficial effect compared to heparin or citrate alone. However, they should always be used in combination with systemic antibiotic treatment, because of the possibility of creating resistance when they are used alone. Over time, progressively lower concentrations of citrate have been applied (from 46.7 to 4%). Even 4% concentrations achieve significantly better results than heparin.

A Food and Drug warning against citrate locks was issued in 2000 following a fatal accident with the 46.7% solution. The 46.7 and 30% concentration ranges are considered unsafe. For that reason, the low 4% concentration is the only one recommended. This is supported by the American Society of Diagnostic and Interventional Nephrology (ASDIN).

According to ERBP, there is not enough evidence for a clinical benefit from ethanol locks. Ethylene diamine triacetic acid (EDTA) has been proposed as an alternative.

For each type of lock, the corrosive or damaging potential on catheter polymers should be taken into consideration.

The use of antimicrobial locks should not be used as an excuse to be less vigilant in applying strict hygienic precautions.

**Exit site dressings**

In addition to ensuring skin antisepsis before and during catheter placement, the exit site, where the catheter emerges through the skin, should be inspected and cared for on a daily basis. The exit site should be covered with a dressing as long as the catheter is in place.

With long-term catheters, gauze is the preferred choice. Gauze should be replaced if it is no longer dry or clean. The patient should be instructed to respect strict hygienic measures by preserving the integrity and dryness of the dressing, and should know what to do in case it becomes wet or disintegrates.

**Exit site and nasal antibiotic ointments**

The use of antibiotic ointment at the insertion site has a beneficial effect in reducing Catheter Related Blood Stream Infections and exit site infections. Application is especially recommended after catheter placement until the insertion site has healed. However the application of mupirocin might be complicated by development of resistance. Prolonging antibiotic ointment application after site healing probably offers
no advantage and has the potential to increase the risk for development of resistance and for *Candida* colonization.

According to ERBP, there is insufficient evidence to routinely use nasal antibiotic ointment in a haemodialysis setting.

**Diagnosis of CRBSI:**

Cultures of blood may be taken from the intravenous catheter to determine if blood that has been residing in the catheter for some time has become infected.

ERBP considers that, in many cases, it may be impossible to puncture a peripheral vein because of non-availability or because it is deemed desirable to preserve veins for creating future access. If a patient is suspected of having a blood stream infection, it is normal practice to take blood samples from a site other than the indwelling catheter. However, as many of the fever episodes that necessitate blood culture sampling occur during dialysis, when the blood flows through the catheter are high, it is likely that blood cultures collected through the catheter will offer similar results to peripheral blood which therefore renders peripheral sampling redundant.

An alternative approach that might increase the chances of identifying responsible organisms is to culture blood or (a) blood clot(s) extracted from the catheter before the start of dialysis. However, a large proportion of patients exhibit symptoms related to CRBSI only during haemodialysis, and make pre-dialysis sampling less successful.

When blood is taken via a vein during haemodialysis, it is possible that the origin of the infection may not come from the catheter but from another source. It is therefore important to exclude other sources of infection by careful history taking; a thorough examination; imaging and if possible, culture of any urine that may be produced by the patient.

To guide antibiotic therapy, it is of utmost importance that each haemodialysis centre maintains a database of all suspected and proven CRBSI and episodes of bacteraemia in general including: the causative organisms; their sensitivity pattern to antibiotics; the potential source (catheter related, pneumonia, urinary tract, etc.); and the outcomes after therapeutic intervention. As a consequence, each unit should be aware of its catheter related infections.

**Management of catheter infection in patients receiving haemodialysis**

**When should a catheter be removed?**

Removal of the catheter should be considered as additional intervention to systemic antibiotic treatment when any of the following severe complications arise: sepsis; infected clot or fibrin sheath; suppurrative thrombophlebitis (inflammation of the vein which produces pus); metastatic infection (where infection breaks away from its point of origin and is carried by the
blood stream to a distant site such as the brain or liver or skin); persistent blood stream infection or persistent clinical signs of infection in spite of 72 hours of appropriate antimicrobial therapy; infection with *S. aureus*, *P. aeruginosa*, or fungi; tunnel infection with fever.

For tunnel infection without fever, topical antibiotic application might be attempted first.

If infection does not resolve, systemic antibiotic treatment should be initiated. If systemic antibiotics fail, the catheter should be removed.

ERBP recommends the insertion of a new tunneled central vein catheter only when the patient remains without fever for ≥ 2 weeks. In the interval, a temporary non-tunneled haemodialysis catheter should be inserted at another site. Using catheters placed purely for a single dialysis session and removed immediately afterwards, might be considered to minimize the risk of colonization of the non-tunneled catheter.

However, in patients on haemodialysis, options for access may be limited. Firstly, removal of a catheter will require another catheter to be inserted, increasing the potential risk of further damage to the central vein. Secondly, access options may already be extremely limited, and additional attempts at central vein cannulation may be impossible or incur a high risk.

If problems are anticipated, an alternative strategy is to exchange the catheter over a guidewire. The optimal time for such replacement is after 72 hours of appropriate and effective antibiotic treatment. However, replacement over a guidewire increases the risk of hardening or narrowing the vein, and is associated with a high treatment failure rate.

Surveillance blood cultures should be obtained one week after completing the antibiotic treatment for the CRBSI if the catheter has not been removed. If these cultures are positive, the catheter should be removed.

In order to preserve future access options, the practice of peripheral blood culture sampling from blood vessels that could potentially could be used for the future for creation of vascular access should be limited or avoided.

In all circumstances, systemic antibiotic therapy should be administered for CRBSI.

**Antibiotic locks**

If catheter removal is deemed unnecessary, undesirable or impossible, an antibiotic lock is an important therapeutic option. An antibiotic lock should not be used alone, but always in conjunction with systemic antibiotics for the recommended periods. Although dwell times generally should not exceed 48 hrs (or 24 hrs for patients with femoral
catheters), renewal of the haemodialysis lock after every dialysis session is considered sufficient.

**Diagnosis of an outbreak of CRBSI**

To understand the reasons for recurrent outbreaks of infection the patterns of micro-organisms’ antibiotic sensitivity should be evaluated including molecular fingerprinting. Dialysis centres should establish standard care protocols for prevention and treatment as well as a quality improvement program. In case of an outbreak of CRBSI, the root cause analysis should assess compliance with these protocols. If compliance is below expectation, retraining and eventually reorganization of care should be considered. If compliance with the protocol is deemed appropriate, modification of the protocol could be considered, and the process of care re-audited.
Appendix v

Why is it important to regularly test my Peritoneal Membrane?

Evaluation of peritoneal membrane characteristics and prescription management: a position statement of ERBP

INTRODUCTION

The peritoneal membrane is a membrane that lines the abdominal cavity and covers the organs that lie in that cavity. Peritoneal dialysis (PD) uses this as a semi-permeable membrane for dialysis. The properties of the membrane are important in selecting the optimum treatment regimen. Its properties and quality vary among individuals and also within the same individual over time so it is important to regularly evaluate its characteristics in order to determine the most appropriate prescription for each individual patient. The recommendations in this ‘position statement’ are based on expert opinions, supported by available evidence and suggest how this should be carried out.

THE NEED FOR TESTS OF PERITONEAL CHARACTERISTICS

Frequency: Tests of peritoneal membrane characteristics should be routinely repeated once a year, or when new clinical problems such as over-hydration, malnutrition, or metabolic disturbances are noticed.

The aims of testing peritoneal membrane function are: to optimize a treatment prescription with regard to the removal of ‘kidney failure related toxins’ of different sizes and fluid volume regulation; and to see how peritoneal membrane function changes over time.

The peritoneal membrane characteristics, specifically the transport rate of toxic solutes and ultra-filtration capacity, are fundamental to PD prescription, and will guide prescription. Based on these differences, a therapy can be tailored to the specific needs of the patient in terms of the ideal duration of different dwells, the number of dwells, and the type of dialysis solution used. An inappropriate prescription can lead to substantial underachievement in terms of the removal of toxic waste products and ultra-filtration, or unnecessary exposure to the high glucose content of dialysis solutions (i.e. heavy bags). For example: using Automated Peritoneal Dialysis with short dwells in slow transporters results in salt retention and hypertension, whilst in patients with a fast transport status, long dwells can be associated with fluid volume overload and hypertension. The peritoneal membrane characteristics of some patients will change as they spend months and years on therapy, usually leading to a decreased ultra-filtration capacity and an increase in the transport rate for small solutes.

Choice and application of test of peritoneal membrane characteristics Although there is insufficient evidence to prefer one test over another to determine a clinical prescription, some tests may give specific information not provided by the classical PET test. Thus the type of test used is dependent on the sort of information required to answer a specific question. Some patients may wish to be aware of what these tests are although most will rely on the expertise
The Peritoneal Equilibration Test (PET) is the most widely used test for evaluation of peritoneal membrane characteristics. The original PET used a fixed fill volume of 2 liters of a 2.27% glucose solution over a 4 hour dwell. There is no evidence that using 1.36% or 3.86% glucose instead of 2.27% glucose influences the results. The impact of a preceding overnight dwell with icodextrin has only been evaluated in one small study, so no recommendation can be made in this regard. Although the original PET allows accurate estimation of small solute transport, it does not provide sufficient information to discriminate among causes of ultra-filtration failure. To answer the latter question, it is recommended to use a 3.86% glucose solution during the PET, with determination of the evolution of D/P_sodium during the dwell. This test has been named “modified PET”. It is advocated to use the 1 hour value of D/P_sodium to estimate the free water transport. This procedure has been named the mini PET. Whereas the mini PET is short, and gives important information on aquaporin function, it fails to provide estimates of net fluid re-absorption from the peritoneal cavity. Formerly PET results categorized patients as high or low transporters which led to confusion. These terms are no longer appropriate for clinical use and prescription management. The current more relevant terminology that has been adopted is “fast”, “average” and “slow” transporters. A useful table in the published ERBP paper on this topic summarizes the properties of these 3 types of patient with recommendations as to the most appropriate PD prescription for each type. When applying tests of peritoneal membrane characteristics, some pitfalls should be considered. These are described in detail in the full version of the ERBP paper.

Peritoneal membrane ultra-filtration failure is defined as a drained volume after a 4 hour dwell of less than 2100ml with a 2.27% glucose solution or one of less than 2400ml with a 3.86% glucose solution respectively. The (theoretical) condition “ultra-filtration failure” should be distinguished from the (clinical) condition “over-hydration”. Clinical over-hydration is the net result of the volume balance of the patient, and is influenced not only by peritoneal ultra-filtration capacity but also by other factors, such as residual urine production, and dietary salt and fluid intake.

For optimal PD prescription management, other parameters indirectly related to peritoneal membrane characteristics should be considered. Fuller details of these points are given here as they are particularly relevant to patients who manage their own PD.

The catheter outflow pattern is most important and should be monitored on a regular basis. The catheter drainage profile is an important guide to prescription management, especially in APD patients. It should be recognized that drainage time is in fact non-dialysis time. Most patients have a typical drainage profile, with a steeper flow rate initially and subsequently a slower rate with virtually no flow at the end of drainage. At the end of the dwell, insufficient dialysate is present in the abdominal cavity to allow the transport of toxins. The dialysate outflow pattern should therefore be monitored too avoid this period lasting too long. Too long periods of non-diffusion should be avoided. This can be achieved by keeping the number of dwells low, and by
starting refill immediately after the “breakpoint”, rather than awaiting complete drainage (this can in most cyclers be done using the “tidal” mode).

**Residual renal function**, both in regard to solute clearance and fluid output, should be monitored on a regular basis by 24 hour urine collection and calculating the mean of urea and creatinine clearance. Residual renal function is not only a major predictor of outcome, it is also an important factor to take into account when making a prescription. Patients with a rapid declining residual renal function often also have a faster deterioration of their peritoneal membrane. It is strongly discouraged to intentionally leave patients over-hydrated in the hope of preserving residual renal function as it has the opposite effect and results in a faster decline of their residual renal function. Furthermore it is an important driver of cardiovascular mortality. Dehydration should also be avoided, as this too can accelerate the deterioration of any remaining renal function.

**Prescription recommendations** do not indicate whether manual PD (continuous ambulatory peritoneal dialysis, CAPD) or automated PD (APD) should be used, as this is a lifestyle issue. Provided the recommendations on the lengths of the dwells are followed, all patients can choose either APD or CAPD based on their preference and lifestyle. When negative ultrafiltration is suspected, as long as mechanical causes and lymphatic re-absorption have been excluded, the dwell time should be shortened rather than increase the glucose concentration of the dialysate. This will simultaneously result improve ultra-filtration and solute removal and avoid unnecessary exposure to glucose.
Appendix vi.

**What sort of dialysis should I choose?**

**Dialysis modality selection: clinical advice from the European Renal Best Practice (ERBP) Advisory Board**

**Introduction.**

There is insufficient medical evidence to support a general preference of HD over PD, or vice versa. Therefore, the initial choice of modality should be made primarily by the well-informed patient.

All renal replacement therapy (RRT) centres should provide, or collaborate with other centres, to offer all available treatment options: PD (including CAPD, APD and aAPD (i.e. Assisted APD), HD (including home HD and nocturnal programmes) and transplantation (including cadaveric and non-cadaveric), thus enabling all patients to select the modality that most suits their lifestyles.

All patients and their families should receive well-balanced information about the different RRT modalities, by means of a structured educational programme. This also applies to late-referred patients and those starting dialysis in an emergency situation, who should receive the information once their condition has stabilized. In some European countries the educational programmes involve experienced patients and their carers supported by health care professionals.

The present paper comprises the clinical advice on modality selection for RRT in patients with end-stage renal disease (ESRD). These recommendations have been issued by an ERBP Expert Group and approved by the ERBP Advisory Board.

Four areas of interest will be discussed:

(i) Initial dialysis modality selection

(ii) Choice between continuous ambulatory PD (CAPD) and automated PD (APD)

(iii) Transition between RRT modalities

(iv) Assisted PD

**What is the right approach to initial dialysis modality selection?**

Most studies suggest a better survival rate for patients on PD than on HD during the first few years after starting therapy.
However, after 2 or 3 years, the outcome on PD becomes equal to HD, or worse, depending upon the study. These differences in outcome seem attributable to differences in the statistical approach, patient mix and the experience that the RRT centre has of using different modalities. Indeed, outcomes on RRT, both in absolute terms and in relative terms (PD vs HD), appear to be strongly influenced by country and centre experience. Based on these findings, the ERBP Expert Group suggests that the ‘PD first’ approach should be presented to the patient as the most logical choice. However, it also feels that there is **not enough hard evidence to consider it mandatory to start with PD.** Therefore, the patient’s preference should be the primary factor in selection as patient satisfaction, compliance with therapy and their quality of life are better if they have been given the opportunity to make an informed choice.

**In most European Countries and also at EU level, it is legally required to inform patients of all treatment modalities.**

There is accumulating evidence that the outcome of patients is jeopardized if they are treated in centres where only one modality is available, or where the experience with alternative dialysis strategies is limited. In those centres, patients are obliged to accept the only available RRT option, or are treated suboptimally because of a lack of experience of other options. All centres should make sure they provide, or at least support in collaboration with another centre, all available modalities, including home HD.

Although no data on randomized controlled trials are available on this topic, some recent well-conceived cohort studies have indicated that outcome of home (daily) HD is superior to conventional in-centre dialysis, and even equivalent to cadaveric transplantation. Even though it may not be feasible for all centres to develop their own freestanding home HD programme, it is strongly advised that centres organize such a programme jointly.

The option of renal transplantation, both cadaveric and from a living donor, should be discussed with the medically suitable patients, as the outcomes of transplanted patients appear to be better compared to those on standard haemodialysis. However, for the elderly and for patients with multiple co-morbidities, this benefit is less clear. The shortage of available organs raises the ethical question of whether patients who are more likely to benefit should be prioritized over others whose predicted outcome is more questionable.

**The following conditions should not be considered as ‘absolute’ contraindications to PD (an absolute contraindication is one which would make PD too risky to contemplate):**

- Physical or mental inability to perform PD
- Older age
• Poor adherence/non-compliance to therapy.
• Obesity.
• Congestive heart failure
• Polycystic kidney disease
• Diverticulosis
• Abdominal hernias
• Portal hypertension
• Liver transplantation

Performing PD requires a minimum of physical skills and mental capacity. It is clear that some physical problems, such as visual impairment and tremor or deformities of the hands, may interfere with PD handling.

In the opinion of the ERBP Expert Group, these problems do not a priori preclude the application of PD as an RRT. Several companies and research groups have invested in the development of tools to ease handling of the PD equipment, and it is the task of the PD team to provide creative solutions to individual problems. Moreover, several centres in the world have gained experience in the so-called ‘assisted PD. In this setting, it is not the patient themselves who performs the PD but a nurse or another assisting person. Assisted PD must be considered as an alternative to in-centre HD for non-autonomous patients. Even with the additional cost of the assistance, assisted PD in developed countries has been reported to be cheaper than in-centre HD.

**Is there a specific recommendation or contraindication for elderly patients?**

There are an increasing number of elderly patients starting dialysis worldwide. When advising such patients on modality selection, the following points should be considered:

Elderly patients starting RRT may have numerous co-morbidities at the initiation of dialysis. Older age is frequently associated with loss of strength, dexterity, vision or hearing. Furthermore, cognitive dysfunction may be present. The commencement of dialysis can be associated with a significant decline in the functional status, including cognitive functioning and assistance may therefore become necessary in self-care patients during the course of their PD treatment. In addition those who care for elderly patients on PD may experience adverse effects on their own quality of life, which may, in turn, lead to a loss of assistance. On the other hand, PD may present some advantages in the elderly patients with ESRD as the arrhythmia and hypotension that may during the HD sessions will be avoided.

Quality of life is particularly relevant for the elderly patients on dialysis. Travel time to and from the HD centre has a negative impact on patient’s quality of life. Home therapy as offered by PD is associated with a better quality of life compared with in-centre HD. In view of the importance of maintaining a good overall quality of life, the option of non-dialytic (or so-called conservative) treatment should also be discussed with the patient
and their relatives.

Is PD appropriate for patients who have problems adhering to their therapy?

Presumed or real non-adherence to the prescribed PD regimen can be a challenge to the PD team. Nevertheless, it is unlikely that non-adherent PD patients will become compliant HD patients. It is important for the caregiver, particularly if there is a sudden change in adherence to discover the reason for this change. It is especially important to find out whether the non-compliance is related to the PD therapy itself or whether it is a general attitude of the patient. In some cases, the cause of noncompliance is a condition that requires attention from the caregiver, such as denial of disease, depression, social problems (like divorce or death of a beloved person), intercurrent illness and cognitive deterioration. Some of these conditions are only temporary and/or can be treated adequately. Some of the adherence problems may be solved by the implementation of assisted PD.

Is PD a realistic dialysis option for obese patients?

There is currently not enough evidence to contraindicate PD in obese individuals. However, several comments on this issue are necessary. Obese patients, especially if diabetic, were shown to have a comparable risk of death after starting on PD compared to HD although such evidence is scanty. Most studies in PD patients have found similar or slightly worse survival in those who are obese compared to those with normal body mass index. Obese patients may need larger dialysate volumes, usually provided by APD, to achieve adequate Kt/V (a measure of the clearance of waste products from the body by the kidney), although the increase in body mass is not associated with a proportional increase in body water volume. In patients with morbid obesity, PD may not be the preferred dialysis modality or is relatively contraindicated as there may be: difficulties in peritoneal catheter placement and tunnel healing process; increased risk of fluid leaking out around the catheter and infection; possible further weight gain due to glucose absorption from the dialysate; as well as a risk of abdominal pain or discomfort.

Congestive heart failure in ESRD and dialysis options.

Congestive heart failure (CHF) is increasingly common in patients with ESRD. PD, with its more subtle and gentle capacity for ultrafiltration, might be a better and more comfortable alternative. The only large registry study comparing the outcome of patients with CHF on PD vs HD was undertaken in the USA and found a higher mortality risk in PD patients. However, according to the ERBP Expert Group, the results of this study cannot be extrapolated to European patients, because of the different case mix and characteristics of the US population together with the fact that no icodextrin was available to help maintain fluid balance in PD patients. Also the statistical methods applied in this paper were biased in favour of HD. Many single-centre reports indicate that PD can improve quality of life. Based on the existing information, it is difficult to
either support or discard PD as a method of choice in CHF patients. One particular subgroup, however, could be that of anuric PD patients with CHF, in which maintaining adequate dry weight is quite difficult.

Furthermore, clinically unapparent overhydration could be present and significant for patients with diminished cardiac reserve, and use of additional specialist objective measures for dry weight assessment is recommended. Careful patient monitoring, control of water and salt intake, efforts to preserve peritoneal and renal function and, in many cases, the use of APD and icodextrin-based PD solutions, that do not use glucose to remove excess fluid, are critical for the management of these patients. However, if maintaining correct dry weight is still impossible to achieve, patients should be promptly transferred to HD, preferably using slow-ultrafiltration, long hour techniques.

**Is there a reason to recommend/prefer CAPD or APD?:**

There is no reason to prefer CAPD over APD or vice versa, as long as the time between the PD fluid exchanges is matched to the patient’s peritoneal ‘transport’ type. The transport type describes how quickly toxins are removed from the blood and glucose is absorbed from the dialysis fluid. The outcomes for both modalities have been found to be equal and choice should be guided by patient preference.

Although several studies have observed that outcomes on CAPD and APD are equal, it is important to maintain the appropriate dwell time for the appropriate patient. Failing to do so might lead to fluid overload and inadequate solute removal. It is conceivable that short dwells can more easily be obtained with the use of a cycler, whereas long dwells seem to be more appropriate for CAPD. Teams should try to accommodate the patient’s lifestyle issues with the underlying membrane characteristics, by making full use of their experience and creativity.

**When and how to change dialysis modality.**

Whilst the first two sections of this publication deal with the choice of RRT modality when a patient approaches ESRD, the present section focuses on the transition from one modality to another once one form of maintenance RRT has been started. **Three types of transition should be considered: HD to PD, PD to HD, and failed renal transplantation to either HD or PD.**

One single modality may not procure adequate treatment over an entire lifespan; therefore, nephrologists sometimes have to recommend switching modalities. The consequences of such decisions should be evaluated, to consider the benefits or threats not only in the short term, but also in the longer term. Patients with chronic kidney disease should be informed, before the start of their RRT, about the possibility of being switched to an alternative modality at a future date. For that reason, unless there are absolute contraindications for a particular modality, pre-dialysis information provided to
patients should cover all possible therapies, without hallmarking any option as ‘impossible’ or ‘bad’.

In the opinion of the ERBP Work Group, the patient’s informed choice of treatment modality should be respected, as long as his/her clinical conditions permit. If a chosen RRT modality becomes inadequate, transition to another therapy should be proposed, and the underlying reasoning explained to the patient. Even in these circumstances, the choice of the well-informed patient should be respected. When patients decide not to follow medical advice, despite obvious treatment failure, it should be recorded that the change in treatment has been recommended but declined. The latter situation cannot be considered as inappropriate adherence to the original modality by the treating physician, as a well-informed patient’s choice takes precedence.

**When to be transferred from HD to PD**

Patients on HD should be informed about the option of PD when they suffer from any the following clinical conditions:

- Intradialytic haemodynamic intolerance (falls in blood pressure) and muscle cramps despite optimal adjustment of dry weight
- Difficulties in creating a well-functioning native vascular access
- Intractable or recurrent ascites (accumulation of fluid in the peritoneal cavity)

The rationale for considering PD in case of irremediable haemodynamic intolerance of HD or incapacitating muscle cramps is obvious. In contrast to HD, PD is a continuous therapy that is not characterized by large volume shifts or sudden changes in serum electrolytes like potassium or calcium. Alternatively, short daily or nocturnal HD, preferably performed at home, may also be considered, in order to improve haemodynamic stability.

Pre-dialysis counselling should include giving the patient information on: the importance of vascular access for HD; the need for preservation of arm veins for placement of vascular access; and the notion that starting with PD is a means of preserving the vascular potential. In HD patients, where creation of a well-functioning native vascular access is not possible, PD should be proposed as a better alternative than the use of permanent central vein catheters, which are associated with substantial morbidity and mortality. Infection risk on PD is comparable to that of HD patients with a native fistula, whereas the infection risk of a tunneled HD catheter is twice as high.

Ascites may be due to heart failure, hepatic failure or cancer. While ultrafiltration during HD may be able to remove fluid from the body and sometimes alleviate the abdominal distension due to ascites, it will often fail to do so. PD may be a better alternative, since fluid can be drained out through the PD catheter. The theoretical concerns of excessive loss of albumin or higher infectious risk seem clinically irrelevant.
It has been demonstrated that the outcome of patients transferred from HD is similar to that achieved in patients who are kept on PD from the start of RRT.

**Transition from PD to HD:**

Patients on PD should be informed about the option of HD when they suffer from any of the following clinical conditions:

- Incapacity to maintain fluid balance.
- Relapsing or persistent peritonitis (inflammation of the membrane enclosing the peritoneal cavity, usually due to infection)
- Incapacity to control uraemic symptoms or to maintain a good nutritional state
- Changes in lifestyle circumstances.
- Declining residual renal function
- Intra-abdominal surgery.
- Sclerosing peritonitis (formation of a thick membrane around the bowel).

**Volume overload** is related to cardiac dysfunction and mortality. Guidance on how to achieve and maintain euvolaemia (i.e. the normal blood volume; neither too much (Hyypervaolaemia) or too little (Hypovolaemia)) in individual PD patients is hampered by two factors:

- the absence of a convenient and accurate device with which to measure volume status.
- lack of insight into the prevalence of and factors associated with volume overload.

Volume overload in PD can have several causes, which can be even present together in the same patient at the same time. The most common causes are excessive dietary intake of salt and/or water, and ultrafiltration failure. Ultrafiltration failure often occurs because the glucose that draws excess fluid from the body into the peritoneal cavity is transported into the blood too quickly. This ‘fast-transport’ status can be readily diagnosed by performing a validated membrane permeability test, and therapy can be adapted accordingly, as described in the EBPG guidelines on this issue (see Appendix v).

Most episodes of **peritonitis, exit-site infection or tunnel infection** can be treated successfully by adding antibiotics to the PD fluid and should not be a reason to transfer patients to HD. However there are some exceptions to this general rule. Exit-site or tunnel infections progressing to or accompanied by peritonitis (i.e. catheter-related peritonitis) with the same organism often require catheter removal. Resistant peritonitis and relapsing peritonitis commonly require catheter removal in order to resolve the problems.

Catheter removal is also needed in fungal peritonitis and in unresponsive cases of peritonitis with mycobacteria or multiple enteric microorganisms. Catheter removal in
these cases requires a period of peritoneal rest before insertion of a new catheter (2 weeks at least and 6 weeks in case of mycobacterial peritonitis). This, of course, requires temporary transition to HD, unless residual renal function is still satisfactory.

The ERBP Work Group feels that insertion of a new PD catheter and resuming PD treatment should be considered if the patient wishes to stay on PD. It should also be kept in mind that persisting or relapsing peritonitis could be a hallmark of poor peritoneal membrane condition, making maintenance of PD risky. Patients should be warned that, in these circumstances, successful PD continuation is uncertain, and that transfer to HD might still be needed some time later. Reinsertion of a new catheter should preferably be done under laparoscopy, in order to visualize and—if necessary—treat adhesions.

**The Importance of Residual Renal Function.**

The importance of residual renal function (RRF) as a determinant of PD patients’ outcome has been demonstrated by numerous studies. The benefits of RRF have been attributed to its role in the maintenance of fluid balance, its association with lower inflammation and better nutritional status, its endocrine functions (erythropoietin production and alpha-hydroxylation of vitamin D) and its contribution to the removal of toxic substances. Based on these data, some have argued that PD patients should be switched to HD in case of a complete loss of RRF; however, it is quite likely that, also in HD patients, RRF is also an important predictor of outcome. In addition, several observational studies have demonstrated that PD in anuric patients is feasible, with acceptable outcomes. Special attention has to be paid, however, to the volume status of these patients. Given the importance of RRF for outcome, maximum efforts should be done to preserve it, by avoiding nephrotoxic insults.

**Surgical procedures** can disturb the integrity of the peritoneal membrane, leading to leakage or insufficient remaining surface area. However, some surgical procedures (e.g. removal of a non-functioning kidney) can be performed without disrupting the peritoneal membrane. It is recommended to inform the surgeons about the importance of preserving peritoneal membrane integrity, and to carefully consider surgical indications to avoid disruption of the peritoneal membrane.

**Is a pre-emptive switch from PD to HD advocated?**

Some nephrologists advocate ‘pre-emptive’ switching of PD patients to HD after 2 or 3 years from PD start, even when every aspect of the treatment is going well. This recommendation is based on the findings that, after a few years, outcome on PD starts to get worse than on HD. PD may also become inadequate with declining RRF and the incidence of sclerosing peritonitis starts to rise with time spent on PD. The ERBP Expert Group endorses the recommendation of the International Society for Peritoneal Dialysis that time on PD alone should not be a decisive factor in itself for transferring patients
from PD to HD. However, with increasing time on PD, physicians should be aware of the potential pitfalls of the technique, and discuss these and the possible alternatives with the patient.

**Is there a recommended choice of dialysis modality for patients with failed renal transplantation?**

In patients with failed renal transplantation who return to dialysis, there is no proven difference in survival between HD and PD. Therefore, the choice of dialysis modality for these patients should be based on the same principles as those applying to the initial modality choice.

There is little data available on the impact of dialysis modality on the outcome of patients with failed kidney transplant. However, PD seems to be underused in this setting, for several probable reasons:

- in most dialysis centres, the majority of patients are on HD.
- the start of dialysis in emergency situations also favours HD.
- the fear of increased peritonitis rate or of rapid loss of RRF in patients transferred to PD.

Higher morbidity and mortality rates in patients starting PD after transplant failure compared to de novo PD patients have been reported. On the other hand, there is no significant difference in survival between these two categories of PD patients after correction for age and co-morbidity. Comparative studies (which are few and retrospective in nature) found no differences in survival of patients with failed renal transplantation on HD versus PD.

The issue of tapering immunosuppression or not after restarting PD is still a matter of controversy, since there is no evidence of the beneficial effects of preserving residual function in the transplanted kidney (similar to non-transplanted patients). On the other hand, the continuation of immunosuppressive therapy implies an increased risk of infections and malignancies. Therefore, the decision is currently based on local experience. Slow reduction of immunosuppressive drugs is probably preferable, as it was shown to be associated with similar RRF after 1 year on PD as in non-transplanted patients, without increasing the risk of peritonitis.

**What does assisted PD mean?**

Assisted PD can be defined as a PD modality performed at the patient’s home with the assistance of a health-care technician, a community nurse, a family member or a partner. Additional funding is necessary when patients are assisted by a nurse or by a health-care assistant. Therefore, when using the term ‘assisted PD’, information regarding the type of assistance must be provided. There are two modalities of assisted
PD: assisted APD and assisted CAPD.

Assisted PD must be considered as an alternative to in-centre HD for non-autonomous patients.

Even with the additional cost of the assistance, assisted PD in developed countries is reported to be cheaper than in-centre HD, although costs may vary between countries. Assisted PD enables nephrologists to increase the use of PD in patients starting dialysis. Community-based nurses must be trained by nurses from the PD centre to perform the connection and the exit-site dressing, and to set up the cycler in case of assisted APD. A 24-h ‘hot line’ to provide medical or nursing counselling to those involved in the patient’s care is needed. The PD centre must deal with organizing the patient follow-up in the PD clinic and hospitalization in the nephrology unit whenever necessary. For assisted APD, only two interventions at the patient’s home are necessary, whereas patients on assisted CAPD need four visits daily. In countries where assisted PD is fully covered by the health-care insurance, most of the patients on assisted PD are treated by assisted CAPD; patients’ cognitive dysfunction and/or anxiety linked to the cycler therapy may explain this preference.

In order to decrease the time spent by nurses at the patient’s home, a non-disconnectable device with ultraviolet flash can be used. Patients on assisted PD must be reassessed regularly to see whether or not they have become competent to perform self-care PD. For patients on assisted APD, family assistance is associated with a lower peritonitis risk compared with nurse assistance. However, the results are equivalent when centres send one of their PD nurses for a visit at the patient’s home on a regular basis; this emphasizes the fact that nurses in charge of assisted PD patients must be trained and re-trained by the nurses from the PD centre. In elderly patients, assisted CAPD is not associated with greater peritonitis risk compared with the family-assisted CAPD.

**Indications for assisted PD**

Nurse- or health-care technician-assisted PD is indicated for ESRD patients who choose PD as RRT modality or in whom HD is contraindicated, who have no contraindication to PD, but are incapable to perform PD exchanges by themselves, and whose family members’ quality of life is affected by the burden of caregiving.

Assisted PD may be indicated for patients starting dialysis or for self-care PD patients who have lost their autonomy.

**Assisted PD for the unplanned dialysis starter**

The unplanned dialysis starter can be defined as a patient who starts dialysis without any vascular access or PD catheter. These patients usually start HD through a venous
catheter. Recently, strategies to use PD for unplanned dialysis starters have been implemented. Assisted PD can be used for a short period of time pending patient education.

Simon Jenkins 18.10.11