

Approach for guideline development

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Chairman EBPG for haemodialysis

The first wave of European Best Practice Guidelines (EBPG) in haemodialysis was completed in spring 2002 and was published in November 2002 in Supplement 7 of Volume 17 of *Nephrology, Dialysis and Transplantation* [1]. This issue contained the guidelines on: (i) measurement of renal function, when to refer and when to start dialysis; (ii) haemodialysis adequacy; (iii) biocompatibility; (iv) dialysis fluid purity; (v) chronic intermittent haemodialysis and prevention of clotting in the extracorporeal system; (vi) haemodialysis-associated infection and (vii) vascular disease and risk factors.

From the start of the development procedure of the first wave, it had been decided that a second wave would follow, dealing with a remaining number of topics of interest. The first meeting of the work group responsible for the writing process was held on 8 April 2003.

The following topics were to be dealt with: (i) intradialytic haemodynamic instability; (ii) vascular access; (iii) malnutrition and acidosis and (iv) dialysis strategies.

Two other topics had originally been planned as well, but were abandoned at this early stage: (i) interdialytic hypertension, because it appeared that the Kidney Diseases Outcomes Quality Initiatives (K/DOQI), the body responsible for the generation of nephrological guidelines for the National Kidney Foundation (NKF) in the United States, was planning at that moment to produce extensive guidelines on this topic, as a section of the 'Clinical practice guidelines for cardiovascular disease in dialysis patients'; in spring 2003 the K/DOQI were already far advanced in the preparation of these guidelines which were due for the beginning of 2005; (ii) Bone disease and mineral metabolism, because K/DOQI was on the verge of finalizing guidelines on this topic, whereas also the Kidney Disease: Improving Global Outcomes (KDIGO) initiative, a new emerging organization aiming at harmonization of guidelines worldwide and

at producing new global guidelines, was preparing a consensus on the topic as well [2].

In June 2003, during the World Congress of Nephrology (WCN) in Berlin, representatives of the K/DOQI, KDIGO and EBPG met to discuss these issues. It was decided to offer the EBPG work group ample opportunity to have an input on the sections on interdialytic hypertension in the upcoming clinical practice guidelines for cardiovascular disease in dialysis patients of K/DOQI. As the latter were planned to contain recommendations on intradialytic haemodynamic instability as well, it was likewise decided that the EBPG work group would have an input in the generation of these recommendations as well. Since EBPG was planning specific and extended guidelines on this topic, however, rather than recommendations, and had the intension to cover a broader spectrum of questions based on a more extended literature review, it was decided to continue the foreseen development of guidelines on intradialytic haemodynamic instability by the EBPG.

While starting the guideline development, it was decided to abandon the concept followed during the previous wave, where each topic was covered by one work group member, under peer review by the entire work group. For the upcoming wave, it was decided to compose subgroups with 3 to 4 experts, each with a chairman, having a coordinating role. The concept of peer review by the entire work group during the whole development process was, however, maintained. It was also decided that the work group on malnutrition would contain a dietician, and that the subgroup on vascular access would contain a vascular surgeon and an interventional radiologist. Furthermore, it was taken into account that the Vascular Access Society had published recommendations on vascular access, and care was taken to include members in the subgroup on vascular access, who had taken part in the development of these recommendations as well.

The work group was composed after approval of its members by the European Renal Association – European Dialysis and Transplantation Association (ERA–EDTA) (Table 1).

Each guideline was divided into a number of major subheadings (Table 2).

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Table 1. Composition of the work group for the second wave of European Best Practice Guidelines for Haemodialysis

Global chair	R Vanholder (Gent, Belgium)
Intradialytic haemodynamic instability	
Chair:	Kooman J (Maastricht, the Netherlands)
Members:	Basci A (Izmir, Turkey) Pizarelli F (Florence, Italy)
Malnutrition and acidosis	
Chair:	Fouque D (Lyon, France)
Members:	ter Wee P (Amsterdam, the Netherlands) Vennegoor M (London, United Kingdom) Wanner C (Würzburg, Germany)
Vascular access	
Chair:	Tordoir J (Maastricht, the Netherlands)
Members:	Canaud B (Montpellier, France) Haage P (Aachen, Germany) Konner K (Cologne, Germany)
Dialysis strategies	
Chair:	Tattersall J (Leeds, United Kingdom)
Members:	Martin Malo A (Cordoba, Spain) Pedrini L (Seriante, Italy)

Table 2. Guideline subheadings

Intradialytic haemodynamic instability	Contributory factors Preventive strategies Treatment strategies
Malnutrition and acidosis	Epidemiology Nutrition Malnutrition Inflammation and nutrition Acid-base disturbances
Vascular access	General aspects Creation of vascular access Monitoring of vascular access Diagnosis of complications
Dialysis strategies	Treatment aspects Patient characteristics Mortality Outcome Augmented types of dialysis

It was further decided to abandon the previous concept of performing our own literature searches by Reference Manager, based on pre-defined keywords, as chosen by the entire work group. Instead, it was decided to outsource the literature searching to a neutral third party, the Cochrane Renal Group (CRG). The search strategies were based on a series of clinical questions, formulated by each work group (Table 3). Each question was further defined by keywords relating to: (i) population of interest; (ii) intervention; (iii) comparison (if any); (iv) outcome(s) of interest and (v) preferred methodology (Table 4). The final search strategies, ~80 in all, were carried out in mid-2004 on Medline (Ovid interface) using MeSH terms and textwords based on the keywords provided (Table 5). The searchers consulted

Table 3. Example of set of crucial questions which would serve as a basis for the literature searches. All questions for the malnutrition/acidosis group are given

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- What is the average nutritional status in maintenance haemodialysis patients?
 - What are the average indices of nutritional status in maintenance haemodialysis patients?
 - What are the minimal/optimal dietary needs in maintenance haemodialysis patients?
 - What are the definitions and the corresponding preferred determination methodologies for assessing malnutrition or factors affecting nutrition in maintenance haemodialysis patients?
 - What is the validity of methodologies for assessing malnutrition in maintenance haemodialysis patients?
 - Which are the preferred methodologies for assessing malnutrition in maintenance haemodialysis patients?
 - Which are the threshold values for assessing malnutrition in maintenance haemodialysis patients?
 - Are indices intermutually correlated in maintenance haemodialysis patients, and are they correlated with other determinants?
 - Which haemodialysis patients are at risk for developing malnutrition?
 - Is malnutrition related with poor outcome in maintenance haemodialysis patients?
 - Is malnutrition related with inflammation in maintenance haemodialysis patients?
 - Which are useful and validated therapeutic methods for malnourished patients in maintenance haemodialysis?
 - How frequent the monitoring of nutritional status in maintenance haemodialysis patients?
 - How should acidosis be estimated in maintenance haemodialysis patients?
 - Does acidosis have a clinical impact in maintenance haemodialysis patients?
 - Which threshold value regarding acidosis should be pursued in maintenance haemodialysis patients?
 - How to treat metabolic acidosis in maintenance haemodialysis patients?
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Table 4. Example of keyword definition based on distinct clinical questions. An example is given for the first clinical question defined by the malnutrition group. Reproduced with permission from *The American Journal of Clinical Nutrition*.

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- Clinical question: What is the average nutritional status in maintenance haemodialysis patients?
 - (i) Population: all
 - (ii) Intervention: protein intake, caloric intake, fat intake, carbohydrate intake
 - (iii) Comparison: aged *vs* medium age *vs* children (age), males *vs* females (gender, sex), longer *vs* shorter on dialysis (vintage, time duration), patients prone to die *vs* survivors (mortality, survival, outcome), level of CRP (inflammation), with general population, in function of BMI, SCrea, albumin, prealbumin, cholesterol, homocysteine
 - (iv) Outcomes of interest: average values, comparison with general population, correlation with parameters under (iii)
 - (v) Methodology: any
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work group chairpersons when necessary to clarify questions and keywords. Each search was rerun in June 2005 to ensure that the most recent literature was provided to the guideline work groups. The CRG specialized register of randomized controlled trials in nephrology, and the Cochrane library database of

Table 5. Search strategy in Medline (Ovid) for malnutrition group question: What is the average nutritional status in maintenance haemodialysis patients?

Search history	
(i)	renal dialysis/or haemodiafiltration/or haemodialysis/or haemofiltration
(ii)	(hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or biofiltration or dialysis).tw.
(iii)	or/1-2
(iv)	(exp peritoneal dialysis/or peritoneal dialysis.tw.) not ((exp peritoneal dialysis/or peritoneal dialysis.tw.) and (renal dialysis/or hemodiafiltration/or hemodialysis, home/or hemofiltration/or hemodialysis.tw. or haemodialysis.tw. or hemofiltration.tw. or haemofiltration.tw. or hemodiafiltration.tw. or haemodiafiltration.tw. or biofiltration.tw.))
(v)	3 not 4
(vi)	Kidney Failure, Acute/
(vii)	5 not 6
(viii)	Energy Intake/or Nutritional Status/
(ix)	(food intake or nutrient intake or energy intake or ((protein adj2 intake) or (calori\$ adj2 intake) or (fat adj2 intake) or (carbohydrate\$ adj2 intake) or (vitamin\$ adj2 intake) or (“trace elements\$” adj2 intake))).tw.
(x)	or/8-9
(xi)	and/7,10
(xii)	exp cohort studies/or follow-up studies/
(xiii)	cross-sectional studies/
(xiv)	or/12-13
(xv)	and/11,14

Table 6. Evidence levels (previous and current system). Reproduced with permission from *The American Journal of Clinical Nutrition*.

Previous system	Current system
A: Randomized controlled trials or meta-analysis	I: Meta-analysis
B: Observational studies, case- control studies, case reports	II: Randomized controlled trials III: Observational and case-control
C: Opinion	IV: Case series Opinion

systematic reviews were also searched for relevant trials and systematic reviews.

Full publications in languages spoken by at least one member of the work group were included: Dutch, English, French, German, Italian, Spanish and Turkish.

Publications on children and adolescents, and on acute renal failure (ARF) were excluded, as well as conference abstracts, editorials and letters. Any publications not conforming to the study designs included in these were also excluded.

It was decided to grade publications according to the evidence levels I–IV provided by the National Health and Medical Research Council (Australia) (Table 6), rather than to use the previous system of levels A–C. In addition, an evidence level ‘opinion’ was obtained as an option for useful recommendations answering relevant questions, for which useful evidence was lacking.

The references retrieved from Medline and the CRG’s specialized register were screened by the

Table 7. READER scoring system

Criteria	Possible score
Relevance	
Not relevant to general practice	1
Allied to general practice	2
Only relevant to specialised general practice	3
Broadly relevant to all general practice	4
Relevant to me	5
Education	
Would certainly not influence behaviour	1
Could possibly influence behaviour	2
Would cause reconsideration of behaviour	3
Would probably alter behaviour	4
Would definitely change behaviour	5
Applicability	
Impossible in my practice	1
Fundamental changes needed	2
Perhaps possible	3
Could be done with reorganisation	4
I could do that tomorrow	5
Discrimination	
Poor descriptive study	1
Moderately good descriptive study	2
Good descriptive study but methods not reproducible	3
Good descriptive study with sound methodology	4
Single-blind study with attempts to control	5
Controlled single-blind study	6
Double-blind controlled study with method problem	7
Double-blind controlled study with statistical deficiency	8
Sound scientific paper with minor faults	9
Scientifically sound paper	10

searchers according to the above criteria, then graded according to the evidence levels, coded with the relevant question number and entered into Reference Manager 10 databases that were emailed to the work groups. Each chairperson gave a final screening of the references for relevance. References not provided by CRG, but considered relevant by all members of each work group were added to the databases.

All references included in the database had to be used for the guideline development.

To correct for differences in quality among different used references, it was further decided to adhere to a quality assessment system. In May 2004, the READER system was selected by the group [3] (Table 7); this scoring system was developed earlier than the GRADE-system which was adopted early in 2005 by KDIGO and K/DOQI [4].

A drawback of the READER system is that it attributes a higher level of quality to controlled studies, even if they are of minor quality (e.g. underpowered), as compared with non-controlled studies of potentially better quality. The GRADE system offers a solution to this problem, by upgrading high quality non-controlled

Table 8. Reviewers selected by EBPG

Name	Country	Expertise
Haemodynamic stability		
Covic A	Romania	Nephrology
Kim MJ	South-Korea	Nephrology
Levin N	USA	Nephrology
Mc Intyre C	UK	Nephrology
Santoro A	Italy	Nephrology
Schneditz D	Austria	Physiology
Nutrition		
Chauveau P	France	Nephrology
Cuppari L	Brasil	Dietician
Descombes E	Switzerland	Nephrology
Guarnieri G	Italy	General Internist
Mitch B	USA	Nephrology
Stenvinkel P	Sweden	Nephrology
Vascular access		
Guenther R	Germany	Interventional Radiologist
Malovrh M	Slovenia	Nephrology
Mickley V	Germany	Vascular Surgeon
Riella M	Brazil	Nephrology
Yu A	China	Nephrology
Polashegg H	Germany	Bioengineer
Dialysis strategies		
Casino F	Italy	Nephrologist
Disney A	Australia	Nephrologist
Garred L	Canada	Bioengineer
Hörl W	Austria	Nephrologist
Jindal K	Canada	Nephrologist
Lopot F	Czechia	Bioengineer

studies and down-grading low quality controlled studies. As the work group had started the scoring process already when the GRADE system was implemented by KDIGO, it was considered impossible to restart and repeat the scoring procedure, and it was decided to use a modified READER system, whereby a similar philosophy of up-grading and down-grading was applied as in the GRADE system.

Before starting the scoring, the process was trained by the whole group in a plenary session, whereby four randomly chosen publications per guideline topic were discussed by all the members together. The publication drafts had been distributed to all the members in advance. The aim was to come to a homogeneous scoring process. Hard evidence (level I–II) was only attributed if enough controlled studies and/or meta-analyses of good quality were available to endorse the guideline.

The hardcopies of the references retained for the final reference databases were distributed among the respective subgroup members. Guidelines and their

rationales were developed within each subgroup, and then submitted to internal review, first within the subgroups, and then among all work group members.

By 12 June 2006, the preliminary drafts of the guidelines were distributed among several experts as external reviewers, both inside and outside Europe. Six expert reviewers were chosen and approved per topic by the entire commission (Table 8). Per topic, at least two of the six selected experts were non-nephrologists and two of the six were non-Europeans (preferably, if possible, one reviewer was non-American, because the guidelines were to be submitted separately for review to K/DOQI as well).

At the same time, the drafts were also posted on the website of ERA–EDTA, and all ERA–EDTA members were contacted by e-mail, announcing this and encouraging them to review. Finally, the guidelines were also sent to K/DOQI, the International Society of Nephrology (ISN), the European Dialysis and Transplantation Nurses Association/European Renal Care Association (EDTNA/ERCA), the EDTNA/ERCA dieticians interest group, the British Dietetic Association Renal Nutrition Group, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Kidney Patients' Federation (CEAPIR). These organizations were asked to distribute the guidelines among experts of their choice within their own organization, again for review.

This external review process was finalized as of 29 July 2006, and the definitive texts were submitted for publication as of 15 December 2006.

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References

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