

EBPG guideline on haemodynamic instability

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Introduction

Definition of intra-dialytic hypotension

In the literature, the definition of intra-dialytic hypotension (IDH) is not standardized and differs between various studies. Most definitions however, take into account either a relative or an absolute decline in blood pressure (BP) as well as the presence of specific symptoms. Although no evidence based recommendation regarding the definition of IDH can be given, the EBPG working group stresses that both a reduction in BP, as well as clinical symptoms with need for nursing intervention should be present in order to accept the presence of IDH. Moreover, the definition of IDH should ideally be equal in the literature and different treatment guidelines. Conforming to the K/DOQI guidelines, a proposed definition is a decrease in systolic BP ≥ 20 mmHg or a decrease in mean arterial pressure (MAP) by 10 mmHg associated with clinical events and need for nursing interventions.

Incidence of IDH

In reviews, a 20% incidence of intra-dialytic hypotension is widely cited [1,2]. The reported incidence in cohort studies varies between 6% and 27% [3,4]. In the largest cohort reported so far, 10% of patients had frequent hypotensive episodes whereas 13% occasionally had hypotensive episodes [5]. The sensitivity for IDH may also vary among individual patients [6].

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Relation between IDH and outcome

In review papers, IDH has been given a putative causal role in myocardial and cerebral ischaemia. A recent study, found significant increases in creatine kinase MB levels at the end of HD therapy and in circulating troponin I levels 44 h following HD after an episode of IDH, in contrast to uneventful treatments [1]. IDH was an independent and negative predictor of long-term fistula outcome [2]. In a longitudinal study, frequent episodes of IDH were found to be related to frontal lobe atrophy [3]. In a cohort of 20 patients with non-occlusive mesenteric ischaemia, all episodes were preceded by IDH [4].

In a case-control study, a relation between IDH and 2-year mortality was observed, which lost significance after correction for confounding factors [5]. In a prospective cohort study of 1244 patients, an independent relationship between IDH and 2-year mortality was observed [6]. However, this study did not include cardiac disease as a potential confounding factor.

Therefore, it remains unknown whether IDH plays a causative role in adverse outcome or is merely a marker of comorbid conditions, which increase the sensitivity for IDH.

IDH may also impair solute clearance, due to compartmentalization of blood volume [7] and premature termination of dialysis sessions.

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Patients at risk for IDH

Few large scale studies have addressed potential risk factors for IDH. The largest multi-centre cohort

study was reported by Tisler *et al.* [1]. Of a cohort of 958 patients from 11 dialysis centres, 96 patients with frequent episodes of IDH were compared with 130 patients with occasional episodes of IDH. Age, female sex, presence of diabetes mellitus, hyperphosphataemia, presence of coronary artery disease, and renal diagnosis other than glomerulonephritis and the use of nitrates were significantly higher in patients with frequent IDH. In multivariate analysis, age, renal diagnosis other than glomerulonephritis, hyperphosphataemia and the use of nitrates were independent risk factors for IDH. In another study, hypotensive episodes occurred frequently in 44% of dialysis patients of ≥ 65 years and in 32% of younger dialysis patients (age < 45 years) [2]. One study also found lower albumin levels in patients with hypotension during haemodialysis [3].

Cardiac abnormalities may increase the risk for IDH. In an observational study in 15 dialysis patients, the decline in BP was larger in patients with systolic dysfunction, compared with patients with normal systolic function [4]. Also, diastolic dysfunction may increase the risk for IDH. In an observational study with 47 haemodialysis patients, those with frequent IDH episodes had more severe concentric left ventricular hypertrophy, lower pre-dialysis BP and impaired diastolic left ventricular filling [5]. Although it is often considered that anaemia is a risk factor for IDH, especially in patients with cardiac disease, there has been no study addressing this relationship.

Also, the existence of autonomous neuropathy was found to be a risk factor for IDH in most [6–11], but not all studies [12,13].

The sensitivity of patients for IDH may not be a stable condition. Seven patients who frequently experienced IDH episodes were found to have large differences in the incidence of IDH over a 24-month period [14]. Moreover, there are seasonal variations in BP behaviour among chronic HD patients [15].

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Pathophysiology of IDH

During haemodialysis combined with ultrafiltration, a decline in circulating blood volume usually occurs, depending upon the ultrafiltration rate and the degree of refill of blood volume from the interstitial compartment. Refill of blood volume depends upon various factors, such as the hydration state of the interstitial compartment, dialysate sodium concentration, capillary permeability, venous compliance and protein balance [1,2]. Accordingly, plasma refilling rate is patient-specific, and the ensuing variations in BV show a large intra-individual as well as inter-individual variability [3,4]. Under physiological circumstances, a decline in blood volume initially leads to an increase in peripheral vascular resistance, due to constriction of resistance vessels, maintenance of cardiac output, due to an increase in heart rate and myocardial contractility, and constriction of capacitance vessels [2,5]. Healthy persons can tolerate a decline in circulating blood volume up to 20% before hypotension occurs [6,7]. However, in dialysis patients, hypotension may occur with a much smaller decline in blood volume [8].

In patients prone to hypotension, the critical blood volume decline at which IDH occurred shows large inter-individual [from 2% to 29%], but also a large intra-individual variation [8,9]. Several mechanisms may be responsible for this phenomenon. First, the normal cardiac response to hypovolaemia, consisting of an increase in heart rate and myocardial contractility, may be impaired. It has been shown that the presence of cardiac disease, leading to systolic or diastolic dysfunction, increases the risk for IDH. At comparable ultrafiltration rates, the decline in BP was larger in patients with systolic dysfunction, compared with patients with normal systolic function [10,11], whereas in patients prone to IDH, left ventricular hypertrophy was more severe and diastolic filling was impaired [10,12]. Although it is likely that cardiac arrhythmias may increase the sensitivity of the patient for IDH, no literature on this subject is available.

Factors related to the dialysis treatment, such as the dialysate buffer and calcium concentration, may influence cardiac contractility [12,13]. In the absence of cardiac disease, no difference in myocardial contractility was observed among patients, with or without frequent episodes of IDH [14].

The presence of autonomic neuropathy, which can be assessed using standardized function tests or spectral analysis of heart variability, may impair the heart rate response during hypovolaemia, although in non-diabetic patients its role in the pathogenesis of IDH remains controversial [15–20]. A bradycardic, so called Bezold-Jarish reflex has also been observed during IDH episodes. This reflex is believed to result from sudden sympathetic withdrawal due to severe ventricular underfilling [5,21,22]. Several papers showed an impairment of sympathetic function, as shown by a reduction in the low frequency heart rate variation and low and high frequency ratio by spectral analysis, in unstable dialysis patients [23,24]. Apart from cardiac factors, the normal reaction of the resistance and capacitance vessels during a decline in blood volume may be impaired during dialysis treatment [25]. A decreased arteriolar constriction may compromise the physiological increase in systemic vascular resistance during hypovolaemia. A reduction in the passive and active constriction of venules and veins, which serve to centralize blood volume during hypovolaemia, impairs venous return [5,26–29].

Various explanations for the reduced reactivity of resistance and capacitance vessels have been proposed, such as induction of cytokines, bioincompatibility of the dialysis membrane, the use of acetate as dialysate buffer, an increased production of nitric oxide or an insufficient increase in vasoconstrictors such as vasopressin during fluid removal [30–34]. Thermal effects appear to be of great importance in the inadequate vascular response during haemodialysis. Haemodialysis induces an increase in core temperature, even when no additional energy is transferred from the extracorporeal circuit to the patient. The increase in

core temperature antagonizes the normal vascular response to hypovolaemia [35–37].

In conclusion, IDH may occur as a result of a decline in blood volume, impaired cardiac response and impaired constriction of resistance and capacitance vessels. Depending on patient- and treatment-related factors, the relative importance of these factors may vary.

Strategies for prevention and therapy of IDH are based upon influencing one or more of these pathogenetic factors.

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Prevention of IDH

1. Evaluation of the patient

Rationale

- **Guideline 1.1.1 Hydration state should be regularly assessed by clinical examination (Opinion).**
- **Guideline 1.1.2 Objective methods to assess fluid state should be considered in a patient with frequent IDH when clinical examination is inconclusive (Level III).**

Incorrect assessment of dry body weight may result either in underhydration or overhydration in dialysis patients. Earlier studies have shown that a significant percentage of unstable patients were normohydrated or underhydrated at the start, and very frequently underhydrated at the end of the dialysis session [1,2].

In underhydrated patients, the interstitial volume is restricted and refill to blood volume is hampered, resulting in a larger decline in blood volume for a given ultrafiltration rate [3]. On the other hand, overestimation of dry body weight may result in hypertension and put the patient at risk for cardiac dilatation and pulmonary oedema.

Physical examination should always be the basis for assessment dry weight in dialysis patients. However, as sometimes physical examination allows no definite conclusion [4], several non-invasive methods have been developed. Cardiothoracic ratio by X-ray is able to detect overhydration [5,6], but has not been formally tested as a tool for the prevention of IDH.

Inferior caval vein diameter, assessed by echography, correlated with blood volume and right atrial pressure and predicted haemodynamic changes during dialysis. Multifrequency bioimpedance analysis was able to predict haemodynamic instability in some [7,8], but not all [9] studies. Bioimpedance analysis is also very sensitive in detecting changes in fluid state [10,11–13]. With the vector bioimpedance method, reactance and resistance measurements are obtained from single frequency bioimpedance measurements. Reference tolerance ellipses, derived from a healthy population, are applied. With the vector bioimpedance method, it was possible to differentiate hypotensive-prone from stable patients [13]. Also thoracic impedance measurements have been used to predict IDH, but evidence is still limited [14].

The biochemical marker cGMP, but not ANP, predicted haemodynamic changes during dialysis

[8,15]. Both cGMP and ANP are released in response to left atrial stretch. However, whereas cGMP was found to be potentially useful in the diagnosis of overhydration, it was not able to predict underhydration [8,15]. Also brain natriuretic peptide, released in response to left ventricular stretch, predicted overhydration, but not underhydration [16].

It has been postulated that a patient-specific individual decline in blood volume exists, below which the patient is at risk for hypotension [17]. One study showed a patient-specific decline in blood volume with a standard deviation <5% in the majority (75%) of patients [18]. However, other studies did not find assessment of BV changes during dialysis to be of use in the prediction of IDH [19,20].

A major issue with the use of objective techniques is the definition of appropriate cut-off values. Although normal values for inferior caval vein diameter (IVCD) have been proposed [8], the timing of measurements is of pivotal importance [21]. For IVCD, Chang *et al.* [22] applied a reference value of 8 mm/m² obtained 2 h after dialysis. Reference values for bioimpedance techniques may be population specific [23,24], although the use of vector bioimpedance [10] might circumvent this problem.

Few studies assessed whether the use of objective techniques is able to reduce the incidence of IDH. In one randomized controlled trial by Chang including 100 patients, the use of vena cava echography resulted in a reduction of IDH, compared with patients in whom dry weight was assessed on clinical grounds. Moreover, quality of life was improved [22,25]. In another study, the same group showed beneficial effects of dry weight assessment by IVCD on cardiac structure [26]. Nevertheless, vena cava echography is operator dependent and may be less reliable in patients with cardiac disease and especially tricuspid insufficiency [21] or pericardial effusion. Moreover, measurements may be difficult to interpret in obese patients and patients with polycystic kidney disease [27]. Under research conditions, inter- and intra-observer variability for IVCD measurement were <5 and 2.5% [27].

Summarizing, although several objective methods were able to predict changes in BP and other haemodynamic parameters during dialysis or the occurrence of IDH, at present only the use of vena cava echography has been shown to result in a reduction of IDH. However, this technique is also operator dependent and may be difficult to interpret in patients with cardiac failure. Moreover, the timing of measurement should be standardized. Although the use of bioimpedance has not yet been shown to result in a reduction of IDH, this technique might be useful to detect changes in hydration state.

Recommendations for research

To establish cut-off values for bioimpedance measurements; to investigate the effect of dry weight

prescription based on bioimpedance measurements on IDH.

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- **Guideline 1.2 Blood pressure and heart frequency rate should be measured frequently during dialysis in order to anticipate IDH (Opinion).**

Rationale

Two types of hypotensive episodes have been distinguished during dialysis (bradycardic and tachycardic). Most frequently, episodes of IDH are preceded by a gradual decline in BP and increase in heart rate [1]. Alternatively, IDH episodes may occur suddenly and be associated with a bradycardic response (Bezold Jarish reflex), which is believed to originate from activation of left ventricular mechanoreceptors due to severe ventricular underfilling [2–5]. In the tachycardic type of IDH, it is conceivable that IDH may be prevented by adjusting ultrafiltration, although no studies have been performed into this subject.

Recommendations for research

To compare clinical monitoring vs device-assisted monitoring in predicting IDH.

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- **Guideline 1.3 Cardiac evaluation should be performed in patients with frequent episodes of IDH (Opinion).**

Rationale

It has been shown that the presence of cardiac disease, leading to systolic or diastolic dysfunction of the heart increases the risk for IDH. An increase in myocardial contractility is a physiological response to a decline in blood volume, which can be impaired by systolic dysfunction of the heart. During comparable ultrafiltration rates, the decline in BP was larger in patients with systolic dysfunction compared with patients with normal systolic function [1]. Diastolic dysfunction increases the sensitivity of the patient for changes in preload, i.e. both for under- and overhydration. In patients prone to IDH, diastolic filling was found to be impaired [1,2]. A potential problem with the assessment of diastolic dysfunction in haemodialysis patients is the fact that indices which are used to assess diastolic dysfunction are preload dependent [3]. Diastolic dysfunction is often related to the presence of left ventricular hypertrophy, but may also be due to myocardial ischaemia or fibrosis [4]. The presence of supraventricular arrhythmias may also compromise ventricular filling, which may be especially evident in patients with systolic or diastolic dysfunction [2]. Echocardiography is a simple and non-invasive tool and was, therefore, considered by the EBPG working group as a useful tool to initiate cardiac evaluation. Based on the echocardiographic findings and the clinical assessment of the patient, further cardiologic evaluation of the patient may be warranted. The working group recognizes, however, that this guideline is opinion based, as no study yet assessed

the effect of cardiac evaluation on the prevention of IDH.

Summarizing, systolic and diastolic function of the heart increases the risk for IDH. No study assessed the effect of echocardiographic evaluation as a tool to modify treatment in order to prevent IDH. Echocardiographic parameters to assess diastolic dysfunction are preload dependent.

Recommendation for research

To establish preload independent markers for diastolic dysfunction. To investigate the role of echocardiography as a tool to modify treatment to prevent IDH.

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2. Lifestyle interventions

- **Guideline 2.1 In order to control inter-dialytic weight gain and reduce the risk of IDH, dietary salt intake should be assessed and not exceed 6 g/day unless contra-indicated (Evidence level III).**

Rationale

A large inter-dialytic weight gain may increase the sensitivity for IDH because ultrafiltration rate has to be increased if dialysis time is not adjusted, leading to a larger decline in blood volume. Although other factors, such as xerostomia, may be involved in thirst in dialysis patients [1], osmotic thirst due to insufficient attention for salt restriction also appears to play a major role in increasing inter-dialytic weight gain in dialysis patients [2]. Salt restriction decreases inter-dialytic weight gain and improves inter-dialytic BP control [3]. Two non-randomized cross-over studies assessed the effect of salt restriction on inter-dialytic weight gain and incidence of IDH. Interdialytic weight gain decreased significantly with salt restriction, as did the decline in relative blood volume, and incidence per session of IDH: 0.71 ± 0.8 (usual sodium intake) vs 0.18 ± 0.5 (salt restriction) [4]. In the other study, the monthly incidence of IDH episodes decreased

from 22% to 7% after strict sodium restriction [5]. Except in patients with obligatory sodium loss, such as salt-losing nephritis, sodium restriction is thus indicated in dialysis patients to reduce inter-dialytic weight gain.

In diabetic patients, hyperglycaemia may stimulate thirst and thus inter-dialytic weight gain [2,6], suggesting that strict glucose control might reduce inter-dialytic weight gain. However, no data on the relation between glucose control and inter-dialytic weight gain in dialysis patients are yet available.

Summarizing, reducing salt intake (2 g/90 mmol Na or 6 g NaCl) can reduce inter-dialytic weight gain and may play a role in the prevention of IDH.

Recommendations for research

To study the role of drugs which may reduce salt appetite (e.g. ACE inhibitors).

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- **Guideline 2.2 Food intake during or just before dialysis should be avoided in patients with frequent episodes of IDH (Evidence level II). In malnourished patients, the haemodynamic effects of food intake during dialysis should be balanced against the nutritional needs of the patient (Opinion).**

Rationale

Food intake during dialysis may lead to splanchnic vasodilation and thus contribute to IDH [1]. Three studies, two randomized cross-over and one non-randomized cross-over study, showed a larger decline in BP and a higher incidence of IDH after food intake [2–4]. Caffeine did not appear to have a preventive effect on IDH [4]. No study has yet assessed the effect of meals taking just before dialysis treatment on IDH. However, it is likely that the haemodynamic effect

will be comparable. In malnourished patients, the haemodynamic effects of food intake during dialysis should be balanced against the nutritional needs of the patient.

Summarizing, food intake during dialysis increases the sensitivity for IDH, whereas caffeine does not seem to have a preventive effect.

Recommendations for research

Assess the haemodynamic effects of meals (light or heavy) before dialysis treatment.

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3. Factors related to the dialysis treatment

3.1 Optimizing ultrafiltration: ultrafiltration profiling and blood volume controlled ultrafiltration

- **Guideline 3.1.1 Pulsed ultrafiltration profiles should not be used for the prevention of IDH (Evidence level III).**

Rationale

By ultrafiltration profiling, the change in blood volume can be influenced. The most commonly used ultrafiltration profiles are characterized by an initially high ultrafiltration rate, followed by a linear decrease in ultrafiltration rate, or intermittent ultrafiltration pulses followed by periods of minimal ultrafiltration. Most ultrafiltration profiles have been studied in combination with sodium profiles and are discussed separately. One cross-over study with 53 patients found a reduced incidence of IDH during linear ultrafiltration, whereas pulsed profiles resulted in an increase in IDH [1]. In contrast, a randomized cross-over study in 12 patients [2] showed an increased incidence of IDH with a linear decreasing ultrafiltration profile. In two randomized cross-over studies, no difference in IDH was observed between treatments with ultrafiltration profiling without sodium modelling and constant ultrafiltration [3,4].

Due to conflicting evidence, no conclusions can be made regarding the use of linear decreasing ultrafiltration profiles for the prevention of IDH.

Summarizing, evidence for the effectiveness of ultrafiltration profiling is conflicting. Pulsed profiles may result in an increase in IDH.

Recommendations for research

To perform larger randomized studies to the effect of linear decreasing ultrafiltration profiling on IDH.

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- **Guideline 3.1.2a Individualized, automatic BV control should be considered as a second-line option in patients with refractory IDH (Evidence level II).**
- **Guideline 3.1.2b Manual adjustment of ultrafiltration according to a fixed protocol based on changes in blood volume should not be performed (Evidence level II).**

Rationale

With blood volume controlled treatments, ultrafiltration rate and/or dialysate conductivity are adjusted according to changes in relative blood volume. This can either be performed automatically by a feedback module in the dialysis machine, which adjusts ultrafiltration and/or dialysate conductivity when the changes in relative blood volume deviate from a preset curve [1,2], or can be performed manually in response to measured on-line changes in blood volume [3]. It is thus possible to prevent the decline in blood volume beyond the point at which the patient is presumed to be at risk for IDH. The existence of a patient specific critical decline in blood volume remains controversial, however (see pathophysiology of IDH). Nevertheless, several randomized cross-over studies have shown a reduction in IDH and intra-dialytic symptomatology with the use of automatic blood volume controlled feedback [1,2,4–6]. Moreover, one study showed an increase in dialysis efficacy with the use of this approach, due to a reduction in

intra-dialytic interventions [1]. Automatic blood volume controlled feedback options are available only on a limited number of dialysis modules. Most studies used the feedback approach in which both ultrafiltration rate and dialysate conductivity are modelled, and in which the mean dialysate conductivity was usually set at 14.0 mS/cm. No adverse effects on sodium balance have yet been reported [2,7]. No comparison with other strategies has been performed.

Regarding manual adjustment of ultrafiltration according to blood volume changes, a multi-centre randomized study that included 443 patients has been performed. In this study, adjustment of ultrafiltration was based on a fixed, non-individualized protocol. In comparison to conventional monitoring, no benefits of blood volume controlled treatments on IDH were observed, whereas an increase in mortality and hospitalization was observed. The authors of this study could provide no definite explanation for these findings [3]. However, mortality in the control group was less than that observed in the prevalent dialysis population.

It is not clear whether the results of this study can be extrapolated to automatic blood volume control, based on individualized blood volume targets. Given the fact that the effect of automatic blood volume feedback control on mortality has not yet been assessed, the EBPG working group felt that, despite demonstrated benefit on IDH, no definite recommendation for the application of automatic blood volume control as a first-line option can be made. However, if available, automatic BV controlled feedback can be attempted as a second-line option in patients with refractory IDH.

Summarizing, various studies have shown a beneficial effect of automatic blood volume controlled feedback in the prevention of IDH episodes. However, an increase in mortality was observed with manual adjustment of ultrafiltration according to BV changes.

Recommendation for research

To investigate the effects of automatic blood volume control on mortality.

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3.2 Dialysate composition

3.2.1 Dialysate sodium

- **Guideline 3.2.1 Although sodium profiling with supraphysiological dialysate sodium concentrations and high sodium dialysate (≥ 144 mmol/l) are effective in reducing IDH, they should not be used routinely because of an enhanced risk of thirst, hypertension and increased inter-dialytic weight gain (Evidence level II).**

Rationale

Dialysate sodium plays an important role in the refill of blood volume from the interstitial compartments. Refill of blood volume from the interstitial to the intravascular compartment will be low if interstitial hydration is low [1]. With high dialysate sodium concentrations, fluid shifts from the intracellular compartments are enhanced, whereas with low dialysate sodium concentrations, disequilibrium between the intra- and extracellular compartments may occur. Thus, with low sodium dialysis, refill of blood volume from the interstitial compartments will be impaired because of the shift of fluid from the interstitial to the intracellular compartments, whereas with supraphysiological sodium concentrations of the dialysate, fluid will shift from the intracellular to the interstitial compartments, which will in turn enhance the refill of blood volume from the interstitial to the intravascular compartment.

Several studies [2–4], but not all [5] found a reduced incidence in IDH or decline in BP in patients treated with conventional (138–140 mmol/l) compared to low (i.e. ≤ 135 mmol/l) dialysate sodium concentrations.

High sodium (i.e. ≤ 144 mmol/l) dialysate has also been assessed in the prevention of IDH. Whereas high sodium dialysate was found to be useful in the prevention of IDH in some [6,7], but not all [8] studies, it was also associated with worsened intra-dialytic BP control, especially in hypertensive patients [6], or increased inter-dialytic weight gain [8].

With sodium profiling, dialysate sodium is modelled during dialysis in order to reduce the decline in blood volume during ultrafiltration. The possibility for sodium profiling is present on most dialysis modules and easy to apply. However, available studies differ widely with regard to mean dialysate sodium concentration and type of sodium profiles. With most sodium profiles, the mean dialysate sodium concentration is

higher (>142 mmol/l) than conventionally used dialysate sodium concentrations (138–140 mmol/l). Sodium profiles can be divided into linearly or stepwise increasing or decreasing profiles, and alternated high–low profiles.

Most studies, but not all [9,10] found sodium profiling to be of use in the prevention of haemodynamic instability during dialysis [6,11–14,17]. However, follow-up time in most studies was short. One study found sodium profiling to be efficacious in only 22% of patients [15].

In most studies, sodium profiles were not combined with ultrafiltration profiling. In a recent study, different sodium profiles with or without ultrafiltration profiling were compared. In general, sodium profiling appeared to be more efficacious when performed in combination with ultrafiltration profiling [13].

The increased dialysate sodium concentration in the prevention of IDH may be of greater importance than the use of the profile per se, as one study did not find a difference in incidence of IDH between sodium profiled treatments and haemodialysis with a mean dialysate sodium concentration of 143 mmol/l [16].

In many [8,9,11,12,15,17–19], but not all studies [10,14,18], sodium profile or high sodium dialysis was associated with an increase in thirst, inter-dialytic weight gain and higher pre-dialysis BP levels, although not all side effects occurred concomitantly in the available studies. When the dialysate sodium concentration is higher than the plasma sodium concentration corrected for the Donnan factor, net inward diffusion of sodium from dialysate to plasma is to be expected [19]. One study compared the efficacy of sodium profile and high sodium dialysis with cool dialysis [6]. Whereas treatment tolerance was improved with sodium profile, high sodium dialysis and cool dialysis compared with standard dialysis, no difference between the different experimental strategies was observed.

Some studies assessed the effect of so-called sodium-neutral profiles (in which mean dialysate sodium concentration is comparable with conventionally used sodium concentrations) on haemodynamic stability. Three studies found a smaller decline in the intra-dialytic BP fall or a reduction in IDH during the sodium neutral profile [20–22]. In one randomized cross-over study the incidence of complicated treatments was less pronounced with a sodium neutral profile when combined with ultrafiltration profiling, but not when performed without an ultrafiltration profile [13]. In two other studies no benefits were observed [16,23]. Due to the conflicting evidence, no recommendation regarding sodium neutral profiles can yet be made.

Individualizing dialysate sodium to the plasma sodium concentration of the dialysate may improve haemodynamic stability during dialysis [24]. However, this approach would appear difficult to perform in daily clinical practice.

It has also become possible to model changes in plasma conductivity, as a surrogate of dialysate

sodium. Recent small studies have addressed the effects of conductivity controlled feedback or prescription of dialysate conductivity based on mathematical models in the prevention of IDH. Although a beneficial effect of conductivity adjustments based on mathematical models was observed, this methodology appears too complicated to perform in daily practice [25]. The usefulness of an automatic algorithm for control of plasma conductivity was studied during paired filtration dialysis, and resulted in a decrease in IDH without negative effects on sodium balance [26]. However, the possibility for plasma conductivity controlled feedback is only possible on a limited number of dialysis modules, and has not been studied systematically during haemodialysis. A preliminary study showed no reduction in IDH with the use of plasma conductivity controlled feedback [27].

Summarizing, most studies, but not all, found high sodium dialysate or sodium profiles to be effective in the prevention of IDH. However, several studies showed increased inter-dialytic weight gain, hypertension and thirst with sodium profiles (level II). Evidence on so-called sodium-neutral profiles is still limited. However, especially when used in combination with ultrafiltration profiling, beneficial effects were observed in some studies. Individualization of dialysate sodium appears promising, but clinical evidence is still limited. From the data available, no difference in efficacy was observed between sodium profiling and non-profiled high sodium dialysis.

Recommendation for research

To investigate the role of plasma conductivity controlled feedback and sodium neutral profiles in the prevention of IDH. To compare the effects of high sodium dialysis or sodium profiling with standard sodium dialysis on cardiovascular morbidity and mortality.

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3.2.2 Dialysate buffer

- **Guideline 3.2.2 Bicarbonate dialysis should be used to prevent IDH (Evidence level III).**

Rationale

Acetate, in the past frequently used as dialysate buffer, has both vasodilating and cardiodepressant effects [1–3]. In various small cross-over studies, a larger decline in BP or higher incidence of IDH were observed with the use of acetate compared with bicarbonate [2,4–7], whereas in one study fewer therapeutic interventions were needed with bicarbonate dialysis [8]. One controlled study showed that ultrafiltration tolerance was significantly increased by using bicarbonate instead of acetate as dialysate buffer [9]. Two studies assessed the effect of a change in dialysate buffer from bicarbonate to acetate in their entire population [10,11]. In one of them, a non-randomized cross-over trial in which the authors switched their entire population from acetate to bicarbonate dialysis, a 50% decrease in the incidence of IDH was observed [11]. Also during haemodiafiltration, less haemodynamic instability was observed with the use of bicarbonate vs acetate as dialysate buffer [12].

Moreover, it has been suggested that dialysate bicarbonate concentrations might influence haemodynamic stability, as alkalaemia may result in a decrease in serum ionized calcium levels [13]. In this randomized cross-over trial, the incidence of IDH was significantly less with a dialysate bicarbonate of 26- vs 32 mmol/l. However, in this trial, also a low dialysate calcium (1.25 mmol/l) concentration was used [13]. In a more recent randomized cross-over trial by the same group, no difference in haemodynamic instability or BP decline was observed when patients were treated with either dialysate bicarbonate concentrations of 26 or 32 mmol/l, even when a low calcium dialysate concentration (1.25 mmol/l) was used. In this trial, the incidence of IDH was lowest when patients were treated with a dialysate bicarbonate concentration of 32 mmol/l and a dialysate calcium concentration of 1.50 mmol/l [14].

Low dialysate bicarbonate concentrations may result in insufficient correction of acidosis with adverse effects on bone metabolism and nutritional state (see EBPG guideline on nutrition/calcium phosphate metabolism).

With bicarbonate dialysis, also a small amount of acetate is present in the dialysate, and this leads to significant intra-treatment acetate transfer in HD [15] and, particularly so, in HDF [16], although the clinical relevance of this phenomenon is as yet unknown. With acetate-free biofiltration, a modified haemodiafiltration technique, no acetate is present in the

dialysate. Nitric oxide production, cytokine activation as well as neutrophil activation were found to be less during acetate free biofiltration compared with acetate dialysis as well as bicarbonate dialysis containing small amounts of acetate [5,17,18].

Acetate free biofiltration was shown to be of benefit in the reduction of IDH in some, but not all papers. However, also the convective principle of acetate free biofiltration and sodium infusion might influence haemodynamic stability (see Dialysate and body temperature), making it difficult to discriminate between the effects of absence of acetate and the other effects.

Summarizing, the decline in BP and incidence of IDH is higher with the use of acetate as dialysate buffer. Standard bicarbonate concentrations have no haemodynamic disadvantage compared with low dialysate bicarbonate concentrations if a dialysate calcium concentration of 1.50 mmol/l is used.

Recommendations for research

To investigate the role of acetate-free on-line haemo(dia)filtration on NO-cytokine synthesis and IDH.

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3.2.3 Dialysate calcium

- **Guideline 3.2.3 The use of a dialysate calcium concentration of 1.50 mmol/l should be considered in patients with frequent episodes of IDH, unless contraindications are present (Evidence level II).**

Rationale

Changes in ionized calcium play a pivotal role in myocardial contractility during dialysis. Several studies showed a lower myocardial contractility between patients treated with a low (1.25 mmol/l) compared with patients treated with a high (1.75 mmol/l) dialysate calcium concentration [1,2]. Moreover, the change in mean arterial pressure during dialysis was inversely related to the change in ionized calcium levels [3] whereas in two studies, one of which was performed in cardiac compromised patients the decline in BP was less with the dialysate concentration of 1.75 mmol/l compared with 1.25 mmol/l [2,4]. In another study, no difference in the BP response was observed between high- and low-calcium dialysate [5]. On the other hand, high-calcium dialysate leads in general to a positive calcium balance during dialysis, whereas calcium balance is generally negative with low calcium dialysate [6]. High calcium dialysate may have short-term adverse effects on arterial stiffness and cardiac relaxation [3,8], although another study did not find an effect of an increase in ionized calcium levels during high-calcium dialysis on diastolic function of the heart [9]. The relation between dialysate calcium concentration and vascular calcifications has not yet been studied.

A dialysate calcium concentration of 1.50 mmol/l has less pronounced effects on calcium balance compared with dialysate calcium concentrations of respectively 1.25 or 1.75 mmol/l. In general, also depending on ultrafiltration, calcium balance is slightly negative with