

### **III.1 Biochemical reactions subsequent to complement and leukocyte activation**

#### **Guideline III.1**

**A. Dialyzer membranes with the lowest degree of complement and leukocyte activation should be applied. Dialyzer membranes that induce strong complement and leukocyte activation, inflammatory reactions, and/or a blunting of the response of leukocytes to stimuli should be avoided.**

*(Evidence level: B)*

#### **Commentary on Guideline III.1**

Next to the impact of membranes on baseline immune responses and on the response to immunologic stimuli, also the capacity of some membranes to adsorb molecules with a negative pathophysiologic impact will be discussed.

##### *Baseline immune response*

*Intradialytic baseline immune activation.* Several dialysis membranes induce activation of elements of

the immune system, which mediate inflammatory reactions, and/or take part in the production of acute-phase proteins. Inflammatory reactions are reflected by complement activation [1–23], production of terminal complement complex [7,15,24,25] and complement receptor expression [26,27], enhanced phagocyte oxidative metabolism [5,11,16,19,23,26,28–31], expression of surface and adhesion molecules [1,3,11,19,21,22,26,32–35], leukocyte aggregation or adhesion to the dialyzer membrane [36–39], production, transcription and receptor expression of cytokines [8,10,21,27,40–56], neutrophil degranulation and release of elastase [7,20,57,58], release or generation of humoral factors or messengers apart from the above-mentioned [20,38,41,59–64], apoptosis [36,65], and activation of other cell systems than granulocytes and monocytes, such as platelets [60,66,67], natural killer cells [68,69] and lymphocytes [44,62]. It is of note that several of the above-mentioned studies are entirely or partly based on *in vitro* or *ex vivo* experiments [2,10,11,16,23,25,30,35,36,38,50–52,57,62].

The most direct consequence of complement and leukocyte activation is leukocytopenia, attributed to intrapulmonary sequestration of leukocytes [1,3,4,11,33,34].

A number of studies restricted to cytokine production [45,50,51,70,71], functional capacity of natural killer cells [68,69,72], and phagocytic free radical production [14], show the induction of systemic inflammatory response. However, these findings are limited to a minority of studies. In addition, the absence of a systemic response does not exclude a local activation within the dialyzer.

*Differences among membranes.* The strongest and/or most rapid activation of the complement and leukocyte systems has been demonstrated with the so-called unmodified cellulosic membranes, whereas this response is blunted with modified cellulose and synthetic membranes [2,3,5,8–10,12,16,19–23,25–27,30–32,34–36,38,42,43,46,48,52–54,58,60–63,66,72–74]. A few studies, however, do not reveal a more pronounced pro-inflammatory response for unmodified cellulose compared with the other membranes [13,22,45,47,50,70,71,75]. The latter studies again mainly concentrate on cytokine production [13,45,50,70,71].

Not all cellulosic membranes induce an equally strong degree of complement activation and/or inflammatory response, whereas not all synthetic membranes are inert towards the complement and the inflammatory systems [7,12,16,17,20,21,24,47,58,62,76]. Even so-called biocompatible membranes with a lower impact on the complement system than unmodified cellulose, might induce a certain degree of intradialytic leukocytopenia [5,12,16,17,21,30,32,75,77,78] or inflammatory reaction [79].

Differences among membranes in their capacity to induce inflammatory response, are not always caused by different degrees of stimulation but may sometimes be the consequence of the presence or absence of the

membrane's ability to remove and/or adsorb inflammatory agents [2,40,49,80,81]. AN69 membranes generate more activated complement than unmodified cellulose, but this effect is neutralized at least at the systemic level by the high adsorptive capacity of AN69 for activated complement [82].

*Non-membrane-related factors (other factors than membranes).* Not only the dialysis membrane, but also particles released from the circuit (e.g. from dialysis tubing) [83], the sterilization mode [84], as well as blood flow and dialysis adequacy [85] may have an impact on elements of the inflammatory response. More importantly, there might be an overlap in induction of inflammatory response between membrane and dialysate effects [8,13,15] (for further details, *see Section IV*).

*Induction of acute-phase proteins.* Not only an inflammatory response, but also the production of acute-phase proteins as a marker of inflammation is modified by complement-activating membranes [13,56,73,86–88]. This induction is not provoked by more biocompatible membranes [56,86]. This type of inflammatory response might affect clinical outcome [47,89–93] (for further details, *see Section VII*).

#### *Stimulated immune response*

*Blunting of intradialytic response.* Leukocytes collected during haemodialysis from patients treated by membranes with a stronger complement-activating impact show a blunted response upon stimulation [5,14,28–30,32,44,53,54,62,94–100]. All these studies are *in vitro* or *ex vivo*. Chronic use of complement-activating membranes also affects long-term leukocyte response [97]. A few studies, in contrast, show an enhanced response upon stimulation during treatment with more complement-activating membranes [14,23,43,48].

*Studied stimuli.* Rarely real infections stimuli such as Staph A are studied [29,97]. Most studies use non-infectious stimuli that are supposed to affect leukocytes in a similar way as infection, e.g. particles such as latex [30,99], zymosan [30,95,99], IgG-coated erythrocytes [95] or heat-aggregated immunoglobulins [95], or humoral stimuli such as formyl-leucine-methionine-phenylalanine (f-MLP) [28,30,96,99], phorbol myristic acid (PMA) [32,99], phytohaemagglutinin (PHA) [44,53,100], or exogenous C5a [28].

#### *Removal by adsorption*

*Adsorptive processes with a positive potential.* Adsorption to the dialysis membrane is an epiphenomenon that points to bioincompatibility. It is of note, however, that in many instances molecules with a negative pathophysiologic impact such as  $\beta_2$ -microglobulin ( $\beta_2$ -m), cytokines, or complement

factors are adsorbed. This is especially the case for a number of membranes with low systemic complement-activating capacity. In as far as these membranes do not adsorb compounds with a positive impact on the clinical condition of the patients, this adsorptive process should be considered as beneficial.

Several membranes with low systemic complement-activating capacity adsorb components with patho-physiologic potential [2,49,80–82,101–107]. This is the case for IL-1 by AN69, polymethylmethacrylate and cellulose triacetate [49,101,107], TNF by AN69, polyamide, cellulose triacetate, polymethylmethacrylate and polysulfone (F60) [101,103,107], low molecular weight proteins by polymethylmetacrylate, EVAL, polysulfone (F60) [102], IL-6 by AN69, polyamide, cellulose triacetate, polymethylmethacrylate and polysulfone (F60) [103,107], IL-8 by AN69, polyamide and cellulose triacetate [103],  $\beta_2$ -m by polysulfone, AN69, polyamide, PMMA and polycarbonate [103,104,106], C3a and C5a by cellulose acetate, cellulose triacetate, AN69 and polymethylmethacrylate [2,80,82,107], and complement factor D by AN69 [81].

Membranes with a very high adsorptive capacity are PMMA and AN69 [102,104,108]. Membranes with an intermediate adsorptive capacity are polyamide and polysulfone [102–104,108]. Although intrinsically a sign of bioincompatibility, this adsorption should be considered as a desirable effect [105,108].

Cuprophane adsorbs relatively little  $\beta_2$ -m [104,106], C5a [2,82], and C3a [2].

*Adsorptive processes with a negative potential.* Adsorption on the membrane surface might decrease the sieving coefficient and clearance of larger molecules ( $> 10\,000$  Da) during the course of the dialysis session [109,110].

Adsorptive processes may also result in the removal of beneficial molecules, such as erythropoietin [111]. The strongest adsorption of erythropoietin occurs with AN69 membranes [111]. This adsorption has no influence on the erythropoietin plasma concentration nor on erythropoietin dose [112].

problems, a negative impact of dialyzers containing unmodified cellulose was demonstrated or suggested: (i) pulmonary function; (ii) nutritional status; (iii) susceptibility to infection; (iv) atherogenesis; (v) residual renal function; (vi) peripheral nerve function; (vii) development of uraemia-related amyloidosis. In addition, a large number of studies point to a relation between the application of unmodified cellulose dialyzers and increased mortality.

#### *Pulmonary function*

*Acute changes.* During haemodialysis with complement-activating dialyzers, leukocytes are sequestered in the pulmonary capillary bed [1,4,113,114]. The use of complement activating membranes has an acute negative impact on pulmonary function and perfusion [115–117]. Changes are less pronounced when less complement activating membranes are applied [116,117]. In one study, expression of leukocyte adhesion molecules and intradialytic hypoxaemia were dissociated from complement activation [118]. Changes in pulmonary function impose a risk especially in patients with precarious pulmonary function [116].

*Chronic changes.* As a result of local intermittent but repeated intrapulmonary release of proteases and free radicals, the potential exists for the induction of chronic pulmonary changes (e.g. fibrosis) [119]; this effect has never been demonstrated directly in haemodialysis patients.

#### *Nutritional status*

*Catabolic response.* Indirect parameters of nutritional status such as serum albumin, pre-albumin, or insulin-like growth factor-1 and direct parameters such as body weight are negatively affected by dialysis with complement-activating dialyzers [73,120]. Dialysis with complement-activating dialyzers leads to net protein breakdown [121–126]. These effects are attributed to the induction of inflammation [47,121,126]. Parameters pointing to protein breakdown are less affected during dialysis with dialyzers that induce less inflammatory response [120–123, 125,126]. PCR, an indirect marker of daily protein intake, is higher in patients treated with less complement-activating membranes [127]. The switch of patients with hypoalbuminaemia, from a bioincompatible to a more biocompatible membrane, was followed by a significant increase in serum albumin [88].

In some studies, however, no arguments were found in favour of catabolism during haemodialysis with complement-activating membranes [128–130]. One of these studies only considered the period during the dialysis session, and not the period after the ending of the dialysis [128], whereas Bergström *et al.* [121] had demonstrated that catabolism was most prominent in the period following the dialysis session. Another study

### **III.2 Clinical morbidity and mortality in response to complement and leukocyte activation**

#### **Guideline III.2**

**A. To achieve an improved clinical outcome regarding morbidity and mortality, the use of large pore/high-flux biocompatible dialyzers should be preferred.**  
(*Evidence level: B*)

#### **Commentary on Guideline III.2**

Several studies point to a relation between the application of unmodified cellulose dialyzers and the development of clinical problems. Many of these studies are observational. For the following clinical

was retrospective and not devoid of selection bias [130]. The possibility should be considered that a negative protein balance is present acutely during and immediately after the dialysis session, with a compensatory positive balance developing several hours thereafter [131].

*Amino acid losses.* Some studies suggest that high-flux membranes induce more important transmembrane amino acid losses into the dialysate than low-flux membranes; in these studies, unmodified cellulose membranes as well as less complement-activating variants were applied as low-flux membranes [122,125]. On the other hand, in at least one study, high-flux membranes were characterized as well by a greater surface area and blood flow, compared with the low-flux membranes entered in the study; if the results were normalized mathematically for these greater surfaces and flows, no more differences in amino acid losses could be demonstrated [125].

#### *Susceptibility to infection*

In at least four studies, it is suggested that infectious morbidity and/or mortality is increased in patients dialyzed by complement/leukocyte-activating membranes [97,132–134]. Two of these studies remained just below the limit of statistical significance [97,134]. The two other studies resulted in significant differences but were based on retrospective analyses of large patient databases, and on multifactorial regression analyses with correction for risk factors [132,133]. One of these two studies was based on registry data [132]. In a prospective follow-up study, synthetic membranes were not associated with a lower infectious risk compared with cellulosic membranes [135]. In the latter study, cellulosic membranes were, however, a mix of dialyzers with high and low complement-activating capacity.

#### *Atherogenesis*

*Oxidative stress.* Haemodialysis patients are characterized by an increased risk of atheromatosis and atherosclerosis and by an early development of these diseases; at the same time, they are subjected to more oxidative stress, which is considered to be a causative factor in atherogenesis [136]. The capacity of dialyzer membranes to induce leukocyte-oxidative activation might contribute to this oxidative stress [5,11,16,19,23,26,28–30,136–142]. A few recent studies evaluate or compare the capacity of membranes to induce oxidative stress. With AN69, an increase was observed in several but not all parameters of oxidative stress [143]; another study, using acrylonitrile and polysulfone as biocompatible membranes, could not demonstrate a rise in lymphocyte reactive oxygen species [144]. A surrogate marker of oxidative stress, 8-hydroxy 2'-deoxyguanosine, was increased when patients were treated with low-flux cellulose membranes, but decreased with polymethylmethacrylate,

polysulfone, or vitamin E-modified regenerated cellulose [145]. Likewise, only cuprophane membranes induced oxidative damage to red blood cells [146]. This aspect is further discussed elsewhere (*see Guideline VII*).

Oxidative stress during haemodialysis with complement-activating membranes has been correlated with increased malondialdehyde and inversely correlated with glutathione peroxidase and erythrocyte dismutase activity [147–149].

Complement activation can also be supposed to induce adhesion of leukocytes to endothelium [150]. During dialysis with complement-activating dialyzers, adherence of leukocytes to endothelial cells and/or leukocyte rolling were inhibited, however [34,96,151,152]. So, the link between dialyzer membranes and atherogenic events has not yet fully been established.

Vitamin E-substituted cellulosic dialyzer membranes might allow to preserve blood anti-oxidative capacity [153] to a larger extent than standard complement-activating dialyzers, and to prevent endothelial dysfunction [154]. Clinical comparisons of vitamin E-substituted membranes with membranes with low complement-activating capacity are, however, lacking at this moment. Vitamin E-substituted membranes showed a greater induction of expression of leukocyte surface molecules, than a synthetic dialyzer membrane [155].

*Lipid profiles.* The application of complement-activating membranes has a negative impact on lipid profiles. According to several studies, this effect is neutralized by membranes with lower complement-activating impact [156–159]. In these studies, it is once more impossible to discern between the impact of biocompatibility and that of pore size [156–158]. Other studies show no difference in lipid profile in spite of difference in complement-activating capacity [160]. One study suggests that flux is the most discriminating factor, as low-flux biocompatible membranes induced no beneficial changes in lipid profile [157].

*Cardiovascular morbidity and mortality.* In two studies, it is suggested that cardiovascular morbidity and/or mortality might be increased when complement-activating membranes are applied [132,134]. The two studies analysed patient databases by multifactorial regression analyses with correction for risk factors. One study was based on registry data [132], one study [132] reached the borderline of significance, whereas the other study only showed a trend [134].

#### *Residual renal function*

In three studies, the use of complement-activating membranes was found to precipitate the deterioration of residual renal function [161–163]. One study was prospective [161] and one contained a retrospective

analysis of prospectively collected data [163]. In at least one study, such a negative impact was not found [164], although a trend was present.

#### *Peripheral nerve function*

In two studies, less complement-activating dialyzers had a more positive impact on peripheral nerve function, compared with more complement-activating dialyzers [165,166]. One study was prospective [165], but it compared haemodialysis with unmodified cellulose membranes to haemodiafiltration with polysulfone.

#### *Uraemia-related amyloidosis*

Amyloidosis occurring in uraemic patients is a specific variant, which mainly invades the osteo-articular system and the tendons (carpal tunnel syndrome); it becomes most often apparent after several years of dialysis treatment or chronic renal failure and/or in the aged dialysis patient; the course of the disease may be seriously invalidating and even fatal [167–174]. The disease is characterized by the deposition of  $\beta_2$ -m as an amyloid protein [171,174–178]. Recent data indicate that  $\beta_2$ -m amyloidosis develops much earlier (sometimes within 2 years after the start of dialysis), than originally supposed [176], or even before dialysis is started.

*Acute effects of dialysis on  $\beta_2$ -m concentration.* Contact of lymphocytes/monocytes with complement-activating membranes enhances generation of  $\beta_2$ -m and decreases  $\beta_2$ -m expression on the cell surface [179].

Serum  $\beta_2$ -m tends to increase during each dialysis session with complement-activating dialyzers, but this is at least in part the consequence of haemoconcentration in the presence of ultrafiltration with small pore membranes, which allow the removal of plasma water but not of  $\beta_2$ -m; correspondingly, during dialysis with large pore dialyzers (sieving coefficient for  $\beta_2$ -m > 0.6), which allow the transmembrane removal of  $\beta_2$ -m, the concentration decreases acutely [106,174,180,181].

When small pore dialyzers were compared with each other in a prospective study, pre-dialysis  $\beta_2$ -m tended to be lower with the less complement-activating membranes [164].

*Long-term effects of dialysis on  $\beta_2$ -m concentration.* Long-term haemodialysis with more biocompatible membranes which are at the same time characterized by a larger pore size, results in a progressive decrease of pre-dialysis  $\beta_2$ -m concentrations; these remain, however, far above normal, even after intensive removal therapy [44,182–184]. A few studies do not confirm the progressive decline of  $\beta_2$ -m with less complement activating or large pore dialyzers [130,169]. One study was, however, retrospective and suffered from selection bias [130]. The effect of

clearance and flux is discussed more in detail in the corresponding section (*see Section II*).

In one study, large pore and small pore polysulfone membranes are compared for long-term evolution of pre-dialysis  $\beta_2$ -m, with a more favourable result for large pore polysulfone, pointing to a role for removal [129]. In a recent, retrospective survey, development of clinical symptoms of  $\beta_2$ -m amyloidosis was most prominent on low-flux bioincompatible membranes, intermediate for low-flux biocompatible membranes, and lowest for high-flux biocompatible membranes, pointing to a combined role of removal and biocompatibility [185]. On the other hand, when small pore dialyzers were compared with each other in a prospective study, pre-dialysis  $\beta_2$ -m was lower with the less complement-activating membranes [164].

*Effect of membranes on uraemia-related amyloidosis.* Long-term dialysis with dialyzers with low complement-activating capacity results in a lower prevalence of uraemia-related amyloidosis and/or carpal tunnel syndrome [134,170,173,183,185–188]. Whether this benefit is attributable to differences in complement and leukocyte-activating capacity is not evident. Alternative mechanisms could be a better removal of  $\beta_2$ -m or rejection of dialysate impurities [44,106,129,182,183,185,187,189,190].

*Advanced glycation.* A proportion of the  $\beta_2$ -m in dialysis-related amyloid is modified by advanced glycation, a chemical modification that by itself is the consequence of oxidation and carbonyl stress [138,175,191–203].  $\beta_2$ -m also binds more avidly to advanced glycation end products (AGE)-collagen [191]. Blood AGE-concentration is higher in patients who develop clinical dialysis-related amyloid disease [197]. AGE- $\beta_2$ -m induces biological inflammatory reactions [194,195,204–206]. One study demonstrates that macrophages that surround  $\beta_2$ -m amyloid fibrils cause phagocytosis rather than synthesis of amyloid fibrils [207].

It is possible that dialysis membrane-related inflammation plays a role in this production of AGE, but there is at present insufficient direct proof for such a chain of events. In a recent study, AGE concentrations were lower in patients treated with biocompatible high-flux polysulfone, than in those treated with bioincompatible low-flux cellulose membranes; higher AGE concentrations were equally found with biocompatible AN69 and polymethylmethacrylate membranes [208].

Some studies offer no arguments that the  $\beta_2$ -m from amyloidosis has been modified structurally, as the structure isoforms that are found in amyloid are not different from the  $\beta_2$ -m isoforms found in urine from healthy individuals [209,210].

#### *Mortality*

Several studies indicate that overall mortality and/or mortality attributable to specific causes is affected

negatively by membranes with complement-activating capacity [132–134,136,211–216]. All these studies were retrospective or at best ‘historically prospective’, but, on the other hand, most of them were undertaken on large databases [132–134,211–213,215–217]. For most studies, pore size remains a confounder, with the exception of one study [213], where the group on modified cellulose, which contains in essence small pore membranes with better biocompatibility, has a better outcome compared with those on unmodified cellulose. Also, correction for small molecular clearance ( $Kt/V$ ) was only rarely applied [213]. In at least two studies, removal of large molecules *per se* had a positive effect on survival, irrespective of membrane biocompatibility [215,216] (for more details, *see Section II*). Up to now, no unequivocal proof has been delivered that small pore biocompatible dialyzers are clinically superior to small pore bioincompatible ones.

Not all studies show a difference in mortality [13,130,170]. Two of these studies, however, were retrospective [130,170]. One study compared convective *vs* diffusive removal rather than biocompatibility [170]. One study was prospective, but was done on small patient groups [13]. It reached the borderline of significance.

reactions [83,219], and may be sequestered in the liver and the spleen, inducing hepatic dysfunction and enhanced blood cell destruction [218,222]. Release of fragments is especially induced by over-occlusion of pump systems [220,221,223]. Pumps in which the rollers are adjusted manually induce less particle spallation than automatically occluding pumps [220].

#### *Release of soluble factors*

Dialysis systems also release soluble factors [220, 221,224–227]. One of these factors is di-(2-ethylhexyl)-phthalate, a plasticizer which has been recovered from the plasma of dialyzed patients. Apart from induction of allergy (see below), the pathophysiologic meaning of this finding remains unclear [220,221,225–228].

Plasticizer release can be reduced by the application of tri-(2-ethylhexyl)-trimellitate as a plasticizer [225,226], and/or by the coating of the inner wall of the tubings, e.g. with PVC-ethylene vinylacetate or PVC-polyurethane [220].

Another released soluble factor is ethylene oxide (EtO), which also induces allergic reactions (see below) [6,224,229–233]. Gamma irradiation for sterilization of plastic materials may result in the release of cytotoxic compounds [234].

Release of particles and of soluble factors can be reduced by adequate pre-rinsing [224,235,236].

### **III.3 Spallation/release**

#### **Guideline III.3**

**A. In order to prevent the release of fragments (solid or soluble) from the dialyzer circuit, and their accumulation in several organs of the body, adequate dialyzer pre-rinsing according to the manufacturers instructions should be performed. If no manufacturer instructions are given, the dialyzers should be pre-rinsed using at least 2 l of rinsing solution. Over-occlusion of the roller pumps should be avoided as well.**

*(Evidence level: B)*

#### **Commentary on Guideline III.3**

Spallation or leaching can be defined as the slow dissolution of solid-phase entities or soluble compounds from material used in the dialyzer circuit into the surrounding blood, and from there into the body organs.

#### *Release of solid materials*

Fragments of dialysis system materials, especially of tubings, are released in the circulation of dialysis patients. These fragments may contain silicone, polyvinylchloride (PVC), polyurethane, or any other polymer used for the assembly of dialysis circuits [218–222]. These fragments induce inflammatory

### **III.4 Reactions to membranes and other dialyzer-related material**

#### **Guideline III.4.1**

**A. Use of dialyzers and tubings sterilized with EtO should be avoided, especially in patients showing otherwise unexplained signs of anaphylactoid reaction (evidence level: B), eosinophilia or elevated IgE (evidence level: C).**

*(Evidence levels: B and C)*

#### **Guideline III.4.2**

**A. Phthalates and other potentially allergenic components of dialyzers and tubings should be avoided if prolonged allergic reactions persist despite avoiding EtO.**

*(Evidence level: B)*

#### **Guideline III.4.3**

**A. The combination of dialysis with AN69 membranes and medical treatment with ACE-inhibitors (ACE-i) should be avoided because of the possibility of severe haemodynamic reactions.**

*(Evidence level: B)*

### **Commentary on Guidelines III.4.1, III.4.2, and III.4.3**

#### *Anaphylactoid reactions*

Anaphylactoid reactions in relation to dialysis become manifest by variable symptoms: chest tightness, back pain, pruritus, flushing, bronchospasm, urticaria, angioedema, and early blood pressure reduction [235–237]. Some of these reactions are life-threatening [237]. Reactions are more prominent with hollow fibre than with plate dialyzers [237,238]. A substantial proportion of patients showing anaphylactoid reactions develop biochemical and/or clinical allergic phenomena to the gas sterilant EtO [6,224,229–233]. Reactions to EtO are less pronounced if dialyzers are thoroughly pre-rinsed. Application of non-EtO sterilized equipment also has a beneficial effect on hypersensitivity reactions [224,235,236].

Also, the plasticizer phthalate anhydride and the sterilant formaldehyde can induce reactions or specific antibody responses [229,239,240]. Phthalates have also been implicated in chemically induced polycystic kidney disease [241]. Phthalate exposure is substantial during haemodialysis with di-(2-ethylhexyl)phthalate-containing tubing material [242]. Flexible materials containing no PVC [243] or PVC supplemented with alternative plasticizers such as di-2-ethylhexyl-adipate are now available [244].

Some authors associate anaphylactoid reactions, and/or eosinophilia to complement activation [84, 240,245–247]. This is not confirmed by all studies [230,238].

#### *Haemodynamic reactions with AN69 membranes and ACE-i*

A specific dialysis-related accident consists of the sudden development of haemodynamic reactions that occur in patients treated with AN69 dialyzers. Most, if not all, of the patients who were affected by these problems simultaneously received ACE-i therapy [233,248–251]. This effect is attributable to bradykinin generation because of blood-membrane interaction (negative charge of AN69), with decreased metabolism of bradykinin induced by the ACE-inhibition [249,251,252]. Such reactions may be avoided in the majority of affected patients by replacing the ACE-i with angiotensin receptor II antagonists [253] or by applying other dialyzer membranes than AN69. Pre-rinsing of dialyzers with alkaline rinsing solutions (pH=8) may also have a preventive effect [254,255].

- the application of an optimal relationship between dialyzer blood flow and access diameter;
  - the prevention of highly negative arterial pressure alarms (exceeding 150 mmHg);
  - the correct positioning of cannulae and needles in the access system;
  - the correct positioning of tubings in the roller pumps;
  - minimizing recirculation;
  - the maintenance of vascular access systems in anatomically correct condition.
- (Evidence level: C)

### Commentary on Guideline III.5

Shear can be defined as the distortion caused by the sliding of blood layers at different speed through the dialyzer circuit. Shear stress-related problems occur in haemodialysis when resistance to flow becomes important enough to cause cell damage and activation. The shear-related biocompatibility problems dealt with in this guideline are modifications or damage to cells or structures induced by this distortion.

#### *Biological effects of shear stress*

Shear stress can induce platelet activation, platelet fragmentation, inhibition of platelet aggregability upon subsequent exogenous activation, loss of leukocyte chemotactic capacity, loss of oxidative burst response of phagocytes, haemolysis, and generation of schistocytes [256–259]. Changes in platelets and leukocytes can be observed from shear stress levels of 10–15 Pa on and become relevant from 25–45 Pa on (if haemodialysis is applied correctly, shear stress levels of 40 kPa can be expected in a single needle setting, and values of 20 in a two needle setting) [256,257].

Clinically significant haemolysis manifests itself by angina-like complaints, intractable hypotension, and oesophageal spasms [258].

#### *Prevention of shear stress-related problems*

Shear stress-related problems can be prevented by keeping blood flow in the dialyzer circuit within acceptable limits and by minimizing resistance to this blood flow [258,260].

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### III.5 Shear stress/haemolysis

#### Guideline III.5

A. Shear stress-related problems/haemolysis can be prevented by:

- the use of large needles/cannulae (14/15 gauge);

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