

The causes of dysfunction can be divided into two major categories: one caused by the uraemic state itself and the other caused by therapeutic intervention.

### Guideline VI.1

**A. To reduce the susceptibility to infection, optimal adequacy of HD should be attained, malnutrition should be prevented or treated, optimum haemoglobin concentration should be maintained, iron overload should be avoided and a dialysis membrane with the lowest degree of complement and leukocyte activation should be used. (Evidence level: B)**

### Commentary on Guideline VI.1

Chronic uraemia has a deleterious effect on the function of polymorphonuclear neutrophils, monocytes, and lymphocytes. Many findings suggest uraemic-toxin accumulation as a factor responsible for defective polymorphonuclear function [49–53]. As a consequence, phagocytosis is impaired in uraemic patients [54–57]. Defective macrophage dysfunction was also demonstrated [58]. Uraemic patients have deficits in cell-mediated immunity [59,60] and antibody production [61]. This can result in cutaneous anergy and abnormal response to HBV and TB.

Optimizing the elimination of solutes that negatively affect immune function may reduce the risk of infection. Although uraemic retention may contribute to the increased risk of infection in uraemic patients, it is clinically difficult to separate the negative effects of uraemia from the many other factors participating in the impaired immune response. An inverse relationship was found between dose of dialysis and mortality. Analysis of cause-specific mortality showed that for each 0.1 increment in Kt/V the adjusted relative risk of death due to infection was 9% less [62].

However, a prospective multicentre study, performed to identify risk factors for bacteraemia in HD patients noted that the urea reduction rates and the Kt/V indexes did not differ from those found in patients who were not infected [8]. The studied population had a relatively high Kt/V. Also, the time elapsed from diagnosis of renal failure until initiation of dialysis [63] and time elapsed from dialysis initiation until occurrence of bacteraemia [11] have not been found to contribute to the incidence of bacteraemia.

The current recommendation of the NKF DOQI is a pre-dialysis or stabilized serum albumin equal to or greater than the lower limit of the normal range, which corresponds to approximately 40 g/l for the bromocresol green method [64]. When more complex parameters of protein-energy malnutrition such as fat mass, fat-free mass, and bone-free arm muscle area were used, the score obtained was significantly correlated with infection related morbidity [65]. The negative effect of malnutrition on immune function, which was shown in non-uraemic patients, has never been

### VI.1 Prevention of infection: management of impairment of the host defence

Dysfunction of the host defence is one of the major functional disturbances in end-stage renal disease [49].

demonstrated in HD patients [66,67]. In a large population of HD patients, a serum albumin concentration of less than 37 g/l was found in 25% [68]. Low serum albumin has been associated with an increased risk of morbidity and mortality [69–72]. In multivariate analyses, low serum albumin has also been found to be independently associated with infection [69] and particularly with septicæmia [14]. In a prospective study of 975 HD patients, the serum albumin was lower at inclusion in patients who developed later a bacteraemic episode than in patients who did not; nevertheless, it was not identified as a risk factor for bacteraemia in a multivariate analysis [8]. Interpretation of such laboratory parameters as risk factors for infection should be regarded with caution, as retrospective studies do not distinguish between actual risks for infection and indicators of inflammation or chronic illness or fluid overload.

The current recommendations for the target Hb in dialysis patients are 11–12 g/dl in the NKF DOQI [73] and greater than 11 g/dl in the European Best Practice Guidelines [74]. In chronic HD patients, granulocyte response to stimulation is correlated to the haematocrit [49]. Granulocyte response improves with rhuEpo therapy [75,76]. A beneficial effect of rhuEpo has also been demonstrated on other aspects of the immune system such as the composition of the lymphocyte subpopulation, cytokine production response upon vaccination, and immunoglobulin production [77,78]. Patients with a haematocrit less than 29% were shown to have a greater mortality rate than those with haematocrit  $\geq 30\%$ . The higher mortality rate was linked to an increase in infectious causes of death [79]. In a prospective study, anaemia was significantly associated with bacteraemia [8].

A number of *in vitro* studies have demonstrated the importance of iron in regulating the expression of T lymphoid cell surface markers, in influencing the expansion of different T cell subsets and in affecting different immune cell functions [80].

Before the use of rhuEpo, iron overload following polytransfusion as assessed by serum ferritin was shown to be a significant risk factor for bacterial infection in HD patients [23,81–83]. Septicæmia with *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* has been reported in patients with severe iron overload [84–86].

It has been shown that removal of iron with DFO or Epo treatment leads to improvement in phagocytic function [75], but DFO seems to favour the development of mucormycosis in HD patients [48,87,88]. In a recent prospective study where more than half of the patients were on Epo therapy, iron overload was no longer a risk factor for bacteraemia [8] but the proportion of severely iron-overloaded patients had dramatically decreased.

However, there is a dichotomy between the *in vitro* data showing that iron suppresses phagocytosis [89,90] and the effects of iron overload *in vivo*. It is known that idiopathic haemochromatosis is not associated with an increased incidence of infection

and that patients with thalassaemia who receive multiple transfusions and develop haemosiderosis have an increased incidence of infections only if they had a splenectomy [91].

To date, the risk of iron overload is no longer related to repeated transfusions but it may be induced by excessive iron supplementation. Few data are available to allow estimation of a safe upper limit of serum ferritin in patients receiving only i.v. iron treatment. The European Best Practice Guidelines [92] recommend to maintain the ferritin concentration at less than 800 ng/ml.

Complement and leukocyte activating dialyzer membranes such as cuprophane not only stimulate baseline leukocyte response, they are also associated with blunting of the response to stimuli, e.g. the immune response during infection. It was suggested that infectious morbidity and mortality are greater in patients treated with complement/leukocyte activating membranes [55,93–96]. Contradictory results were obtained both in retrospective [97] and prospective [8] studies and we still need a large prospective study to demonstrate the influence of biocompatibility on susceptibility to infection (for details see Guideline III).

responsibility of *S. aureus* for bacteraemia might originate in chronic staphylococcal nasal carriage. Nasal carriage of *S. aureus* leads to an increased risk of bacteraemia in most studies [63,98,99,103,104] but not in all [8].

Given the ability of *S. aureus* to adapt to antimicrobial exposure, the administration of systemic antimicrobials for carriage does not appear to be an optimal approach. Mupirocin is a topical anti-staphylococcal agent that inhibits RNA and protein synthesis. Intranasal mupirocin eliminates nasal colonization in haemodialysed carriers [105,106]. Intranasal mupirocin used on a regular basis strikingly decreases the risk of *S. aureus* bacteraemia in HD patients [101,107–109] and it is cost effective [109,110] but prior mupirocin use was shown to be a significant risk factor of resistance [111]. Because the high relapse rate observed in HD patient after short-term nasal mupirocin treatment, a study was conducted with long-term (2 years) once-weekly application of mupirocin [101]. Eradication of nasal carriage was obtained in 96.3% of the carriers and only one single mupirocin-resistant *S. aureus* strain was observed.

Applied to the insertion site of internal jugular cannulae in patients undergoing cardiothoracic surgery, mupirocin reduced the rate of colonization of cannula tips by coagulase-negative staphylococci [112]. In a randomized, prospective trial of patients haemodialysed with non-tunnelled venous catheters for 4–142 days, mupirocin applied to the insertion site significantly reduced the risk of *S. aureus* skin and catheter colonization, exit-site infection and *S. aureus* bacteraemia [113].

The systematic use of nasal mupirocin in all identified *S. aureus* carriers on HD should be compared with the use of mupirocin by a subgroup of *S. aureus* carriers who are at particularly high risk of bacteraemia. Such patients should include those with a past history of *S. aureus* infection and those dialysed through a central venous catheter [8].

### VI.3 Prevention of infection: management of the vascular access

#### Guideline VI.3.1

**A. To prevent infection, vascular access should be a native fistula whenever possible.**  
(Evidence level: B)

#### Commentary on Guideline VI.3.1

The single most frequent site of infection in HD patients is the vascular access site [9,10,23].

The risk of vascular access infection is strongly associated with the type of vascular access. In a standardized surveillance of HD vascular access systems, 4.6 infections per 1000 dialysis sessions (ds) were identified. This rate was 2.5/1000 ds for permanent

fistulae or grafts, 13.6/1000 ds for permanent catheters and 18.4/1000 ds for temporary catheters [114]. Patients with a PFTE graft were found to have a 29–33% greater risk of bacteraemia than patients with a native fistula [8,14].

Many studies have demonstrated that bacterial infections are more frequent with external catheters [11,12,14,23,63,115–117]. This high risk of infection is linked to the presence of foreign material and to the special affinity of bacteria for artificial devices [118]. Once bacterial contamination enters these systems, bacteriae may easily stick to the polymer materials and to the fibrin sheath that covers them.

#### Guideline VI.3.2

##### A. For permanent arteriovenous fistula or grafts:

- **Patients should adopt good personal hygiene habits.**  
(Evidence level: B)
- **Clean technique for skin preparation should be used before cannulation of native fistula.**  
(Evidence level: C)
- **Aseptic technique should be optimally used and is strongly recommended for cannulation of grafts.**  
(Evidence level: C)
- **HD staff training for fistula cannulation is mandatory to avoid poor needle insertion.**  
(Evidence level: C)

#### Commentary on Guideline VI.3.2

All vascular access systems may become infected due to breaches in the protective barrier and frequent manipulation. In HD patients poor personal hygiene is a risk factor for vascular access infection [82].

Cannulation of an access site places the HD patients at risk for infection by bacterial contamination.

An aseptic technique for skin preparation is as follows: the patient washes the access arm just before being positioned for cannulation, the needle cannulation sites are located and palpated prior to skin preparation, dialysis staff handwash and wear sterile gloves. All materials used to cannulate the access except fluid containers are placed on a sterile area next to the patient. Povidone-iodine or chlorhexidine solution is applied to the skin over the access and allowed to dry for 2–3 min. Sterile barriers are placed above and below the prepared area. The fistula needles are then inserted and the insertion sites are covered with sterile band-aids.

In a retrospective study, this technique has been shown to control outbreaks of access-site infections due to *S. aureus* [82] but in a prospective randomized study, no significant difference in vascular access-site infection was found between patients prepared with aseptic technique and those prepared using clean technique [82]. The clean technique differs from the aseptic technique by the use of clean barriers and non-sterile gloves.

## **VI.2 Prevention of infection: management of host colonization by *Staphylococcus aureus***

### **Guideline VI.2**

#### **A. To reduce *S. aureus* infections in HD patients**

- **All high-risk patients, such as those with a past history of *S. aureus* infection and those dialysed through a central venous catheter, should be screened for nasal colonization.**  
(Evidence level: B)
- **Intervention to eradicate *S. aureus* nasal carriage should be considered in these high-risk *S. aureus* carriers.**  
(Evidence level: B)

### **Commentary on Guideline VI.2**

*Staphylococcus aureus* infections are both common and life-threatening in HD patients. *Staphylococcus aureus* causes infection of the angioaccess, bacteraemia, and endocarditis. Evaluation of *S. aureus* isolated from HD patients by bacteriophage typing and restriction endonuclease digestion of plasmid DNA supports the hypothesis that *S. aureus* causing infections in HD are of endogenous origin [98]. One of the main reservoirs of *S. aureus* is the nose [99,100].

The prevalence of *S. aureus* carriage is high in HD patients, ranging from 46 to 62% [101–103].

A previous history of *S. aureus* bacteraemia is a significant predictor of subsequent bacteraemic episodes in chronic HD patients [8]. This tendency towards recurrence combined with the predominant

responsibility of *S. aureus* for bacteraemia might originate in chronic staphylococcal nasal carriage. Nasal carriage of *S. aureus* leads to an increased risk of bacteraemia in most studies [63,98,99,103,104] but not in all [8].

Given the ability of *S. aureus* to adapt to antimicrobial exposure, the administration of systemic antimicrobials for carriage does not appear to be an optimal approach. Mupirocin is a topical anti-staphylococcal agent that inhibits RNA and protein synthesis. Intranasal mupirocin eliminates nasal colonization in haemodialysed carriers [105,106]. Intranasal mupirocin used on a regular basis strikingly decreases the risk of *S. aureus* bacteraemia in HD patients [101,107–109] and it is cost effective [109,110] but prior mupirocin use was shown to be a significant risk factor of resistance [111]. Because the high relapse rate observed in HD patient after short-term nasal mupirocin treatment, a study was conducted with long-term (2 years) once-weekly application of mupirocin [101]. Eradication of nasal carriage was obtained in 96.3% of the carriers and only one single mupirocin-resistant *S. aureus* strain was observed.

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**Guideline VI.3.3**

**A. Insertion of (permanent) central venous catheters should be considered as a surgical procedure and only be performed by trained and experienced medical staff in a dedicated clean area under aseptic conditions.**

*(Evidence level: C)*

**B. Only appropriately trained staff should perform catheter dressing changes and catheter manipulation.**

*(Evidence level: B)*

**C. Catheter connection, disconnection, and interventions should be performed under aseptic conditions by trained dialysis staff with the patient wearing a surgical mask.**

*(Evidence level: A)*

**D. A dialysis catheter should only be used for HD or related procedures.**

*(Evidence level: C)*

**Commentary on Guideline VI.3.3**

The difficulties of insertion predispose to infection [119] and infection rates increase when catheter dressing changes and manipulations are performed by inadequately trained staff [120]. *Staphylococcus aureus* is the leading cause of catheter-exit infection and bacteraemia in HD patients. Bacteraemia and tunnel-tract infection are the leading causes of catheter loss [121]. *Staphylococcus aureus* nasal carriage is frequent in HD patients and a surgical mask worn by the patient and the nurse when the catheter is accessed reduces the spread of infectious droplets and reduces contamination of the catheter site [12,103,104,122].

Full barrier precautions during insertion of the central venous catheter (sterile gloves, long sleeved sterile gown, mask, cap, and large sterile sheet drape) reduce the incidence of catheter-related bacteraemia compared with standard (sterile gloves and small drape) precautions: 0.08/1000 and 0.5/1000 catheter days respectively,  $P=0.02$  [123].

Excessive manipulation of central venous catheters increases the risk for catheter-related infection [124].

**C. Excision of the fistula is required in cases of infected thrombi and/or septic emboli.**  
(*Evidence level: C*)

#### **Commentary on Guideline VI.4.1**

Native arteriovenous fistula infections are generally localized and have been shown to respond well to i.v. antibiotic therapy without surgical intervention in most instances [125]. No further studies were found devoted to this subject.

#### **Guideline VI.4.2**

**A. Infected grafts should be treated with appropriate antibiotics given intravenously and continued for 2–4 weeks depending on the presence of bacteraemia and usually needs surgical intervention.**  
(*Evidence level: B*)

#### **Commentary on Guideline VI.4.2**

Several studies have examined the infection rates of prosthetic PTFE haemoaccess grafts in a variety of patient populations. In all studies infection rates are significantly greater than in patients with native vessel fistulae [126]. Infected PTFE grafts frequently require intervention in addition to antibiotic therapy. The infections vary in severity ranging from localized cellulitis to abscess formation and bacteraemia.

Graft salvage techniques can be successful [125–129]. One option for treatment of a localized abscess is incision and drainage. Another possibility includes incision and drainage followed by isolating the infected segment by ligating the graft [130]. Subsequently, the isolated infected segment may be excised and replaced by a new piece of PTFE, thus restoring graft continuity, and a new subcutaneous tunnel should be created. If infection involves the anastomosis, the entire subcutaneous tunnel, or if multiple abscesses are present a complete graft excision is mandatory [130,131].

### **VI.4. Treatment of vascular access infection**

#### **Guideline VI.4.1**

**A. Local infection of a native arteriovenous fistula without fever and without bacteraemia should be treated with appropriate antibiotics for at least 2 weeks.**  
(*Evidence level: C*)

**B. Infection of a native arteriovenous fistula with fever and/or bacteraemia should be treated with appropriate antibiotics given intravenously and continued for at least 4 weeks (longer if metastatic infection is present) and puncture sites should be changed.**  
(*Evidence level: C*)

#### **Guideline VI.4.3**

**A. If a HD patient has an infected non-tunnelled short-term central venous catheter, the catheter should be removed and cultured.**  
(*Evidence level: C*)

**B. Tunnelled permanent catheter-exit infections should be treated with 2 weeks of appropriate antibiotics (4 weeks in cases of bacteraemia).**  
(*Evidence level: C*)

**C. The catheter should be removed if a tunnel-tract infection is present or the patient has evidence of infection for more than 36 h.**  
(*Evidence level: C*)

**D. If the catheter is not removed despite bacteraemia, antibiotic lock therapy after each dialysis session should be considered for 2 weeks in conjunction with parenteral therapy.**

*(Evidence level: B)*

### Commentary on Guideline VI.4.3

It is important to distinguish between catheter skin exit, tunnel-tract infections, and bacteraemia [132]. Skin-exit infection is recognized by the presence of erythema around the exit of the catheter. If erythema is present a culture swab and blood cultures should be taken and the patient started on empirical antibiotic therapy. If blood cultures are negative and the swab culture positive the patient should receive at least 2 weeks of the appropriate antibiotic. If a tunnel-tract infection is present the catheter should be removed. Patients with catheter-related bacteraemia need to be treated aggressively with parenteral antibiotics at the first suspicion of bacteraemia. Catheter-mediated bacteraemia is the major reason for catheter loss and has been associated with a high rate of mortality and morbidity including metastatic infections [133,134].

Despite initial reports of catheter salvage with i.v. antibiotics associated with an antibiotic lock injected in the catheter lumen after each dialysis sessions for 2 weeks [135], in a large trial of patients with catheter-mediated bacteraemia systemic antibiotics alone were able to salvage less than 25% of the catheters and 22% of the bacteraemic patients had complications including osteomyelitis, endocarditis, septic arthritis, and death [121].

### Guideline VI.4.4

**A. All patients with a vascular access-related infection should have two separate cultures of blood samples taken from a peripheral vein, before initiation of antibiotic therapy.**

*(Evidence level: A)*

**B. Methicillin or derivatives should be the first choice in order to avoid development of glycopeptide resistance. Vancomycin is usually recommended in hospitals or countries with an increased incidence of methicillin-resistant staphylococci (MRSA), and in known carriers of MRSA. Additional empirical coverage for Gram-negative bacteriae including *Pseudomonas aeruginosa* with a third or fourth generation cephalosporin should be used in severely ill or immunocompromised patients.**

*(Evidence level: B)*

### Commentary on Guideline VI.4.4

Staphylococci are the most common causes of vascular access-related infections. Although there are no data that support the use of specific empirical therapy for

those infections, vancomycin is usually recommended in those hospitals or countries with an increased incidence of MRSA [132]. Between 25 and 30% of vascular access bacteraemic episodes are due to Gram-negative bacilli [7,11,13]. Therefore, additional empirical coverage for Gram-negative bacteria may be needed for patients with severe sepsis [132]. Initial antimicrobial therapy should be given intravenously. Once the microorganism is isolated and antibiotic susceptibilities are known, appropriate antibiotics should be administered.

## **VI.5 Prevention and management of TB in HD patients**

### **Guideline VI.5.1**

**A. A tuberculin skin test (purified protein derivative of tuberculin; PPD) should be done in all high-risk patients such as immunosuppressed and malnourished patients.**  
(*Evidence level: C*)

**B. TB should not be excluded by a negative PPD.**  
(*Evidence level: B*)

**C. All the dialysis patients with unexplained fever, weight loss, anorexia, hepatomegaly, unexplained pulmonary infiltrates, pleural effusion, ascites, or lymphadenopathy should be vigorously evaluated for an active focus of TB.**  
(*Evidence level: B*)

**D. Prophylaxis of TB in HD patients with a positive PPD is recommended.**  
(*Evidence level: B*)

**E. In patients with a negative PPD test, preventive therapy should be considered if they have been exposed to a patient with clinically active TB.**  
(*Evidence level: C*)

### **Commentary on Guideline VI.5.1**

The varied presentation of TB in dialysis patients with an increased incidence of extrapulmonary disease makes an early diagnosis difficult [28–30,33,34,136].

Among dialysis patients, a positive PPD test was observed in only 40–60% of patients with TB [137,138]. This low sensitivity of the PPD test in patients is probably due to the defective cell-mediated immunity associated with uraemia [59,139–141].

Prophylaxis of TB in patients with a positive PPD was recommended by the Advisory Council for the elimination of TB [142]. A 6-month course of isoniazid (INH) prophylaxis was shown to be beneficial in non-uraemic patients [143]. Monotherapy with rifampicin is also effective. A protocol combining rifampicin and pyrazinamide with a 2-month duration will be implemented by the NIH in the near future [144]. No data are available for prophylaxis in HD patients.

### Guideline VI.5.2

**A. The principles of treatment of TB in the general population apply to dialysis patients but there are no controlled studies with regard to the optimum treatment regimen in HD patients. Modifications of dose are required for most antitubercular drugs in HD.**

*(Evidence level: B)*

#### Commentary on Guideline VI.5.2

Prolonged half time of INH in ESRD is controversial. Some investigators recommend 150–200 mg/day in adults [145] and others recommend full doses [146]. INH is dialysable and 73% of the dose of the drug is removed by 5 h of HD [145]. Therefore, INH should be administered after dialysis. Dialysis patients are at increased risk of developing INH toxicity and a supplementation of 100 mg/day of pyridoxine is recommended in HD patients receiving INH [147].

The metabolism and excretion of rifampicin are not dependent on the kidneys; however, a reduction of the dosage in dialysis patients to half the regular dosage is recommended [148]. Data on dialysability of rifampicin is limited but the drug characteristics suggest that it is not significantly dialysed [149].

Ethambutol is principally excreted by the kidneys [148], and it is also removed by HD. A dosage of 8–10 mg/kg is recommended in HD patients and the dose should be administered after HD [149]. Frequent monitoring of levels is essential to prevent toxicity.

Most authors who have made recommendations concerning the treatment of TB in uraemic patients have ignored the potential therapeutic contribution of pyrazinamide. Of those who considered it possible use some recommended that it should be avoided because of ‘accumulation and arthralgia’ [150], while others recommended administration in reduced dosage (12–20 mg/kg/day) [151]. However, given the pharmacokinetic properties of pyrazinamide the latter dosages are insufficient to reach the required serum concentrations (25 mg/l) for optimal therapeutic effect [152]. Controlled clinical trials have shown that thrice weekly treatment is therapeutically more effective than daily dosage [153] and such an approach reduced the risk of arthralgia [154]. It is, therefore, recommended that HD patients should be treated with 40 or 60 mg/kg of the drug given 24 h before the start of each dialysis session [152].

**B. Screening should be repeated every 3–6 months once on HD depending on the prevalence of HBV infection in the unit.**

*(Evidence level: C)*

### **Commentary on Guideline VI.6.1**

Serological tests for the detection of viral markers include HBs Ag, HBe Ag, anti-HBe, anti-HBc, and anti-HBs. They are mandatory to detect HBV infection and to determine which patients should be vaccinated.

### **Guideline VI.6.2**

**A. Screening for HCV antibodies should be performed in all patients starting HD or transferring from another unit.**

*(Evidence level: A)*

**B. Screening should be repeated at least every 6 months once on HD.**

*(Evidence level: C)*

**C. HCV screening should include an ELISA assay and a confirmatory testing with a more specific assay (RIBA).**

*(Evidence level: B)*

### **Commentary on Guideline VI.6.2**

The tests recommended in the first place are second and third generation ELISA assays. Positive tests should be confirmed by analytic tests such as RIBA (Recombinant ImmunoBlot Assay) [155]. However, if plasma ALT is persistently elevated in patients who are anti-HCV negative, in the absence of another aetiology, testing for HCV RNA should be considered [156]. The detection of HCV RNA by reverse transcriptase–polymerase chain reaction (RT–PCR) has been used as the gold standard to identify HCV infection [157] but there are difficulties in interpreting this test. HCV RNA has been detected in only 52–93% of dialysis patients with anti-HCV [157]. Several possibilities could account for the presence of anti-HCV antibodies in the absence of HCV RNA. Viraemia could be intermittent and the number of copies of HCV RNA may be less than the limit of detection. Antibody to HCV may persist even after the viral RNA has disappeared. On the other hand, only 83% of HCV RNA-positive dialysis patients are positive for anti-HCV antibodies and 2.5–12% of anti-HCV-negative dialysis patients test positive for HCV-RNA [157]. The patient may be in the ‘window’ period between infection and seroconversion. After anti-HCV antibody has persisted for a certain period of time it can disappear despite the persistence of HCV RNA [158].

Routine serological testing for HCV is a useful tool for monitoring the incidence and the prevalence of the infection in a dialysis unit, for monitoring

## **VI.6 Prevention and management of HBV, HCV and HIV in HD patients**

### **Guideline VI.6.1**

**A. Screening for HBV markers should be performed in all patients starting HD or transferring from another unit whether they received anti HBV vaccination or not.**

*(Evidence level: A)*

nosocomial HCV transmission and optimizing patient care [159].

### Guideline VI.6.3

**A. Screening for HIV infection should be done in all patients starting HD or transferring from another unit after getting informed consent. Once on routine HD, screening is not recommended.**

*(Evidence level: C)*

#### Commentary on Guideline VI.6.3

Identification of HIV carriers with end-stage renal disease should be encouraged because of several reasons: appropriate counselling to prevent transmission, to advise on the contraindication for transplantation, anti-retroviral therapy, and prophylaxis against opportunistic infections.

However, if universal precautions are adequately respected the risk of transmission from patient to patient is very low and according with the CDC recommendations, routine screening of HD patients for HIV infection is not necessary [43,160].

### Guideline VI.6.4

**A. Universal precautions for prevention of transmission of blood-borne pathogens in the health care setting should be rigorously respected in all HD units. These include:**

- cleaning and disinfection of instruments, machines and environmental surfaces after each treatment;
- avoidance of sharing articles among patients;
- frequent hand washing and use of disposable gloves;
- use of protective eye wear and face mask.

*(Evidence level: C)*

**B. Dialyzed HBs Ag-positive patients should be treated in separate rooms with dedicated machines.**

*(Evidence level: C)*

**C. In addition to universal precautions, which are the most efficacious preventive measures, treatment of anti-HCV patients in separate areas with dedicated staff is recommended in units with a high prevalence of HCV infection.**

*(Evidence level: C)*

#### Commentary on Guideline VI.6.4

Probably blood transfusions were initially the main source of introduction of the HBV and HCV into dialysis unit. The use of HBs Ag-free blood since 1970 and more recently the systematic screening of blood donors for HCV has led to disappearance or a dramatic decrease in the incidence of post-transfusion hepatitis.

Before the availability of passive and active immunization against HBV, general prophylactic measures were the only means of preventing and controlling HBV infection in dialysis units. They are still the only means of protection against the spread of HCV and HIV [161].

Several observations argue that nosocomial transmission is the principal mode of HCV infection in HD units. Some HD patients with HCV have never received a blood transfusion. The prevalence of HCV-positive patients on HD is greater in patients treated in centres than in patients maintained on home HD and those on peritoneal dialysis [162,163]. Molecular evidence for nosocomial spread of HCV has been offered by virological studies [164,165–170].

Recommendations for the prevention of spread of any type of hepatitis within dialysis centres were given as early as 1968 by the Public Health Laboratory Service [171]. ‘Recommended precautions for patients undergoing HD who have AIDS or non A non B hepatitis’ were published in 1985 by the CDC [172] and updated in 1988 as ‘Universal precautions for prevention of transmission of blood-borne pathogens in health-care setting’ [173].

Strict adherence to the general disinfection measures seems sufficient to prevent transmission of HBV particularly when few patients are HBs Ag-positive in a dialysis unit [174]. Nevertheless, the use of separate rooms and monitors for the dialysis HBs Ag-positive patients was recommended [171,175].

Contamination of hospital environmental surfaces and secondary patient-to-patient transmission are due to poor aseptic techniques and strict enforcement of universal precautions prevents HCV transmission among HD patients [176]. Although universal precautions must be accomplished in an obligatory manner they are not always carried out by the dialysis staff [177].

Whether or not HCV-positive patients should be treated in separate rooms is still debated. Some authors suggest the need for such isolation in order to limit interindividual contamination [178]. Several arguments are not in favour of such segregation. First, a substantial part of uraemic patients with PCR demonstrating HCV-RNA viraemia has a negative serology and are not identified if systematic and repeated PCR is not performed. Secondly, strict enforcement of universal precautions and systematic disinfection of the machines after each treatment has been shown to fully prevent HCV transmission to HD patients [176]. However, in a large prospective multicentre study where the prevalence of HCV infection at baseline was 32.1%, an increased risk for HCV infection was associated with anti-HCV prevalence of 30% or greater and personnel-patient ratio less than 28.2/100 patients [179]. Therefore, in addition to universal precautions, which are the most efficacious preventive measures, treatment of anti-HCV patients in separate areas with dedicated staff is recommended in units with a high prevalence of HCV infection [166].

Isolation of patients with AIDS and asymptomatic carriers of HIV and the use of separate machines are not recommended [173]. In dialysis units that conform to the practice guidelines recommended by the CDC, the risk of patient-to-patient transmission of HIV is very low [160]. The only reported cases of patient-to-patient transmission of HIV have been reported from developing countries where universal precautions were not followed [43,180].

### Guideline VI.6.5

**A. Passive immunization or passive-active immunization against HBV should be applied for post-exposure protection after accidental inoculation in staff as preventive treatment in both health care workers and dialysis patients when unresponsive to vaccination.**  
(*Evidence level: B*)

### Commentary on Guideline VI.6.5

Trials of post-exposure passive immunization with anti-hepatitis B human immunoglobulin (HBIG) preparation showed high, although not absolute, protection after accidental inoculation or projection of HBS-Ag positive material [181–183]. The protective efficacy of combined HBIG and hepatitis B vaccine was shown to be superior to that of HBIG alone [184].

### Guideline VI.6.6

**A. A combination of AZT, lamivudine, and a protease inhibitor should be recommended for HD staff members accidentally exposed to HIV.**  
(*Evidence level: C*)

### Commentary on Guideline VI.6.6

After an accidental occupational HIV exposure, there is a window of opportunity during which anti-retroviral therapy can establish its effects. The duration of this window of opportunity is not known. However, it is presumed that the chance of killing the virus is best if treatment is started within 1 h of exposure [44].

The risk of acquiring infection following an occupational exposure is only 0.32% [185] and there are no published randomized trials of AZT for post-exposure prophylaxis to health care workers exposed to HIV. Nevertheless, the US Public Health Service Guidelines recommend a combination of AZT and lamivudine for most parenteral exposures. The addition of a protease inhibitor is suggested for high-risk exposures (those with high viral loads) [186]. Therefore, exposure due to needle prick should be treated with a triple therapy.

### Guideline VI.6.7

**A. Active immunization against HBV should be undertaken in all HD staff members.**  
(*Evidence level: A*)

**B. Either a 0-, 1-, 6-month or a 0-, 1-, 2- and 12-month vaccination schedule should be used.**  
(*Evidence level: B*)

**C. Monitoring of acquired antibody titre is advisable in these subjects. Additional doses should be administered to staff members who do not develop protective antibody titres (threshold level 10 mIU/ml).**  
(*Evidence level: C*)

### Commentary on Guideline VI.6.7

Members of the HD staff may be infected by accidental needle pricks, contamination of cuts or skin lesions, blood spraying into eyes or mouth, eating, or smoking in the dialysis ward.

Although the pool of chronic HBs Ag carriers among HD patients has decreased, thus reducing the risk of contamination, new patients, especially those arriving in emergency conditions, may introduce HBV in the HD unit with the risk of contamination of staff members.

At present, several recombinant vaccines are available and all have been proven to be immunogenic in healthy subjects with seroconversion obtained in 95% or more of recipients [187,188]. Vaccination protocols in healthy adults differ among countries. Two main schedules are proposed: a 0-, 1-, 6-month or a 0-, 1-, 2- and 12-month schedule [189]. The latter protocol induces comparable anti-HBs titres following primo vaccination but higher titres following the booster injection at 1 year and may be more advantageous in terms of long-term protection [190].

Few, but an unpredictable number of health care workers develop no or low response. Therefore, in highly exposed staff members post-vaccination testing of antibody titres should be considered in order to offer an additional course of vaccination to the low responders and to propose to the still non-responsive subjects to move to less exposed work.

Staff members having isolated anti-HBc and/or low titre anti-HBs antibodies should receive one vaccine dose and if an increase in anti-HBs titre is not observed they should complete another full vaccination course [191].

### Guideline VI.6.8

**A. Patients with progressive chronic renal failure should be vaccinated against HBV preferably before they start on HD.**  
(*Evidence level: B*)

**B. HD patients who have not been previously immunized against HBV should be vaccinated.**

*(Evidence level: A)*

**C. Anti-HBs testing is recommended 1–2 months after the primary series has been completed and 6–12 months thereafter, depending on the local incidence of HBV infection. Additional doses should be administered to patients who do not develop protective antibody titres (threshold level 10 mIU/ml). Subsequent routine testing is recommended every 6 months. A booster dose is recommended if the anti-HBs titre is less than 10 mIU/ml.**

*(Evidence level: C)*

### Commentary on Guideline VI.6.8

All HB vaccines have a significant protective effect against acquiring HBV infection in chronic HD patients [192–196]. However, development of anti-HB antibodies is inhibited by the defective immune response that characterizes the uraemic patient [50,59] and approximately 50–60% of the dialysis patients develop a protective anti-HBs response when the standard protocol recommended for healthy subjects is used either with plasma-derived vaccines or DNA recombinant vaccines [193–191, 196–198].

The importance of vaccination early in the course of renal disease or before dialysis is started has been stressed because it appeared to increase the rate of response [199] but impairment of the response to HB vaccine was shown even at an early stage of chronic renal failure [200]. Nevertheless, early vaccination should give better results than a vaccination performed late in the course of chronic renal failure.

Thus, reinforced protocols were proposed to overcome the deficient response of dialysis patients [201]. Three double doses or four single doses induced a significantly greater proportion of responders and significantly greater anti-HBs titres.

The intradermal (ID) route was used to enhance the seroconversion of dialysis patients to the HB vaccine [202–207]. However, there are no data regarding long-term protection and the ID route is not currently recommended.

Because of the low response to vaccination, the shorter duration of immunity and potential loss of antibodies, regular anti-HBs testing is recommended.

### Guideline VI.6.9

**A. To inhibit HBV replication alpha interferon (IFN $\alpha$ ) and/or lamivudine should be administered to transplant candidates who have biopsy-proven HBV-chronic liver disease.**

*(Evidence level: C)*

### Commentary on Guideline VI.6.9

IFN $\alpha$  is the most effective drug to inhibit viral replication [208]. However, there are few data concerning the administration of IFN to HD patients with chronic hepatitis B [209]. IFN is poorly tolerated in these patients and pharmacokinetic studies demonstrated impaired IFN metabolism with increased bioavailability in HD patients [210,211]. On the other hand, immunodeficiency is known to be a negative predictive factor of the antiviral effect of IFN therapy [209]. The preliminary data available from a small and uncontrolled trial showed that IFN is safe and effective in inducing biochemical remission [212].

Lamivudine is a nucleoside analogue able to inhibit the DNA polymerase activity of the virus [213]. This drug is effective but has severe and frequent neuromuscular side effects. It has been recently given to six dialysis patients, candidates for kidney or combined kidney and liver transplantation and has been shown to be effective in inhibiting HBV replication [214].

Whether IFN or lamivudine might offer the potential of making renal transplantation a feasible option in HD patients with chronic HBV hepatitis remains to be elucidated.

### Guideline VI.6.10

**A. Alpha IFN should be considered for HD patients with biopsy-proven chronic hepatitis due to HCV awaiting renal transplantation.**

*(Evidence level: C)*

### Commentary on Guideline VI.6.10

Alpha IFN has been used with a fair degree of success in patients with chronic hepatitis due to HCV [157]. Among HD patients, the initial response to IFN has been encouraging [215–218]. However, as in the case of non-renal patients, relapses are common after stopping treatment and long-term outcomes are unknown. IFN is poorly tolerated in HD patients with a high drop out rate [215,216,218].

The risk of long-term development of chronic liver disease after renal transplantation has led to propose treating dialysis patients with chronic hepatitis C who are candidates for renal transplantation. The course of IFN treatment should be interrupted at transplantation, but is not a reason to postpone transplantation if a kidney becomes available.

**VI.7 Vaccine recommendations for patients on chronic HD (except HB vaccination)**

**Guideline VI.7.1**

**A. Pneumococcal polysaccharide vaccine may be recommended especially in the elderly HD patients.**

**Revaccination is also recommended 5 years after the previous dose.**

*(Evidence level: C)*

### Commentary on Guideline VI.7.1

More than 75% of the dialysis patients have an adequate response to the vaccine [219–222] but their antibody titres are considerably less than those of healthy vaccinated adults [219,220,223] and decline rapidly [219–221].

The Advisory Committee on Immunization Practice (ACIP) recommended a standard vaccination to all dialysis patients 2 years of age or older and revaccination 3–5 years after the first dose of pneumococcal vaccine [224].

### Guideline VI.7.2

**A. Influenza vaccine is recommended annually before the beginning of the influenza season for HD patients.**

*(Evidence level: B)*

### Commentary on Guideline VI.7.2

In HD patients there is an increased risk of influenza-related mortality [225,226]. Influenza vaccination of HD patients according to current recommendations results in an effective humoral immune response [227,228] but the post-vaccination titre is often less in dialysis patients than in immunocompetent subjects [227–229].

### Guideline VI.7.3

**A. Patient on dialysis should receive the diphtheria and tetanus toxoids as recommended for healthy people.**

*(Evidence level: B)*

### Commentary on Guideline VI.7.3

All inactivated vaccines and toxoids are safe and effective when used in dialysis patients. These patients should receive the same doses and schedules recommended for immunocompetent persons [230,231]. In adults the standard anti-tetanus vaccination produces satisfactory response but a rapid decline in antibody titres sometimes occurs leading to an absence of protection 6 months later [232].

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**VI.7 Vaccine recommendations for patients on chronic HD (except HB vaccination)**

**Guideline VI.7.1**

**A. Pneumococcal polysaccharide vaccine may be recommended especially in the elderly HD patients.**

**Revaccination is also recommended 5 years after the previous dose.**

*(Evidence level: C)*

### Commentary on Guideline VI.7.1

More than 75% of the dialysis patients have an adequate response to the vaccine [219–222] but their antibody titres are considerably less than those of healthy vaccinated adults [219,220,223] and decline rapidly [219–221].

The Advisory Committee on Immunization Practice (ACIP) recommended a standard vaccination to all dialysis patients 2 years of age or older and revaccination 3–5 years after the first dose of pneumococcal vaccine [224].

### Guideline VI.7.2

**A. Influenza vaccine is recommended annually before the beginning of the influenza season for HD patients.**

*(Evidence level: B)*

### Commentary on Guideline VI.7.2

In HD patients there is an increased risk of influenza-related mortality [225,226]. Influenza vaccination of HD patients according to current recommendations results in an effective humoral immune response [227,228] but the post-vaccination titre is often less in dialysis patients than in immunocompetent subjects [227–229].

### Guideline VI.7.3

**A. Patient on dialysis should receive the diphtheria and tetanus toxoids as recommended for healthy people.**

*(Evidence level: B)*

### Commentary on Guideline VI.7.3

All inactivated vaccines and toxoids are safe and effective when used in dialysis patients. These patients should receive the same doses and schedules recommended for immunocompetent persons [230,231]. In adults the standard anti-tetanus vaccination produces satisfactory response but a rapid decline in antibody titres sometimes occurs leading to an absence of protection 6 months later [232].

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