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Chinese Clinical Practice Guideline for the Management of "CKD-PeriDialysis"- the Periods Prior to and in the Early-Stage of Initial Dialysis

Chinese Experts Group of the Guideline for the Management of 'CKD-PeriDialysis'[1], Chinese Non-government Medical Institutions Association

The National Experts Group on Nephrology have developed these guidelines to improve the management of pre-dialysis and initial dialysis patients with chronic kidney disease (CKD) (two periods contiguous with dialysis initiation termed here 'PeriDialysis CKD'). The pre-dialysis period is variable, whereas the initial dialysis period is more fixed at 3 months to 6 months after initiating dialysis. The new concept and characteristics of 'CKD-PeriDialysis' are proposed in the guideline. During the CKD-PeriDialysis period, the incidence rate of complications, mortality and treatment cost significantly increases and the glomerular filtration rate (GFR) rapidly decreases, which requires intensive management. The guideline systematically and comprehensively elaborates the recommendations for indicators to be used in for disease evaluation, timing and mode selection of renal replacement therapy, dialysis adequacy evaluation, and diagnosis and treatment of common PeriDialysis complications. Finally, future research directions of CKD-PeriDialysis are proposed. CKD-PeriDialysis management is a difficult clinical issue in kidney disease, and the development and implementation of these guidelines is important to improve the management of CKD-PeriDialysis patients in China, which could ultimately improve survival rates and quality of life, and reduce the medical burden.

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KEYWORDS: chronic kidney disease; CKD PeriDialysis period; complication; end stage kidney disease; replacement treatment

INTRODUCTION

Epidemiological survey data shows that the global prevalence of chronic kidney disease (CKD) was 9.1%, and the total number of patients was nearly 700 million in 2017.[1] The prevalence of CKD in China was 10.8%, and the total number of patients was approximately 120 million.[2] CKD increases the risk of morbidity and mortality from cardiovascular and cerebrovascular diseases.[3] Some patients ultimately progress to end-stage kidney disease (ESKD), which requires dialysis or kidney transplantation. CKD affects multiple systems and organs, leading to various complications, such as hypertension, anemia, water electrolyte and acid-base balance disorders, and CKD mineral and bone disorder,[4,5] all of which require substantial medical resources. Therefore, CKD is an important public health issue. In the past 30 years, many clinical practice guidelines for CKD have been developed, including early screening and intervention of CKD, diagnosis, and treatment of various comorbidities and/or complications. However, to date, there is still a lack of management practices for pre-dialysis and initial dialysis patients.

Improving the management of predialysis and initial dialysis patients is important to improve the survival and quality of life of patients with CKD. Therefore, we invited Chinese nephrologists to collect information, review the literature, and discuss and develop the "Chinese Clinical Practice Guideline for the management of 'CKD-PeriDialysis'". These guidelines, outlining recommendations for disease diagnosis and treatment, will aid nephrology professionals in the management of "CKD-PeriDialysis."

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SECTION 1 DEFINITION AND CHARACTERISTICS OF CKD-PERIDIALYSIS

I. Definition

CKD-PeriDialysis is defined as the period from when a patient's estimated glomerular filtration rate (eGFR)

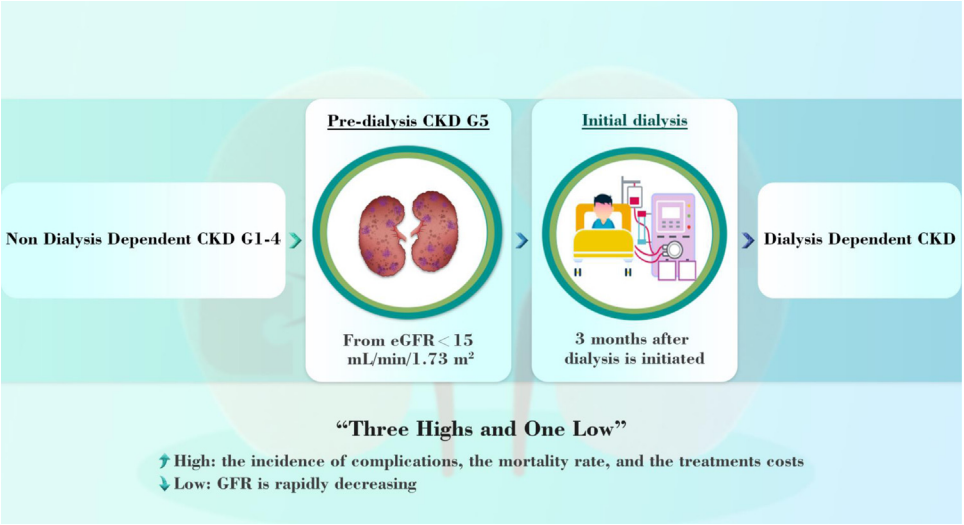

Figure 1. CKD-PeriDialysis. CKD, chronic kidney disease; GFR, glomerular filtration rate.

decreases to less than 15 ml/min per 1.73 m^2 until 3 months after dialysis is initiated. It thus includes 2 stages, namely predialysis and initial dialysis. The total duration of both of these stages can be approximately 1 to 2 years, with the longer period often being the predialysis phase in CKD G5.

II. Characteristics of CKD-PeriDialysis

Majority CKD-PeriDialysis patients currently have the following characteristics (refer to Figure 1):

(i) "three highs and one low" where the incidence of complications, the mortality rate, and the treatments costs are high, and GFR is rapidly decreasing;
(ii) A progressively larger proportion of ESKD patients is elderly, due to the increasing ages of the general and dialysis populations;[4,6-8]
(iii) In the past, the main etiological causes of ESKD in China have been glomerulonephritis, diabetic nephropathy, hypertensive renal damage, etc. More recently, the proportion of ESKD patients with diabetic nephropathy gradually increased from increasing age and population dietary changes;
(iv) The proportion of patients with planned dialysis is low.[7-11]

Due to the above particularities in CKD-PeriDialysis patients, it is necessary to improve individualized management.

SECTION 2 MANAGEMENT OF PREDIALYSIS CKD

Predialysis is a transitional stage for ESKD patients. Most patients may have a series of symptoms, metabolic disorders, and related complications. Comprehensive disease assessment, timely management, and regular monitoring are important in this stage. Also, systematic predialysis patient education and joint decision of renal replacement therapy with patients could facilitate a seamless and safe transition to the dialysis stage.

I. Disease Assessment and Monitoring

1. CKD Progression Assessment

1.1 Assessment Indicators. Urinary albumin-to-creatinine ratio, serum creatinine and cystatin C are widely available. GFR can be estimated using the CKD-EPI formula based on serum creatinine levels. For patients with muscle atrophy or liver dysfunction, GFR should be estimated using the CKD-EPI formula based on serum creatinine and cystatin C levels. The rate of eGFR decline is a direct determinant of the risk for progression to ESKD. An annual decrease in eGFR levels of $\geq$5 ml/min per 1.73 m^2 or macroalbuminuria (urinary albumin-to-creatinine ratio >300 mg/g) indicates rapid progression of CKD.[12,13] In a recent study, large between-individual variation in eGFR slopes (ml/min per 1.73 m^2/year) was noted as follows: $\geq$5 in 41.1%, between 1 and 5 in 29.1%, and <1 in 29.8% of 630 patients.[14]

1.2 Frequency of Assessment. To detect those who progress more rapidly than those who progress more slowly or not at all, it is recommended that all predialysis patients with CKD Stage G5 should be assessed at least once every 2 months.[12,13]

2. Blood Pressure (BP) Assessment

2.1 Assessment Indicators. BP is assesed using office BP measurement, home BP measurement, and ambulatory BP measurement. Home BP measurement and ambulatory BP measurement are supplements to the standardized office BP measurement. Standardized

office BP measurement refers to measurements obtained according to the recommended preparation procedures, which include properly preparing the patient, using the proper technique for BP measurements, taking the proper measurements needed for diagnosis and treatment of elevated BP, properly document the accurate BP readings, averaging the readings, and providing BP reading to patients.[15-19]

2.2 BP Measurement Methods.

2.2.1 Office BP measurement/home BP measurement. Electronic BP measuring instruments are recommended to measure BP. Before the measurement is taken, patients should rest for 3 minutes to 5 minutes and abstain from tea or coffee for 30 minutes. The measurement should be taken at least twice, with an interval of 1 minute to 2 minutes, and individual results should be used to find an average. The patient should be seated, have feet flat on the floor, and refrain from talking.

2.2.2 Ambulatory BP measurement. The patient should wear a BP monitor for a day in which the patient's activities are "usual". BP should be measured every 30 minutes for 24 hours. The arm must be kept still when a BP measurement is being taken, and the time at which the patient goes to sleep and wakes up should be recorded. The instrument will display the mean daytime and night-time BPs for the 24 hours. It is important to assess the "nocturnal dip."

2.2.3 Measuring BP in upper arm ipsilateral to the internal fistula. BP measurements should not be taken from the operated side of the upper arm of the arteriovenous fistula (AVF).[16] It is not recommended to measure BP in the same extremity if the vascular access is in the upper arm or is a graft.

2.3 Frequency of Assessment.

BP should be measured at each visit. A daily average should also be calculated from 2 home BP recordings.

3. Volume Load and Cardiac Function Assessment

3.1 Assessment Indicators.

3.1.1 Clinical assessment. BP, degree of dependent edema, presence of pulmonary moist rales or jugular venous engorgement, and change in weight.[20,21]

3.1.2 Biomarkers. N-terminal pro-B-type natriuretic peptide (NT-proBNP), and troponin.[20-22]

3.1.3 Imaging. Chest X-ray, echocardiography, and bioelectrical impedance analysis.[20,22]

3.2 Assessment Frequency.

3.2.1 Volumes should be assessed at initial diagnosis and monthly in patients without volume overload; total body water and extracellular volume can be measured by bioimpedance, if available.

3.2.2 Troponin detection is recommended for patients with a history of heart failure (HF) on admission for etiological diagnosis (such as acute myocardial infarction) and prognosis evaluation of patients with acute HF.[20-22] BNP and NT-proBNP diagnostic thresholds should be increased according to renal function stage;[23] NT-proBNP has better diagnostic sensitivity and specificity than BNP in patients with different CKD stages.[24]

3.2.3 NT-proBNP should be measured every 2 weeks in patients with unstable disease or HF and who require drug dose adjustment. NT-proBNP should be measured once every 1 month to approximately 2 months in stable patients.[20-22]

4. Assessment of Electrolyte and Acid-Base Balance Disturbances

4.1 Assessment Indicators.

These include blood potassium, sodium, chloride, and HCO_3^- levels. Hyperkalemia is defined as a plasma potassium level of greater than 5.0 mmol/l.[25,26] Hyperkalemia is the most common electrolyte disorder in CKD-PeriDialysis patients. A recent meta-analysis with individual person data found an adverse prognosis even when baseline potassium was only slightly elevated within the normal range. Hyperkalemia at extreme levels (potassium $\geq$6.5 mmol/l) represents a clear clinical urgency that can be life-threatening.[27] Milder hyperkalemia ($\geq$5.5 mmol/l) should prompt a review of contributory factors and be carefully assessed.[28,29] Medications of interest include renin-angiotensin-aldosterone system inhibitor (RAASI), aldosterone antagonists, nonsteroidal anti-inflammatory drugs, trimethoprim containing antibiotics and potassium-sparing diuretics used in the 90 days before presentation. Patient age is a risk factor for hyperkalemia at any threshold, doubling the hyperkalemia incidence rate with each 10-year increase from the age of 40 years. Presence of hyperkalemia is 20 times greater in those with an eGFR $<$30 ml/min per 1.73 m^2 and increased 4 to 5 fold in those who have diabetes, HF, and peripheral arterial disease.[30]

4.2 Assessment Frequency.

4.2.1 The prevalence and severity of metabolic acidosis in patients with CKD progressively rises as GFR falls, especially at the ESKD stage. It is suggested to measure HCO_3^- once every 2 months to approximately 3 months.[28,29]

4.2.2 Regardless of whether the patient uses RAASI or not, blood electrolyte levels should be measured at the first visit and each subsequent visit for patients in the predialysis phase. Electrolytes are typically measured monthly in those who have initiated dialysis. If a RAASI is initiated, potassium should be rechecked after 1 week to 2 weeks.

4.2.3 If hyperkalemia is detected, or gradually increases, all factors that may cause hyperkalemia, including dietary indiscretion or prescription of a RAASI, must be assessed. Once pseudohyperkalemia is

excluded, hyperkalemia should be treated in a timely manner, blood potassium should be rechecked within 24 hours to 48 hours, and the treatment plan should be adjusted according to blood potassium level.

4.2.4 Serum potassium should be measured in patients with diabetic kidney disease (DKD) at least once a month. Patients treated with RAASI may need a higher frequency of testing.

4.2.5 An electrocardiogram is required when hyperkalemia is suspected. Electrocardiography may be not sensitive enough to diagnose hyperkalemia, but treatment may need to be initiated if the electrocardiogram changes, even before the potassium result is available.[28,29]

5. Anemia Assessment

5.1 Assessment Indicators. These include blood cell count, hemoglobin level (Hb), reticulocyte count, and the iron metabolism status, including serum ferritin (SF), serum iron, total iron-binding capacity (a measure of transferrin), and transferrin saturation.[31–33] Transferrin saturation and ferritin can miss functional iron deficiency when an erythropoiesis-stimulating agent (ESA) is administered. Reticulocyte Hb content is a snapshot, and changes in percent hypochromic RBCs are superior to other iron parameters in detecting functional iron deficiency.[34] To identify the causes of CKD anemia, clinicians should measure serum folic acid and vitamin B_{12}, perform a fecal occult blood test, and, if necessary, conduct bone marrow aspiration examination to rule out anemia due to malnutrition, gastrointestinal bleeding, and hematologic diseases.

5.2 Frequency of Assessment. Predialysis patients with CKD G5 should have monthly Hb tests and iron metabolism parameters tested every 2 months. The frequency of assessment may be adjusted in conjunction with the clinical need.[31–33]

6. Blood Glucose Assessment for Diabetic Patients

6.1 Assessment Indicators. These include blood glucose level (fasting plasma glucose, 2-hour plasma glucose); glycosylated hemoglobin, and glycosylated albumin (GA). Continuous glucose monitoring can be used when available.[35–39]

6.2 Assessment Frequency.

6.2.1 Blood glucose. For patients with unstable predialysis blood glucose, fasting blood glucose should be monitored before 3 meals, 2 hours after 3 meals, and at bedtime every day. For patients with stable blood glucose, fasting blood glucose should be monitored once or twice a week[37–39] and 7-point profile blood gulucose measurement (fasting blood glucose before 3 meals, 2 hours after 3 meals and bedtime) should be conducted at least once a month.[37–39]

6.2.2 Glycosylated hemoglobin. Monthly testing of glycosylated hemoglobin is recommended for patients with DKD and every 3 months for patients without DKD.[37–39]

6.2.3 GA: Patients with DKD should be tested for GA every 3 months; patients without DKD should be tested at least annually.[37–39]

7. Assessment of Mineral and Bone Disorders in CKD

7.1 Assessment Indicators.

7.1.1 Biochemical parameters. These include serum calcium, phosphorus, intact parathyroid hormone (iPTH), alkaline phosphatase (ALP), and serum 25 (OH) D level.[40,41] Serum ALP derives from various tissues. High levels of bone specific ALP are strongly associated with short-term mortality in dialysis patients.[42] Longitudinal assessments of bone specific ALP may be useful for treatment monitoring in nondialysis dependent CKD and dialysis-dependent patients.[43] Dynamic bone disease is not always associated with negative outcomes and therefore antiresorptive medications could be used more often. However, there is no proof of benefit and the absence of good data on "harm" does not mean there is no harm.[44]

7.1.2 Bone disease assessment indicators include bone mineral density, bone biopsy, bone collagen metabolic turnover markers.[40,41]

7.1.3 Vascular calcification indicators include coronary artery calcification, heart valve calcification, abdominal aortic calcification, etc.[40,41]

7.2 Frequency of Assessment. Refer to Table 1.

8. Nutritional Status Assessment

8.1 Assessment Indicators[45-48].

8.1.1 Energy intake and anthropometric measurements. These include body mass index, triceps skinfold thickness, upper arm muscle circumference, dietary intake, and handgrip strength.

8.1.2 Biochemical parameters include serum albumin, transferrin, prealbumin, and serum cholesterol.

8.1.3 Subjective comprehensive nutritional assessment: refer to Table 2.

Table 1. Frequency of assessment of mineral metabolism and vascular calcification in CKD-PeriDialysis patients

Item	Assessment frequency
Calcium	1/1–3 mo
Phosphorus	1/1–3 mo
iPTH	1/3–6 mo
ALP[a]	1/12 mo[b]
25 (OH) D	According to the baseline level and the decision for intervention
Vascular calcification	1/6–12 mo

ALP, alkaline phosphatase; iPTH, intact parathyroid hormone; 25 (OH) D, serum 25 hydroxyviyamin D.
[a]If available and hepatic disease present, bone-specific ALP is recommended.
[b]If iPTH levels are elevated, testing every 6 months is recommended.

Table 2. Subjective comprehensive nutritional assessment scale

Item	Grade A (well nourished)	Grade B (mild-to-moderate malnutrition)	Grade C (severe malnutrition)
Recent weight change	None/Increased	Less than 5% reduction	More than 5% reduction
Diet change	None	Decrease	No food/low energy liquid diet
Gastrointestinal symptoms	None/decreased appetite	Mild nausea, vomiting	Severe nausea, vomiting
Change in mobility	None/decreased	Ambulatory	Bedridden
Stress response	None/low	Moderate	Height
Muscle wasting	None	Mild	Severe
Triceps skinfold thickness (mm)	Normal (> −8)	Mild decrease (6.5–8)	Severe decrease (<6.5)
Ankle edema	None	Mild	Severe

2.2 Assessment Frequency. Should be assessed every 2 months.[45–48]

II. Patient Education

Patients with CKD face a higher risk for kidney failure, cardiovascular disease, and mortality than patients without CKD, but individual risks vary.[3] Patient education is widely recognized as a necessary component to CKD care, because evidence exists that CKD education increases patient knowledge, self-management, and activation across the stages of CKD.[49] Unfortunately, Chu *et al*.[50] suggest that serious deficits remain in patient awareness of CKD, including those with the highest risk for progressing to kidney failure. Approximately half of the The National Health and Nutrition Examination Survey (NHANES) participants with moderate or high risk for progression to kidney failure were unaware of their kidney disease and the degree of CKD awareness had remained unchanged for 18 years. Reasons for the dismal state range from limited knowledge about health care providers' limited knowledge of current guidelines, and fear of inciting unwarranted stress in patients with low-risk CKD. Provider and system level factors also occur, including limited incentives for education, challenges in explaining CKD and CKD risk, and poor access to decision support tools. On an individual patient level, interactive teaching sessions, integrated goal setting, multidisciplinary group approaches, the inclusion of family and caregivers, use of digital media, and frequent scheduled sessions may be particularly effective. Education of CKD requires educational interventions not only at the individual and community level but also at the provider level. Education and CKD awareness may be most efficiently focused on patients at high risk of developing kidney failure, benefits in recognizing CKD exist even among those at low risk of CKD because those with CKD are at risk of adverse drug events due to the high proportion of drugs cleared by the kidney.

A recent study of 175 patients receiving hemodialysis has shown a wide variation on patient activation measure scores. The patient activation measure assesses an individual's knowledge, ability, skills, and confidence in self-managing chronic conditions. Of the patients, 68% were categorized into levels indicative of suboptimal levels of patient activation. Patient activation measure scores were not significantly associated with adherence to dialysis treatments (interdialytic weight gain or number of missed dialysis treatments) but rather to depression and anxiety about their treatments.[51] Integration of patient activation measure into dialysis care,[52] changes in the training of the health care team, as well as changes in the delivery care models so that we move toward a more active role for patients in their care, is recommended.

It is necessary to establish good communication and follow-up with predialysis CKD patients and their families. Education should begin at CKD G4, eGFR <30 ml/min per 1.73 m^2. They should be educated about the following:

(i) Renal structure and function, main clinical manifestations of CKD and prevention and treatment, as well as indicators of kidney function.
(ii) The mode of selection of renal replacement therapy, including the principles, indications, contraindications, operating methods, and precautions of renal transplantation, peritoneal dialysis (PD), and home or in-center hemodialysis. The patient's family and nursing staff should also be educated on the treatment options for renal failure; [53–55]
(iii) Diet, lifestyle, and upper limb vascular protection for CKD patients[56] and avoidance of catheters at the start of dialysis.[57] Caregiver involvement in vascular access planning may be essential.[58]
(iv) Patients should be followed up every 1 month to 2 months to detect relevant indicators.

SECTION 3 PREPARE FOR DIALYSIS

I. Dialysis Mode and Timing

1. Dialysis Indications and Timing

1.1 For patients who choose dialysis treatment, the timing of dialysis initiation is mainly based on uremic signs and symptoms, including electrolyte acid-base metabolism disorders, which are difficult to control; volume overload; HF; metabolic encephalopathy; or

protein energy wasting (PEW), etc. This is preferable to making decisions based on serum creatinine levels or eGFR.[53-55] Early dialysis has not reduced costs or mortality.[59] The most common symptoms of advanced CKD are pain, fatigue, sleep disturbance, itching, nausea and vomiting, cognitive impairment, anxiety, and depression. Patients describe symptoms as having a deleterious effect on their quality of life, suggesting that symptom alleviation may meaningfully improve patient-reported outcomes.[60] Though improving mortality remains the primary goal of kidney replacement therapy, there is an urgent need to focus on improving symptom management in order to improve quality of life in advanced CKD.

1.2 The presence of one or more of the following uremic clinical manifestations is an indication to initiate emergency dialysis treatment:[53-55]

1.2.1 Signs and symptoms, including neurological signs and symptoms caused by uremia, pericarditis, anorexia, refractory acid-base imbalance or electrolyte imbalance, unexplained weight loss, refractory itching, and bleeding;

1.2.2 Volume overload or hypertension not controlled by medication. Achieving euvolemia is one of the major challenges when treating advanced CKD/ESKD patients.

1.2.3 Progressive malnutrition refractory to intervention.

1.3 For uremic signs and symptoms (anorexia, nausea/vomiting, pruritus, sleepiness, difficulty concentrating, fatigue, poor energy, and pain), attention should be paid to rule out other reversible causes that can manifest similar clinical findings, and these reversible factors need to be corrected before deciding to start dialysis.

1.4 The timing of dialysis initiation should not be based on eGFR alone. However, close monitoring is required when eGFR is $<$15 ml/min per 1.73 m^2. The patient's clinical complications should be taken into consideration when deciding to start dialysis. The likelihood of receiving dialysis at eGFR levels of 10 to 24 ml/min per 1.73 m^2 generally increases over time. In one USA health care system in northern California, among patients with an eGFR of 10 to 13 ml/min per 1.73 m^2, the 1-year odds of initiating dialysis increased by 5.3% compared to higher eGFR values.[61]

The level of eGFR at which long term dialysis was started during the past 2 decades internationally has been influenced by a variety of system-level, physician-level,and patient-level factors.[62] On a national level, perspectives from opinion leaders[63] combined with high-profile, consensus based national clinical practice guidelines, such as the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF KDOQI) and the Kidney Disease: Improving Global Outcomes (KDIGO), initially a "healthy/timely" dialysis start,[64] included efforts to promote the placement of AVFs at higher eGFR levels. The latter may have promoted accepting dialysis at relatively higher eGFR levels. However, after the publication of the Initiating Dialysis Early and Late (IDEAL) study,[64] which found no systematic clinical benefit for initiation of earlier versus later dialysis, there was an immediate decrease in the eGFR at the initiation of dialysis to values, typically $<$10 ml/min per 1.73 m^2 in a country such as Canada.[65]

The current standard of care is that when eGFR is between 5 and 10 ml/min per 1.73 m^2, patients can start dialysis treatment, and when GFR decreases to $<$5ml/min per 1.73 m^2, dialysis treatment must be initiated.[66,67]

2. Dialysis Mode Selection

2.1 A patient-centric approach should be taken when selecting the mode of dialysis. Clinicians should fully assess the patient's disease status, consider their wishes, and select dialysis mode in combination with local medical resources and accessibility, health insurance reimbursement policies, and available facilities.[53-55] Given the perceived limited role in the choice of dialysis treatment, themes most often reported by patients as important include remaining as independent as possible, maximizing quality and quantity of life, and flexibility in daily schedule. In a questionnaire of 180 USA patients with advanced CKD making a modality choice, almost half the hemodialysis patients believed that the decision for hemodialysis had largely not been their choice; this lack of choice was only reported by 3% of PD patients.[68] In general, there is the need for interventions to improve shared decision making on dialysis treatment options, targeting both patients and clinicians.

2.2 Selection of Dialysis Mode. Most patients with ESKD are candidates for both hemodialysis and PD. Once modality has been initiated, few differences exist although the risk for 30-day readmission is higher for patients on home-based PD compared to in-center hemodialysis therapy.[69] Interventions to improve transitions in care between the inpatient and outpatient settings are needed, particularly for patients on PD therapy.

2.2.1 Contraindications for hemodialysis include inability to establish vascular access or unstable cardiovascular function.

2.2.2 Contraindications for PD include peritoneal cavity occlusion and loss of peritoneal function caused by various aetiologies. Anuria is not a contraindication for PD.

II. Plan to Establish Vascular Access in Patients who Choose Hemodialysis Without Contraindications to This Modality

1. Vascular Protection of Upper Limbs

1.1 Patients should be educated at the time of diagnosis of CKD G3 about upper limb vascular protection, including the following: (i) hospitalized patients wear a medical warning bracelet; (ii) unnecessary upper limb venipuncture infusion or blood tests should be avoided. Indwelling trocars in the upper limb vein, subclavian vein, or peripherally inserted central catheter, etc. should be avoided. If upper limb venipuncture is required, the dorsal veins of the hand can be considered; (iii) perform hand and/or arm exercises for patients with poor vascular conditions before and after AVF is created; (iv) give appropriate treatment as soon as possible for patients with upper limb skin lesions.[56,70]

2. Timing of Vascular Access Establishment

2.1 If the patient chooses hemodialysis as the mode of renal replacement therapy, maintenance hemodialysis treatment should be started within 6 months. The clinician should evaluate the patient and establish the autogenous AVF as the first choice. Preoperative ultrasound vein mapping should be performed in all patients before placement of AVF, which provides a noninvasive and objective morphological and functional assessment of the peripheral arterial and venous systems used for fistula creation.[71,72] Arteriovenous grafts (AVGs) can be established 3 weeks to 6 weeks before dialysis initiation if required by the patient. Obtaining vascular access for a self-sealing ready-to-use vascular graft can wait until up to a few hours or days before dialysis is required. Patients who have significant uremic symptoms that are difficult to control with conservative treatment should undergo AVF or AVG surgery as early as possible.[56]

2.2 AVFs require maturation in some patients and interventions for both AVFs and AVGs are relatively common. Once successfully matured, AVFs have fewer maintenance interventional requirements.[73] It should be noted that initial catheter dependence in the USA[74] and Europe is not uncommon, particularly in the elderly. In many western nations, more than 60% of patients start with a catheter because of late referral and urgency for dialysis. In USA, creation of an AVF versus AVG was associated with greater catheter dependence at 3 months (82.8% vs. 41.2%), but lower catheter dependence at 12 months (14.2% vs. 15.8%) and at 36 months (8.2% vs. 15.0%).[74] In Mexico, in 78 consecutive younger patients (average age 36 years), 19 AVFs (23.2%) failed to mature, and additional 15.9% had cannulation failure. AVF 1-year and 3-year survival was 67.8% and 63.5%, respectively after interventions. Therefore, it is imperative that vascular access planning and construction is started much earlier than currently being done.

III. Planned Implantation of Abdominal Catheter in Patients who Choose PD

1. Timing

The abdominal catheter is usually implanted 2 weeks before PD is initiated. If PD needs to be initiated urgently, the abdominal tube can be implanted 24 hours to 48 hours before PD is initiated.[75] However, dwell volumes should be reduced to prevent leakage and healing and/or sealing of the tunnel.

2. Methods

The 3 methods for implanting an abdominal peritoneal catheter include direct vision surgical incision, laparoscopic, and percutaneous "blind" catheterization. Currently, most PD centers in China use direct vision surgical incision or percutaneous catheterization. Laparoscopic catheterization is mostly used in patients with a previous history of abdominal surgery or prior catheter floating.[75]

SECTION 4 INITIAL DIALYSIS MANAGEMENT

I. Initial Hemodialysis Management

1. Predialysis Infection and Bleeding and Coagulation Assessment

1.1 Indicators of infection. Test patients for serological indicators of hepatitis B and C virus, HIV, and syphilis before initial dialysis or when referred to a new dialysis center, to determine the dialysis treatment area and arrange for a slot on a hemodialysis machine.[76]

1.2 Bleeding and coagulation parameters include platelets, prothrombin time, partial thromboplastin time, and antithrombin activity. Appropriate anticoagulants should be selected for dialysis based upon the test result of these parameters.[76]

2. Initiation of Dialysis

2.1 Planned Initiation of Hemodialysis. The mode of dialysis should be selected and vascular access should be obtained before the patient needs to initiate dialysis. This is called planned initiation of hemodialysis. The goal is to reduce catheter use at initiation with its known complications.

Unplanned initiation of dialysis is when dialysis needs to be initiated and vascular access has not yet been obtained and the patient needs to be hospitalized, or if the selected mode of dialysis is not possible for the patient.

In clinical practice, it is suggested that >70% of patients should initiate dialysis on a planned basis (the current rate in China is 40%–50%). Worldwide, about

50% to 80% of patients begin with a catheter because planning does not begin early enough, even among the elderly patients. The European Renal Best Practice Guidelines suggest that prediction equations work well to differentiate risk of end-stage renal disease versus death among older patients with low eGFR. The kidney failure risk equation and mortality risk equation for kidney disease can guide decision making and permit more timely preparation for renal replacement therapy.[77]

2.2 Emergency initiation of hemodialysis. Hemodialysis which is initiated immediately in patients with life-threatening conditions is called emergency initiation of hemodialysis. It is required when uremic patients have severe hyperkalemia, hypertension, or HF (usually due to volume excess) that is difficult to control with drugs.

3. Hemodialysis Mode Selection

Among incident hemodialysis patients with substantial residual kidney function, incremental hemodialysis is a safe treatment regimen and is associated with greater preservation of residual kidney function. Those with the lowest residual function must be started with a full regimen because their mortality risk is higher during the first year of dialysis.[78]

3.1 Conventional Hemodialysis. Patients with a residual renal function of eGFR $\geq$ 5ml/min per 1.73 m^2, daily urine volume of $\geq$600 ml and who are generally in good condition can undergo dialysis 2 to 3 times a week for 4 hours each. However, residual renal function needs to be monitored every month and the frequency of dialysis should be gradually increased if renal function progressively decreases. For patients with an eGFR $<$5 ml/min per 1.73 m^2, hemodialysis should be performed 3 times a week for 4 hours each.

3.2 Short-duration "daily" hemodialysis is recommended for 6 times a week for 2.0 to 2.5 hours each.

3.3 Prolonged hemodialysis is rcommended for 6 to 8 hours 3 times a week [extended hours hemodialysis].

3.4 The frequency or duration of dialysis should be increased in patients who gain an excessive amount of interdialytic weight (body weight $>$5%), are struggling to maintain a dry weight, have poor BP control or frequent intradialytic hypotension, have difficulty achieving small molecule adequacy, have severe refractory hyperphosphatemia, or have severe, metabolic acidosis, and/or hyperkalemia. Additional indications for intensification of dialysis include the presence of barriers to maintaining employment or pursuing educational opportunities.

3.5 Low-flux and High-flux Dialysis. Dialysis membrane materials with good biocompatibility should be used for both high-flux and low-flux intermittent hemodialysis treatment. High-flux dialysis increases middle molecule toxin removal, but it does not improve survival in maintenance hemodialysis patients relative to low-flux hemodialysis. Whether hemodiafiltration improves outcomes is currently unclear.[79] In the only randomized clinical trial (RCT) showing a clear survival benefit of hemodiafiltration, study groups were not well balanced, because hemodiafiltration patients were younger and had a lower Charlson Comorbidity Index and less often a central venous catheter.[80] Two large ongoing RCTs comparing high-flux hemodialysis with post dilution high-volume hemodiafiltration should clarify whether hemodiafiltration is indeed associated with lower mortality and has a beneficial effect on quality of life.[80,81] Each dialysis center can choose low-flux or high-flux dialysis by weighing the potential benefit of reducing cardiovascular death against treatment cost and accessibility.

4. Initial Hemodialysis Prescription

During the initial 3 to 5 hemodialysis sessions, patients are prone to disequilibrium syndrome. Although maintenance hemodialysis has been a routine procedure for over 60 years, this syndrome remains poorly understood. Evidence points to increased brain water content after the dialysis procedure, indicating that water had moved down an osmotic gradient into the brain. Measures to avoid its development are crucial. Using standard hemodialysis, the approach widely recommended is to slowly lower the blood urea concentration which requires a gradual increase in dialysis dose, known as induced dialysis.[53–55] Alternatively, modern hemodialysis machines allow for sodium modeling so that the sodium concentration osmolality can be kept more constant during the treatment.

4.1 Dialysis Time. The duration of the initial dialysis session should not exceed 2.5 hours. Proceeding sessions can be gradually lengthened until the conventional dialysis duration is reached.

4.2 Blood Flow Rate. The blood flow rate of the first hemodialysis should be low (within the range of 150–200 ml/min). During proceeding sessions, the blood flow rate should be gradually increased to 4 times the patient's body weight. Blood flow at higher blood flows (400 ml/min), commonly used in the United States, that deliver a higher dose of dialysis (urea clearance index [Kt/V] from about 1.31–1.72 as in the Hemodialysis Study) have not improved outcomes.[82] However, extending time to 7 hours 3 times weekly at lower dialyzer blood flow has been shown to associate with better survival among European patients treated with hemodialysis.[83]

4.3 Dialyzer Membrane Area. A small dialyzer area (1.3 m^2–1.5 m^2) can be used for initial dialysis to reduce the risk of disequilibrium syndrome. A larger dialyzer

area is recommended for maintenance dialysis to ensure dialysis adequacy.

4.4 Dialysate flow rate is usually set at 500 ml/min in China. In general, a ratio of 2:1 of dialysate to blood flow provides adequate Kt/V at optimal cost. If severe disequilibrium syndrome occurs during initial dialysis, dialysate flow rate can be reduced.

4.5 Dialysate Composition. For routine dialysis, the dialysate Na^+, K^+ and Ca^{2+} concentrations can be individualized according to the patient's predialysis volume load; BP control; and blood sodium, potassium and calcium levels. Potassium dialysate concentrations less than 2 mmmol/l should be avoided.

4.6 Dialysate temperature should be set at 36.5 °C, but can be individualized to suit the patient's needs. Lower dialysate temperature reduces intradialytic hypotension but is uncomfortable for the patient.

4.7 Determination of Ultrafiltration (UF) Volume and UF Rate. The UF volume and rate should be set according to the patient's volume status, cardiopulmonary function, urine volume, and BP. The dry weight should be gradually achieved in 1 month to 3 months. If there is no volume overload or severe hypertension initially, the UF volume should not be set. However, if there is volume overload and severe hypertension, the UF volume for each dialysis should be <4% of the patient's body weight and UF rate should be <0.15 ml/kg/min. If the patient has severe peripheral edema, acute pulmonary edema, etc., then the UF volume and rate need to be increased, but with careful attention for the occurrence of intradialytic hypotension. Currently, the recommendation in US patients is to not exceed an UF rate of <13 ml/kg/h.[84] Higher UF rates during a hemodialysis session are known to be associated with a higher propensity to intradialytic hypotension, sudden cardiac arrest, and mortality.

4.8 Dialysis Frequency. To avoid disequilibrium syndrome during induced dialysis, the weekly dialysis frequency should be increased appropriately. Initial dialysis can be received 3 to 5 times in the first week, and then gradually transitioned to 2 to 3 times a week depending on the patient's response to treatment, residual renal function, and body volume status, etc.

4.9 Anticoagulant Selection. The main agents used in clinical practice for anticoagulation during hemodialysis are unfractionated heparin (UF heparin) and low-molecular weight heparin. Heparin-induced thrombocytopaenia type II, occurs less frequently with low-molecular weight heparin than UF heparin. low-molecular weight heparin has a number of potential advantages, apart from cost. A wide array of newer anticoagulants are becoming progressively available, each with unique advantages and disadvantages. In maintenance hemodialysis patients with an increased risk of bleeding, a "no heparin" dialysis may be undertaken, or regional anticoagulation considered.[85]

4.9.1 Unfractionated heparin should be given as an anticoagulant in patients who are not at clinical risk of bleeding disorders, have no significant lipid metabolism disorders or abnormal bone metabolism, and have plasma antithrombin activity III above 50% and normal or mildly elevated platelet count, prothrombin time, and partial thromboplastin time values.[76]

4.9.2 Low-molecular weight heparin is recommended as an anticoagulant for patients with an antithrombin activity of more than 50%, a near-normal platelet count, severe abnormal fat metabolism and bone metabolism, prolonged partial thromboplastin time and prothrombin time, and potential bleeding risk, but who do not have any clinical bleeding disorders.[76]

4.9.3 For patients with clinically significant bleeding disorders, significant bleeding tendency, or significantly prolonged plasma partial thromboplastin time and prothrombin time, sodium citrate is recommended as the anticoagulant, or dialysis without anticoagulant is recommended.[76]

4.9.4 For patients who are at greater risk of cardiovascular disease due to other primary diseases such as diabetic nephropathy and hypertensive renal impairment, but who have normal or elevated platelet count and normal or hyperactive platelet function, daily administration of antiplatelet drugs is recommended as the basic treatment.[76]

5. Dialysis Adequacy Assessment

Dialysis adequacy is clinically defined as a state in which the patient achieves and maintains a good clinical state throughout dialysis treatment. Dialysis adequacy is also quantitated as the clearance of small solutes by dialysis and is often represented by urea and measured using the Kt/V, which includes the single-pool Kt/V, the equilibrium Kt/V, and the weekly standard Kt/V and urea reduction ratio.[53-55,76]

5.1 Clinical Evaluation. In principle, patients should be in a state of volume balance; acid-base, electrolyte, and calcium-phosphorus metabolism should be within acceptable ranges. Nutritional and anthropomorphic measurements should be acceptable.

5.1.1 Symptoms of uremic toxin accumulation. Symptoms such as nausea, vomiting, insomnia, and restless legs syndrome imply that dialysis adequacy is inadequate.

5.1.2 Clinical manifestations or biochemical abnormalities caused by water and sodium retention include hypertension, weight change, edema, HF. If these are present, bioelectrical impedance analysis may be performed in medical facilities, if available. Bioimpedance spectroscopy alongside total body water measurement can be used as a guide for volume management,[86] but this methodology has had limited efficacy in improving clinical outcomes.[87]

5.2 Hemodialysis Adequacy Indicators. Urea clearance rate represents the clearance level of small solutes. The commonly used indicators are single-pool Kt/V and urea reduction ratio and the clearance of medium and large molecular toxins are indexed by β2-microglobulin. Though the effective clearance of uremic toxins helps to improve the quality of life and prognosis of patients, the Kt/V value is not predictive of the survival rate of patients once it reaches a minimum value of 1.2. It is recommended that single-pool Kt/V $\geq$1.2 and urea reduction ratio $\geq$65% be achieved in hemodialysis. Ideally, values of single-pool Kt/V $\geq$1.4 and urea reduction ratio $\geq$70% will be achieved. Clinicians can include β2-microglobulin in the quality control and management of daily hemodialysis. In hemodialysis patients, β2-microglobulin should be reduced by at least $\geq$30% and ideally by $\geq$50% and patients should have a membrane clearance rate of $>$20 ml/min. During the initial dialysis phase, individualized goals should be set for the above parameters based on patient status.[3,53-55,76]

It should be recognized that the urea clearance provided by current dialysis methods is on many occasions approaching theoretical limits with the blood flows and membranes areas available, particularly in larger patients. In these longer treatment times of more frequent treatment may become necessary. Currently, many investigators are studying other solutes which are less effectively cleared than urea by dialysis but likely contribute more to the residual uremic illness suffered by hemodialysis patients. Work is in progress on various methods which could be employed to increase the clearance of such nonurea solutes. Future clinical studies will be required to assess the extent to which increasing solute clearances of these "middle molecules" or "uremic toxins" improves patients' health.

6. Hemodialysis Prescription Adjustment

6.1 Adjustment of the Mode of Dialysis to Increase Sodium Exclusion in the Body. Sequential dialysis is recommended for patients who struggle to control sodium levels through reducing dietary salt, who have a higher serum sodium concentration before dialysis, or who are thirsty after dialysis. When blood sodium concentration is high (during dialysis), UF can significantly increase sodium exclusion, with a better effect on BP control. [76] However, 1 study has reported that routine use of sodium profiling to prevent intradialytic hypotension is associated with higher all-cause and cardiovascular mortality[88] and should be used with caution.

6.2 Individualizing dialysate sodium concentration helps to maintain the patient's sodium balance. For patients with normal or elevated predialysis serum sodium levels, the dialysate sodium concentration can be gradually tapered by measuring the patient's serum sodium concentration before 3 dialysis sessions and multiplying the average of the 3 sessions by 95% to get an individualized dialysate sodium concentration standard.[76]

6.3 Prolonging the duration of dialysis, increasing the dialysis frequency, using hypothermic dialysis (dialysate temperature $\sim$35.5° C) or adjustable sodium dialysis or a UF curve are solutions for patients who cannot effectively control interdialytic weight gain using the above methods. If necessary, slow continuous UF therapy can also be used to remove the excess sodium and water in the patient's body as much as possible to achieve dry weight. These treatment options are also suitable for patients who have complications such as cardiac insufficiency or insufficient RAAS/sympathetic reactivity, or who cannot control their dry weight during dialysis due to hypotension.[76]

II. Initial PD Management

Approximately 11% of people with kidney failure worldwide are treated with PD. Data published in the second Global Kidney Health Atlas commissioned by the International Society of Nephrology (ISN) revealed extraordinary disparities in the provision of kidney replacement therapy (by various modalities). A study of international practice of PD in 160 countries showed that 30 countries did not provide PD at all, particularly in Africa and lower-income countries. Average exchange volumes were inadequate (defined as $<$ 3–4 exchanges/day or equivalent on automated PD) in 28% of countries. Most countries did not measure patient-reported PD outcomes.[89]

1. Evaluation

The condition of the abdomen, including previous abdominal surgeries, hernias, or digestive system diseases, needs to be evaluated for PD patients.[90-92]

It is crucial to maintain good nutrition that maintains serum albumin.[93] The hazard ratio for mortality progressively increases with lower serum albumin. Trends in the change of serum albumin are important as well. Compared with those in whom serum albumin remained level over 6 months, those patients in whom serum albumin increased by approximately 0.3 g/dl

during that period experienced lower all-cause, cardiovascular, and infection-related mortality. Conversely, those in whom serum albumin decreased by >0.2 g/dl experienced higher mortality. These findings were confirmed over a 5-year follow-up period.[94]

2. Mode of PD

Different modes of dialysis are selected according to the patient's peritoneal transport characteristics, urea Kt/V and creatinine clearance, nutritional status, and residual renal function.

2.1 Continuous Ambulatory PD (CAPD). Currently CAPD is used in most PD patients and is the most commonly used model in China.

2.2 Automated PD (APD). APD has the advantage of reducing the risk of complications related to increased intra-abdominal pressure. It is also associated with a low incidence of peritonitis and better quality of life, therefore, its use in ESKD has gradually increased in China. APD is divided into 4 modes as follows: (i) intermittent PD, (ii) continuous cyclic PD (CCPD), (iii) nocturnal intermittent PD, and (iv) tidal PD. Each mode has its applicable population.

3. Peritoneal Dialysate

Peritoneal dialysate should be used with a neutral pH. Low glucose degradation products can be used as a possible measure to protect residual renal function and peritoneal function. For PD patients with insufficient peritoneal UF and difficulty in maintaining a normal volume, icodextrin peritoneal dialysate can be used once daily for prolonged dwell.

4. Initial PD Prescription

4.1 Clinical Status. The dialysis mode (CAPD or APD) is determined after a comprehensive assessment of the patient's characteristics and integration of the patient's wishes and lifestyle. The dialysate glucose concentration should be determined according to the patient's volume status. The initial dialysis dose should be determined according to the patient's residual renal function. Dialysis should be started with 1.5% glucose peritoneal dialysate and then gradually increased depending on the residual renal function. However, after the initial decision for prescription of dialysis is made, patients should be closely observed for changes in PD UF volume and volume status. If volume overload cannot be corrected by other methods, the glucose concentration in the peritoneal dialysate should be increased appropriately. The dialysis dose includes the total 24-hour volume of dialysate and the volume per exchange. Currently, most CAPD dialysis doses are 6 to 10 liters per day. CAPD exchanges approximately 2 liters depending on the specification of the dialysate.[90-92]

4.2 Body Surface Area and Residual Renal Function.

4.2.1 Body surface area. In general, patients with a large body surface area require large dialysis doses.[91]

4.2.2 Residual renal function. Residual kidney function should be determined for all individuals doing PD. High-quality PD prescription should aim to achieve and maintain clinical euvolaemia, taking residual kidney function and its preservation into account. Patients with good residual renal function may consider starting dialysis with a lower dialysis dose or appropriately shortening the dialysate dwell time. It is imperative to improve the monitoring of residual renal function and adjust the dialysis prescription during follow-up.[91]

5. Adjustment of PD Prescription

5.1 Dialysis Adequacy. Clinicians should be encouraged to alter the prescribed dialysis dose individualy in response to the patient's clinical symptoms, residual renal function, laboratory parameters, solute clearance, volume, nutritional status, and treatment goals. The small solute clearance evaluation indicators (Kt/V and creatinine clearance rate) should be evaluated when the patient is in a stable clinical state. Total Kt/V of residual and dialytic guide the adequacy on PD. The first evaluation should take place 1 month after dialysis is initiated, and then every 3 months to approximately 6 months following that.

Patients with peritonitis must be evaluated 4 weeks after the condition is resolved. Maintaining fluid balance is essential for improving patient outcomes. Volume load, uremic symptoms, and malnutrition must be monitored if targets are not met, and appropriate adjustment of the PD prescription should be considered.[91,95]

5.2 Modification of PD Prescription.

5.2.1 Peritoneal transport characteristics should be evaluated periodically. Peritoneal equilibration tests (PETs) are used to evaluate the peritoneal transport characteristics. There are 2 methods for conducting PETs, namely the standard method and the modified method. The latter uses 4.25% (instead of 2.5%) glucose peritoneal dialysate to evaluate the peritoneal UF function. PETs should be performed 2 weeks to 4 weeks after the start of dialysis to measure the patient's baseline value, and then PETs should be repeated every 6 months. If changes in peritoneal function are clinically suspected, PETs should be conducted as soon as possible. Patients with peritonitis should have PETs 1 month after the inflammation is controlled.[91]

5.2.2 Dialysis prescription adjustment based on peritoneal transport characteristics. For patients with

high transport capacity, the dwell time of dialysate should be shortened, or APD can be adopted. Either CAPD or APD is suitable for patients with average transport capacity. The dialysis dose should be increased for patients with low transport capacity, or alternatively, a larger dose of ADP therapy can be given. Dynamic observations of PETs help to adjust the dialysis prescription in a timely manner and achieve dialysis adequacy.[91]

5.2.3 For patients with uremic symptoms, the PD dose should be increased even when the minimum clearance goal is achieved.

5.2.4 The anuric patients may not achieve an adequate standardized Kt/V with PD. An intermittent regimen, a 24-hour PD mode should be the first choice for these patients.

5.2.5 Assessment of volume status. The goal should be that the patient achieves a normal weight and volume status during dialysis, without volume-dependent hypertension, HF, pulmonary edema, serosal effusion, interstitial retention, and peripheral edema.

SECTION 5 MANAGEMENT OF CKD-PERIDIALYSIS COMPLICATIONS

I. Vascular Access Related Complications

1. Vascular Stenosis

1.1 Diagnosis. Imaging should be done as soon as possible after any physical examination, blood flow measurement, or static venous pressure is persistently abnormal. Imaging techniques include color Doppler ultrasound, computed tomography angiography, and digital subtraction angiography, of which digital subtraction angiography is the gold standard for diagnosis. Prolonged hemostasis after needle removal could be considered as another indication to study a vascular access for outflow stenosis.

1.2 Intervention Indications. Intervention is indicated when the degree of local stenosis exceeds 50% of the diameter of nearby normal vessels and one of the following conditions are present: the total blood flow within the fistula is $<$500 ml/min; the blood flow set in the dialysis prescription cannot be met; the venous pressure of dialysis increases; puncture is difficult; the adequacy of dialysis decreases; or abnormal signs appear in the fistula.[56]

1.3 Intervention Methods. Intervention methods include percutaneous transluminal angioplasty (PTA) and surgery. Either surgery or angioplasty can be selected for patients with vascular stenosis (AVG or AVF), which is close to the arteriovenous anastomosis or the anastomotic venous side, whereas PTA is preferred for patients with vascular stenosis which is close to the puncture site(s).

2. Acute Thrombosis

2.1 Acute thrombosis is usually found close to the anastomotic stoma and the outflow tract of an internal fistula. Arterial limb stenosis tends to develop within 5 cm to 6 cm of the AV anastomosis. Thrombosis at the arterial is uncommon in AVG. Outflow AVF stenosis thrombosis tends to occur in the outflow tract (the cephalic arch).

2.2 If thrombosis is detected, intervention should be performed as early as possible. The measures for intervention include the following: drug thrombolysis, Fogarty catheter thrombectomy, surgical incision and thrombectomy, and fistula reconstruction. The cause of thrombosis should be removed or treated.[56] Twardoski described a technique of high dose thrombolytic infusion (urokinase) to restore the patency and blood flow rate of dysfunctional or thrombosed CVC.[96]

3. Venous Hypertension

3.1 Clinical Manifestations. Signs of venous hypertension include limb edema which is still present 2 weeks after a fistuloplasty, or if limb edema or chest wall varices develop ipsilateral to the fistula during its use.

3.2 Intervention Methods.

3.2.1 The preferred treatment for central venous stenosis is PTA.[56]

3.2.2 Stent implantation can be considered in the following situations: (i) if there is elastic recoil after angioplasty (residual stenosis more than 50%) and (ii) if there is a recurrence of stenosis within 3 months.[56]

3.2.3 If PTA failure occurs, the fistula can be ligated to relieve symptoms of venous hypertension.[56]

4. Aneurysm

4.1 Diagnosis. Anuerysm usually occurs months or years after the internal fistula surgery and is accompanied by pulsation. In an AVF, the aneurysm wall contains the whole layer of the vessel wall. In grafts, dilations are pseudoaneurysms. In an AVF, the diameter of the aneurysm is often more than 3 times larger than the inner diameter of adjacent normal vessels, and the inner diameter is often $>$2 cm. The cause is usually the result of one site cannulation (not buttonhole) with some degree of increase in intraluminal increase in pressure.

4.2 Indications for intervention include skin damage such as thinning, ulceration, infection, or pain; secondary thrombosis affecting the blood flow of the fistula; increased venous pressure; limited puncture area; ischemic symptoms in the hand; or high output HF.[56]

4.3 Intervention Methods.

4.3.1 Patients with aneurysms of less than 3 cm or which are not at risk of rupturing can be closely observed to prevent punctures, and wrist protection should be worn.[57]

4.3.2 For aneurysms larger than 3 cm or which are at risk of rupture, treatment can be selected according to the location of the aneurysm and the patient's own vascular conditions.[56]

5. Hemodialysis Access Induced Distal Ischemia

American Society for Diagnostic and Interventional Nephrology describes hemodialysis access induced distal ischemia as a serious condition resulting in significant hemodialysis patient morbidity.[97] It is necessary to understand this syndrome and its management. Most cases can be managed conservatively without intervention. Some cases requiring intervention may be treated using techniques within the scope of practice of the interventional nephrologists whereas other cases require vascular surgery. Hemodialysis access induced distal ischemia should be differentiated from the acute neurologic emergency after placement of an AVF graft, which is due to stealing from the blood supply to major arm nerves.[98]

5.1 The establishment of an AVF can result in hemodialysis access induced distal ischemia, a group of clinical syndromes in which local hemodynamics change. This can result in the reduction of distal limb blood supply and ischemic changes, mainly manifested as limb coldness, pallor, numbness, pain and other symptoms, and necrosis in severe cases.[56]

5.2 Clinical Classification. Hemodialysis access induced distal ischemia is graded from I to IV, according to the degree of clinical ischemia as follows:

Grade I: Pallor, cyanosis and/or coldness in hands, but no pain;

Grade II: The above symptoms (Grade I symptoms) are aggravated and exercise and/or dialysis causes pain;

Grade III: pain at rest;

Grade IV: ulcer, necrosis, gangrene and other manifestations of tissue loss in the limbs.

5.3 Treatment.

5.3.1 Conservative treatment. For patients with mild symptoms (Grade I or II), hand warming, functional exercises, other methods (i.e., wearing a glove), and drugs to improve blood circulation can be used;[56]

5.3.2 Surgical treatment is required for patients with severe ischemic symptoms (Grades II, III and IV). Surgical methods include radial artery ligation at the distal end of the anastomosis, PTA, fistula flow restriction, inflow artery remodeling, and ligation of the fistula.[56]

6. Dialysis Access-Associated Steal Syndrome

Dialysis access-associated steal syndrome is a limb-threatening condition, which occurs in up to 8% of hemodialysis patients.

6.1 Diagnosis. Dialysis access-associated steal syndrome is characterized by ipsilateral hand hypoperfusion, such as rest pain, sensory or motor dysfunction and ulceration; when severe, can lead to irreversible hand ischemia and potential need for digit amputation.[99,100]

6.2 Treatment. Surgical management of dialysis access-associated steal syndrome includes ligation, banding, distal revascularization with interval ligation, revision using distal inflow, proximalization of arterial inflow, and distal radial artery ligation.[99-101]

II. PD Catheterization Related Complications

1. Peritoneal Dialysate Leakage

1.1 The catheter should be well-fixed after operation to avoid traction, facilitate the healing of catheter outlet, and reduce the occurrence of leakage.[75]

1.2 Delaying dialysis for 1 week to 3 weeks may be considered for patients who are new to dialysis.[91]

1.3 For patients on PD, temporary hemodialysis or reduction of dialysate exchange volume may be considered to reduce abdominal pressure.[91]

1.4 Surgical repair should be considered for patients with recurrent dialysate leakage. Dialysis catheter removal should be considered for patients with failed surgical repair or not undergoing surgery.[91]

2. Poor Drainage of Dialysate

2.1 To reduce the occurrence of poor draining of peritoneal dialysate after surgery, the patient's stools should be kept unobstructed, knee flexion or squatting and other movements on the bed should be avoided, and maintaining normal activities should be encouraged for young patients.[75]

2.2 Different measures can be taken, including irrigation with heparin-containing fluids to relieve blood clots and fibrin clots, changing position to increase drainage volume, and surgical relief of omental wrapping.[75]

3. Hernia

Generally, surgical repair is required before dialysis treatment or in parallel with PD catheterization. Constipation and heavy lifting should be avoided after surgery, and the dialysate exchange volume should be reduced for at least 1 week.[75]

4. Peritoneal UF Failure

4.1 Diagnostic Criteria. UF failure is defined by 4.25% glucose peritoneal dialysate, 2 liters drainage after 4 hours of abdominal dwell, and UF volumes of less than 400 ml.[75]

4.2 Treatment. The cause of UF failure should be treated. Water and salt intake should be controlled at the same time and the dialysis regimen should be adjusted to maintain volume balance. If necessary, treatment should be combined with hemodialysis or the patient switched to hemodialysis.[75]

III. Dialysis Disequilibrium Syndrome

Dialysis disequilibrium syndrome (DDS) is an acute complication that occurs during or soon after hemodialysis. It is characterized by electroencephalogram abnormalities and the presence of systemic and neurological symptoms.

1. Clinical Manifestations

1.1 Symptoms. Mild cases may present with headache, nausea, vomiting, agitation, seizures, and unresponsiveness. In more severe cases, patients will present with convulsions, disturbance of consciousness, and even coma.[76]

1.2 Electroencephalography is characterized by an abnormal increase in brain wave intensity.[76]

1.3 Cerebrospinal fluid is characterized by a decrease in cerebrospinal fluid pH decreased and $HCO3^{-}$, and an increase in the partial pressure of carbon dioxide.[76,102]

2. Prevention

2.1 The rapid removal of large solutes in a short period should be avoided for patients initiating dialysis. Serum urea nitrogen should not decrease to more than 30% to 40% during initial dialysis. Low-efficiency dialysis methods are recommended, including reducing the blood flow rate, shortening the time for each dialysis (limited to 2h–3h), and using a dialyzer with a smaller surface area.[76]

2.2 The occurrence of DDS can be reduced through sequential dialysis with dialysate using sodium concentration profiles. In addition, regular and adequate dialysis, increasing the frequency of dialysis, and shortening the duration of each dialysis are all beneficial in preventing DDS.[76]

3. Treatment

3.1 In mild cases, the blood flow rate only needs to be slowed down enough to reduce solute clearance, excessive changes in plasma osmolality, and pH. For patients with muscle spasms, hypertonic saline or hypertonic glucose can be infused at the same time, and dialysis should be terminated if DDS is not relieved by the above treatment.[76]

3.2 In severe cases, dialysis should be terminated immediately, cerebrovascular accidents need to be ruled out and mannitol infusions can be given. Other corresponding treatments can then be given according to the therapeutic response. Coma due to DDS generally improves in 24 hours.[76]

IV. Intradialytic Hypotension (IDH)

Understanding and study of IDH are restricted by the absence of a consensus medical definition. Many studies use a decrease in systolic BP (SBP) by a specific amount (20, 30, and 40 mm Hg) or nadir SBP below a threshold (90, 95, and 100 mm Hg.[103] The most commonly used are the European Best Practice Guidelines-2007[104] and KDOQI Clinical Practice Guidelines (2005),[105] a decrease in SBP >20 mm Hg in combination with clinical events and interventions. USA definitions use a nadir SPB of <90 mm Hg with no requirements for symptoms.

IDH in China is generally defined by the presence of the following: a decrease in SBP of more than 20 mmHg; a decrease in mean arterial pressure of more than 10 mmHg during hemodialysis; or an intradialytic nadir SBP below 90 mmHg with clinical signs or symptoms that require medical intervention.[106] The incidence of hypotension during hemodialysis ranges from 20% to 30%. Frequent episodes of hypotension are associated with rapid loss of residual renal function, congestive HF, cardiac arrhythmias, and cognitive impairment. Studies have demonstrated that the major risk factors associated with IDH are diabetes, higher interdialytic weight gain, female gender, and lower body weight.[107] There is a correlation between the occurrence of IDH (Nadir <90) in >30% of treatments and mortality.

1. Prevention

1.1 Accurate assessment of patient's dry weight.

1.2 Patient Education. Patients should consume a low salt diet to control interdialytic water intake[108] and minimize eating during dialysis.[108]

1.3 Treatment of primary diseases leading to hypotension (e.g., anemia, etc.).

1.4 Adjustment of antihypertensive medications.

1.5 Prolonging length of dialysis.

1.6 Reduce the UF rate, monitor blood volume during dialysis, and terminate UF dehydration if blood volume decreases too much (i.e., <80% of initial value).

1.7 If necessary, gradually reduce the dialysate temperature. However, the dialysate temperature should not be lower than 35 °C, and the patient should be monitored for adverse reactions.

2. Treatment: Treatment for IDH is Invariably Reactive

2.1 Trendelenburg or supine position of the patient;

2.2 Stop UF;

2.3 Infuse normal saline;

2.4 Dopamine injections (20–40 mg) may be considered for patients with refractory intradialytic hypotension who fail to respond to the above treatment. Intravenous injection can be given using a micropump if necessary.

2.5 If the above treatment is ineffective, dialysis can be terminated prematurely.

V. Dialyzer Reaction

Dialyzer reactions often occur in initial dialysis patients. There are 2 categories of reactions, namely type A (allergic reaction) and type B. The differences

Table 3. Dialyzer reactions

Item	Type A dialyzer reaction	Type B dialyzer reaction
Onset time	More than 5 min after the start of dialysis, some delay to 30 min	30–60 min after the start of dialysis
Symptoms	Severe, manifested as skin itching, urticaria, cough, sneezing, runny nose, abdominal pain, diarrhea, dyspnea, shock, and even death	Mild, manifested as chest pain and back pain
Cause	Ethylene oxide, dialysis membrane materials, use of dialyzer, dialysis fluid contamination, heparin allergy, high-sensitivity population and application of ACEI drugs, etc.	The reason is unclear, which may be related to complement activation
Prevention	Avoid using ethylene oxide to disinfect dialyzers and blood tubing; Adequately rinse the dialyzer and blood tubing before dialysis Stop ACEI drugs Switch to another dialyzer type	Switch to synthetic membrane dialyzer Reused dialyzers may have some preventive effect
Treatment	Immediately terminate dialysis Clamp the blood tubing and discard the blood in the tubing and dialyzer; In severe cases, antihistamines, hormones, or epinephrine are treated Cardiopulmonary support as needed	Exclusion of other causes of chest pain; Symptomatic and supportive treatment Oxygen inhalation Continue dialysis if condition improves

ACEI, angiotensin-converting enzyme inhibitors.

between the 2 categories and the treatment options available are shown in Table 3.[76]

VI. Hypertension

1. BP Measurement Methods for Dialysis Patients

The mean value for office BP should be calculated from 6 measurements taken after initial dialysis. Home BP measurement should be calculated as the average of all values recorded in 3 days to 6 days. Recent study showed that mean differences between predialysis and home SBP were 19.1 ("home lower"), 3.7 ("home and predialysis similar"), and −9.7 ("home higher").[109] Ambulatory BP measurement automatically measures BP every 15 minutes to 30 minutes and provides daytime, night-time, and 24-hour mean BP.

2. Refer to Table 4 for Diagnostic Criteria

3. Treatment Target

BP targets of <140/90 mmHg are recommended for patients with CKD-PeriDialysis. Targets of ≤130/80 mmHg are recommended for patients with concomitant DKD if tolerated.[15-19]

4. Treatment

4.1 Lifestyle Management.

4.1.1 Recommendations for lifestyle changes include limiting sodium salt intake before dialysis to 5 to 6 g per day, adjusting diet, quitting smoking, and limiting alcohol intake. In populations with high sodium intake as in China, replacing some of the sodium with potassium reduces systolic and diastolic BP in the adult population.[110] Furthermore, in the predialysis phase, depending on the patient's potassium level, substituting 25% of the daily dietary sodium with potassium may also reduce BP but must be done carefully.

4.1.2 Weight should be maintained within a healthy range, and weight gain should be limited to <4% (2−3 L) between dialysis sessions.

4.1.3 Exercise for at least 30 minutes, 5 times a week, is recommended for predialysis patients with stable cardiovascular function.

4.2 Volume control is important for the treatment of hypertension for CKD-PeriDialysis patients. During the PeriDialysis period, changes in BP should be closely monitored to determine the effect of dialysis on hemodynamics and aid the individualized selection of antihypertensive drugs.[16]

4.3 Medication.

4.3.1 Continual use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors is recommended for predialysis CKD patients who are already using these drugs. Patients who have not previously received RAASI should not be started on RAASI. CKD-Peridialysis patients often require treatment with 2 or more antihypertensive drugs, including calcium antagonists and α/β blockers. Combining angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers and direct renin inhibitor should be avoided. During RAASI treatment, the patient's blood potassium level should be monitored. Hyperkalemia associated with use of RAASI can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping

Table 4. Diagnostic criteria for OBPM, HBPM, and ABPM hypertension

Dialysis mode	HBPM	ABPM	OBPM
HD	Mean BP ≥135/85 mmHg measured on 6 days on a nondialysis day within 2 weeks[a]	24-hour mean BP ≥130/80 mmHg	≥ 140/90 mmHg
PD	Mean BP ≥135/85 mmHg measured for 7 consecutive days	24-hour mean BP ≥130/80 mmHg	≥ 140/90 mmHg

ABPM, ambulatory blood pressure measurement; BP, blood pressure; HBPM, home blood pressure measurement; HD, hemodialysis; PD, peritoneal dialysis; OBPM, office blood pressure measurement.
[a]Select the day of the week without dialysis for measurement.

RAASI. Consider reducing the dose or discontinuing angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment. The selection of antihypertensive drugs should take into account the patient's clinical conditions and adverse drug reactions.[16]

4.3.2 Additional considerations for hemodialysis patients include the following:

(i) BP can be controlled through the use of sequential dialysis, which increases sodium removal from the body, or the use of an individualized concentration of sodium dialysate.[16]

(ii) Patients who still cannot effectively control weight gain between dialysis sessions should limit their salt intake and increase the length of dialysis.[16]

4.3.3 Additional considerations for PD patients include the following:

(i) Before initiating or increasing antihypertensive drugs, the patient's volume status should be assessed.[16]

(ii) Loop diuretics can be used to reduce volume load in patients with residual renal function.[16]

(iii) Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are recommended; these drugs can delay the loss of residual renal function in patients in addition to lowering BP.[16]

VII.HF

The prevalence of HF among patients with CKD is nearly 30%. Its presence with CKD and anemia is labeled cardiorenal syndrome, type 4. The mortality rate in this syndrome increases with CKD severity and it is one of the leading causes of emergency and inpatient treatment.[111]

1. Diagnosis and Treatment Pathway of CKD Complicated with HF

For ESKD patients who are suffering from shortness of breath, palpitation, edema, etc., clinicians should assess the patient using the following: the history of heart disease, a physical examination, a chest X-ray, an electrocardiograph examination, an ultrasonic cardiogram, and detection of blood biochemical indicators (BNP, NT-ProBNP). These assessments can then be used to make a diagnosis.[20,111]

2. HF Type

HF can be categorized according to the level of ejection fraction as follows: HF with reduced ejection fraction, HF with midrange ejection fraction, and HF with preserved ejection fraction.[20,111] HF with reduced ejection fraction, HF with midrange ejection fraction, and HF with preserved ejection fraction account for 63%, 19%, and 18% of the total population of patients with CKD and HF, respectively.[112]

3. Treatment

3.1 Control of hypertension and hyperglycemia

3.2 Correction of Volume Overload. Refer to Hypertension Treatment section

3.3 Medication.

3.3.1 RAASI, beta-blockers, neprilysin inhibitors, and or sacubitril-valsartan are recommended for HF with reduced ejection fraction.[20]

3.2.2 RAASI, β-blockers, and neprilysin inhibitors are not recommended for HF with midrange ejection fraction and HF with preserved ejection fraction.[20,111] Recently, sacubitril-valsartan has been used for the treatment of HF with preserved ejection fraction.[113]

VIII. Infection

The incidence of infectious complications in predialysis patients is 3 to 4 times that of the general population. The most common sites of infection in patients with ESKD are the lungs and urinary tract.[114,115]

1. Hemodialysis-Related Infection

1.1 Etiology. These are mainly bacterial infections and hematogenous infectious diseases (such as hepatitis virus, HIV infection, etc.).[76]

1.2 Prevention.

1.2.1 Dialysis isolation and disinfection systems should be implemented. Disposable dialyzers are recommended but if reusable dialyzers are used, the relevant guidelines for infection control should be strictly adhered to.[76,116]

1.2.2 Clinicians should ensure that hemodialysis related materials have been disinfected, and there is adequate cleaning of the dialysis environment, such as the dialysis room and equipment, to avoid cross infection. Antibiotics should be given as a preventative measure before catheterization, and strict aseptic techniques should be utilized during the catheterization operation.

1.2.3 Avoid unnecessary blood transfusion.

1.2.4 Markers of hepatitis B virus, hepatitis C virus, Treponema pallidum, and HIV viral should be assessed once every 1 month to 3 months for initial dialysis patients,[117] and once every 6 months for patients on long-term dialysis.[76,117]

1.2.5 Patients on dialysis should receive vaccinations for hepatitis, pneumonia, and seasonal influenza (and now COVID-19).

1.3 Treatment.

1.3.1 Infection management with a temporary catheter or a catheter with a cuff. If unexplained chills or fever occurs, particularly during or after dialysis, treatment should be terminated. If the local area is tender and inflamed, the white blood cell count is elevated, positive blood culture bacteria is revealed, or other manifestations are present, the catheter should be

removed immediately. The catheter tip should be sent for bacterial culture, and the patient should be given appropriate antibiotic therapy.[76]

1.3.2 Management of AVF infections. AVF infections are rare, but they are more common in long-term hemodialysis patients who have a skin infection near the fistula or in patients who are immunocompromised. Once a fistula infection is suspected, antibiotics should be prescribed based on pathogenic microbiological surveillance. A combination of broad-spectrum antibiotics and vancomycin is recommended for initial empirical treatment, however, antibiotics should be adjusted based on susceptibility results. The initial treatment for an autogenous fistula infection should be at least 6 weeks. In rare cases, fistula infections may require surgical treatment.[76]

1.3.3 Management of AVG infection. Prevention of AVG infections is very important. Strict aseptic techniques should be utilized during the operation and prophylactic use of antibiotics before operation can reduce the infection rate after AVG. Infections which occur in the early stages after the operation are easy to spread because the artificial vessel has not yet healed. Therefore, if the site becomes infected, all the artificial vessels should be removed and the arterial anastomosis should be reconstructed. Most infections that occur in the late stage are caused by pathogens that colonize the skin and are mainly caused by puncture practice. Once the area has become infected, bacteremia and the spread of infection after dialysis become more likely. Therefore, early detection and timely treatment are important. Systemic antibiotics should be prescribed and infected vessels should be removed.[117]

2. Peritoneal Dialysis-Related Infections

Peritoneal dialysis-related infectious complications include PD-related peritonitis and catheter-related infections.[91,115]

2.1 Prevention of Peritoneal Dialysis-Related Infections.

2.1.1 Routine examination of abdominal drainage and catheter exit site infection is recommended.[91,115]

2.1.2 The double-bag dialysate system should be used to flush the solution before filling for CAPD treatment.

2.1.3 Patients and/or nursing staff should receive regular training on the updated operating techniques, and intensive training is required if aseptic operating techniques are not up to standard.

2.1.4 One hour before abdominal penetration, first-generation cephalosporin antibiotics should be given.

2.2 Peritoneal Dialysis-related Peritonitis.

2.2.1 Diagnostic criteria[91]

Peritonitis can be diagnosed in PD patients when 2 or more of the following conditions are met:

(i) Abdominal pain and turbid ascites with or without fever;

(ii) White blood cell count $>100\times10^6$/L, neutrophil percentage $>50\%$ in dialysate effluent;

(iii) Pathogenic microorganisms present in the dialysate effluent.

2.2.2 Treatment recommendations include the following:

(i) The empirical treatment for peritonitis includes antibiotics which are indicated against both positive and negative bacteria (including *Pseudomonas aeruginosa*). Drugs should be selected according to the spectrum of common pathogenic bacteria and drug sensitivity in the region, combined with the patient's previous history of peritonitis until bacterial culture and antibiotic susceptibility results are obtained.[91]

(ii) Intraperitoneal antibiotics are recommended. They can be administered continuously (during each peritoneal dialysate exchange) or intermittently (with only one peritoneal dialysate exchange per day or at intervals of several days).[91]

(iii) Subsequent treatment. The use of antibiotics should be adjusted accordingly depending on the results from the microbial culture and the drug susceptibility testing of the effluent. The course of anti-infective treatment lasts at least 2 weeks; severe or special infections can take 3 weeks or longer.[91]

2.3 Catheter Related Infections.

2.3.1 Diagnostic criteria. The clinical manifestations of catheter-related infections are local pain, swelling, scab, erythema, or serous secretion, etc. Infection can be diagnosed when there is secretion from the site of infection. Samples should be collected for bacterial culture with a wipe.[91]

2.3.2 Treatment recommendations include the following:

(i) Empiric anti-infective treatment can be started immediately after the diagnosis of a catheter-related infection, or treatment can be started according to the results of the microbial culture from the secretion and the drug sensitivity test.[91]

(ii) General treatment includes enhanced local care and the use of antibiotic creams. In severe cases of infection, a wet compress of a gauze soaked with hypertonic saline can be applied to the catheter site for 15 minutes, once or twice a day.[91]

(iii) Empirical anti-infective treatment is recommended to select sensitive antibiotics for *Staphylococcus aureus*. If the patient has a previous history of *Pseudomonas aeruginosa* catheter infection, the antibacterial spectrum of the antibiotics used should also cover this bacteria.

Table 5. Iron deficiency and metabolic disorders

Patients	Absolute iron deficiency	Relative iron deficiency
CKD predialysis and peritoneal dialysis patients	SF <100 μg/l and/or TSAT <20%	SF is normal, while TSAT is decreasing (prompting that the storage of iron are sufficient while the utilization of iron is impaired)[31-33]
Hemodialysis patients	SF <200 μg/l and/or TSAT <20%	

CKD, chronic kidney disease; SF, serum ferritin; TSAT, transferrin saturation.

(iv) Subsequent treatment. The choice of antibiotics should be adjusted after obtaining secretion culture and drug susceptibility results. Oral antibiotics are generally given unless the causative agent of infection is methicillin-resistant staphylococcus aureus.[91]

(v) Refractory tunnel infections usually require extubation. Removal of the subcutaneous cuff may be beneficial for the treatment of refractory tunnel infection and anti-infective treatment should be continued after subcutaneous cuff stripping.[91]

IX. Anemia

1. Diagnostic Criteria

1.1 Diagnostic Criteria for Anemia. Anemia can be diagnosed in adults (living at sea level) when hemoglobin <130 g/l in men and <120 g/l in nonpregnant women.[31-33]

1.2 Iron deficiency and metabolic disorders (refer to Table 5)

2. Treatment Timing and Treatment Target

2.1 Overall Goals. Blood transfusions should be avoided, cardiovascular events should be prevented, and cognitive function and quality of life should be improved or maintained.

2.2 Timing of Treatment. As Hb decreases faster in dialysis patients than in nondialysis patients, Hb levels <90 g/l should be avoided and anemia treatment should be initiated when Hb is <100 g/l in CKD-PeriDialysis patients.[31-33]

2.3 Treatment Target.

2.3.1 Hemoglobin target. Hb levels should be maintained between 100 to 120 g/l, but should not exceed 130 g/l. The target value can be adjusted individually depending on the patient's age, dialysis method, dialysis time, and drug treatment time, as well as whether there are any other complications or comorbidities.[31-33,118]

2.3.2 Target of iron metabolism. Iron parameters should be maintained. Current guidelines recommend SF in the range 200–500 μg/l, and transferrin saturation in the range 20% to 50%. It should be noted that in Japan, Korea, and China, patients receive much less parenteral iron than in western nations. SF levels > 300 μg/L are the rule rather than the exception.

2.4 Therapeutic Drugs. Therapeutic drugs for renal anemia include iron, ESAs, and hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI).[31-33,119-121] The predialysis population is at high risk of cardiovascular events, and the cardiovascular effects of drugs should be considered when treating anemia.[20,122]

2.4.1 Iron therapy should be given to patients with absolute iron deficiency. For CKD-PeriDialysis patients, oral iron supplementation should be given with a starting dose of 150 to 200 mg/day (elemental iron). If oral iron is not well tolerated or is ineffective, intravenous iron therapy should be given instead. Intravenous iron therapy is effective treatment for anemic hemodialysis patients who have SF ≥500 ng/ml and transferrin saturation ≤25% and are receiving adequate epoetin.[123] Life-threatening hypersensitivity reactions may occur with any intravenous iron. During the first treatment with intravenous iron, patients should be monitored for vital signs 60 minutes before the infusion, and necessary emergency drugs should be on standby. Intravenous iron therapy should be avoided if there is an active systemic infection in anemic patients with CKD.[31-33] We recommend that SF should not exceed 800 μg/l in patients treated with iron, and iron management should be reviewed when ferritin is >500 μg/l.[31]

2.4.2 ESAs include recombinant human erythropoietin (rHuEPO), darbepoetin alfa, and continuous erythropoietin receptor activator. Risk factors such as iron deficiency or inflammatory status should be normalized, as much as possible, before ESA treatment is initiated. When ESAs are given, the dose should be adjusted according to various factors, such as the patient's Hb level, the rate of change of Hb, the dose of ESA given, and the patient's clinical condition. The initial dose of ESAs should be in the lower range. The specific doses are as follows:

(i) rHuEPO: 50 to 150 IU/kg/week in 1 to 3 divided doses.

(ii) Darbepoetin alfa: 0.45 μg/kg every 1 to 2 weeks.

(iii) continuous erythropoietin receptor activator: 0.6 μg/kg every 2 to 4 weeks.

2.4.3 HIF-PHI: HIF-PHI is a small molecule oral drug that promotes erythropoietin (EPO) production by inhibiting proline hydroxylase activity. This helps the levels of EPO to reach the physiological range, resulting in improved Hb levels in patients, regardless of the inflammation status. It could also increase the absorption, transport, and utilization of iron by the body and reduce the iron dosage.[119-121] Global multicenter phase III clinical studies have confirmed that roxadustat is effective in improving and maintaining Hb levels in nondialysis and initial dialysis CKD patients, without increasing the risk of cardiovascular events.[124,125] Oral treatment with HIF-PHI is also more convenient for

PeriDialysis patients. The starting dose of HIF-PHI is determined according to the patient's body weight, any previous doses of ESAs, and various other factors, including basal Hb level and iron metabolism. The starting dose for dialysis patients should be 70 to 100 mg (body weight <60 kg) or 100 to 120 mg (body weight ≥60 kg) orally, 3 times in 1 week. The starting dose for nondialysis patients should be 50 to 70 mg (body weight <60 kg) or 70 to 100 mg (body weight ≥60 kg), orally, 3 times in 1 week.[124,126] The dose can be adjusted depending on the patient's condition.

2.5 Hb levels should be monitored every 2 weeks at the beginning of the treatment until the patient is stable. Hb should then be monitored at least once a month to avoid large changes in concentration in a short period of time. Hb fluctuations should not exceed 20 g/l within 4 weeks. Upregulation or downregulation of drug dosage (in the range of 25%) should be implemented until Hb reaches and maintains the target values.[31-33]

2.6 Various factors such as malnutrition and inadequate dialysis in patients can lead to low response rates to renal anemia treatment. There should be an evaluation of risk factors for the aggravation of renal anemia and other diseases which may be causing anemia. The underlying causes of anemia can then be treated.[31-33]

X. PEW

Protein energy wasting is a state of decreased protein and energy substance stores in the body with clinical manifestations characterized by insufficient dietary protein and caloric intake, low body mass index, hypoalbuminemia, micro-inflammatory state, and progressive skeletal muscle wasting.[45-48] PEW is present in 18% to 48% of predialysis CKD patients, up to 75% of ESKD patients, and 28% to 54% of maintenance hemodialysis patients.[46,127-129] The causes of PEW are multifactorial,[130] including metabolic acidosis, low-grade chronic inflammation, increased protein degradation, and loss of amino acids and proteins during the dialysis procedure, as well as decreased appetite and insufficient food intake.

1. Diagnostic Criteria

These include but are not limited to the following nutritional indicators. Different indicators reflect different aspects of nutritional status. The diagnostic cut-off value of each indicator is given for reference:[45,46,48]

1.1 Serum biochemical parameters include serum albumin <38 g/l, prealbumin <300 mg/l, and total cholesterol <2.6 mmol/l.

1.2 Body Weight. Body mass index <23 kg/m^2; >5% weight loss at 3 months or >10% weight loss and <10% body fat percentage at 6 months.

1.3 Muscle Mass. Muscle consumption (>5% reduction in muscle mass in 3 months or >10% reduction in muscle circumference within 6 months), reduction of upper arm muscle circumference greater than 10% of the median upper arm circumference of the same population.

1.4 Intake. Dietary protein intake <0.6 g/kg/day and energy intake <25 kcal/kg/day for at least 2 months in predialysis patients, or dietary protein intake <0.8 g/kg/day in dialysis patients.

2. Prevention

A low protein diet is recommended for predialysis CKD patients, with a significant increase in protein requirements after the initiation of dialysis. The intake of water, potassium, sodium, and other substances depends on the patient's residual renal function, the number of dialysis sessions, and the dialysis modality. After dialysis, patients should have a total caloric intake of 30 to 35 kcal/kg per day, a protein intake of 1.0 to 1.2 g/kg/day, and at least 50% high-titer high-quality protein.[45,46] Improving dialysis adequacy, inflammatory status, and anemia could reduce the occurrence of PEW.[131-133]

3. Treatment

PEW should be treated with comprehensive measures, including optimization of the dialysis regimen, protection of residual renal function, addressing the causes of PEW (such as acidosis, infection, fluid overload, etc.), and prescription of oral nutritional supplements.[46,131-133]

3.1 Oral Nutritional Agents. CKD patients should be given an early nutritional risk screening and evaluation, and oral nutritional supplements (such as essential amino acids or α-keto acids) should be given to patients early.

3.2 Parenteral Nutrition. Parenteral nutrition is a convenient and effective method for dialysis patients who cannot take oral nutrition.

3.3 Other Treatments. Other treatments include exercise, anabolic hormones, appetite stimulants, etc. There is still little research evidence on the benefits of these treatments and careful selection is recommended.

XI. CKD Mineral and Bone Disorder

CKD mineral and bone disorder is a serious complication in predialysis patients, with a high risk of disability and mortality. Studies have reported an incidence of hypocalcemia, hyperphosphatemia and

high iPTH in Chinese hemodialysis patients of 35.9%, 58.6%, and 45.4%, respectively.[40,41]

1. Treatment

1.1 Maintaining normal blood calcium levels and reducing hyperphosphatemia:

1.1.1 Restriction of phosphorus intake (800–1000 mg/d). Under the premise of moderate protein intake, foods that have a low phosphorus/protein ratio and low phosphorus absorption rate should be selected. The consumption of foods containing a large number of phosphate additives should be limited.[40,41]

1.1.2 The dialysate calcium concentration should be in the range of 1.25 to 1.50 mmol/l, and the concentration of calcium ion in the PD fluid should be 1.25 mmol/l.[40,41]

1.1.3 Adequate dialysis. Increasing the length of time on dialysis or increasing the frequency of dialysis can remove serum phosphorus more effectively.

1.1.4 When serum phosphorus level increases progressively and continuously, phosphate lowering therapy should be started. Phosphate binders should be considered according to serum calcium, serum phosphate, and iPTH levels. Serum phosphorus is 0.87 to 1.45 mmol/l in normal adults. The elevated serum phosphorus should be reduced to as close to the normal range as possible during the CKD-PeriDialysis period. Calcium-based phosphate binders significantly increase the risk of hypercalcemia, vascular calcification and cardiovascular events, and the use of calcium-based phosphate binders should be limited to only one of the following conditions: hypocalcemia, hyperphosphatemia, or a high level of iPTH.[40,41] Non-calcium-based phosphate binders are recommended as first-line phosphate binders. Currently, the most commonly used calcium-free phosphate binders are sevelamer and lanthanum carbonate.

1.2 Correction of Secondary Hyperparathyroidism.

1.2.1 The optimal iPTH level in predialysis patients is still unclear. The iPTH level should be maintained at 2 to 9 times the upper limit of normal in dialysis patients. An appropriate maintenance range is 150 to 300 ng/ml.[40,41]

1.2.2 The following drugs should be prescribed: (i) active vitamin D3 (calcitriol); 0.25 to 0.5 ug/time, once a day, or 2 ug/time, 3 times a week, depending on the patient's condition. (ii) active vitamin D analogs (e.g., paricalcitol); 5 to 10 ug/time, 3 times a week, adjusted according to iPTH levels; (iii) calcium-sensing receptor agonists (e.g., calcimimetics); the recommended starting dose of cinacalcet is 25 mg/time, once daily, and the dose should be adjusted every 3 weeks or more, 25 mg each time, with a maximum daily dose of 100 mg.

1.2.3 Active vitamin D and its analogs should be given in combination with calcimimetics for the treatment of severe secondary hyperparathyroidism.[40,41]

1.3 Routine use of active vitamin D and its analogs is not recommended for adult patients with CKD G5, not on dialysis, however, they can be used in patients with severe, progressive hyperparathyroidism.[40,41]

1.4 Parathyroidectomy. Severe secondary hyperparathyroidism refractory to medical treatment. Severe secondary hyperparathyroidism is defined as persistent serum iPTH >800 pg/ml that is refractory to medical treatment for 3 months.[40,41]

XII. Hyperglycemia Management

The prevalence of diabetes in patients with CKD-PeriDialysis ranges from 26% to 29%. The management of blood glucose in PeriDialysis patients is complex and the effect of dialysate composition on blood glucose needs to be monitored. For example, the use of glucose dialysate in PD patients may cause hyperglycemia, whereas the use of sugar-free dialysate in the initial dialysis of hemodialysis patients may cause hypoglycemia.[76,91]

1. Glycemic Targets

The glycemic targets for patients with PeriDialysis diabetes. GA target should be <20% (GA <24.0% for patients with previous cardiovascular events and hypoglycemic episodes). The glycosylated hemoglobin control target should be 7.5% to 8.5%.[35-39]

2. Treatment

2.1 Insulin.

2.1.1 In principle, insulin therapy is recommended as the first line treatment for PeriDialysis patients. As insulin clearance is reduced, the starting dose often needs to be reduced and the dose needs to be increased in a stepwise manner.[35-39]

2.1.2 Dialysis seriously affects blood glucose and insulin levels, and patients with DKD often require additional insulin for dialysis. The insulin injection dose and time on nondialysis days can differ from dialysis days. Clinicians should monitor patients for hypoglycemic reactions caused by insulin on dialysis days and during dialysis.[35-39]

2.1.3 Patients undergoing PD should receive a subcutaneous injection of short-acting insulin.

2.2 Oral Antidiabetic Drugs.

2.2.1 Drugs which have little effect on the kidney and a low risk of hypoglycemia can be used before dialysis. These include dipeptidyl peptidase 4 (DPP-4) inhibitors and sulfonylureas. Biguanides, sodium-glucose cotransporter inhibitors and thiazolidinediones are not recommended.

2.2.2 In principle, there is no clear contraindication for the use of oral hypoglycemic agents after the start

of dialysis. However, their use should be standardized, and patients should be assessed in case the dose needs to be adjusted or there is a risk of hypoglycemia.[35-39]

2.3 Pancreatic glucagon-like peptide 1 receptor agonists should be used with caution in CKD-PeriDialysis patients.

3. Dialysate and Dialysis Dose

3.1 Glucose free dialysate is not recommended for hemodialysis patients with normal blood glucose. A dialysate glucose concentration of 5.5 mmol/l is recommended.[76]

3.2 Icodextrin dialysate and amino acid dialysate are recommended as peritoneal dialysate for patients with DKD. The PD regimen and dialysis dose should be selected according to peritoneal transport characteristics.[91]

XIII. Hyperkalemia

1. Diagnostic criteria

Hyperkalemia is diagnosed when serum potassium concentration ≥5.0 mmol/L in patients on CKD-PeriDialysis.[25,26,134]

2. Potassium lowering therapy should be initiated as early as possible if serum potassium levels and electrocardiograms indicate hyperkalemia. Once CKD-PeriDialysis patients are hyperkalemic, they are prone to recurrences. Long-term management of serum potassium needs to be implemented.[134]

3. Treatment

3.1 Patients with PeriDialysis hyperkalemia should consume a low potassium diet, RAASI dosage should be adjusted, and oral potassium binders could be prescribed. The use of potassium-wasting diuretics should be considered based on the patient's residual renal function and the urine output.[134] If there is an acute increase in blood potassium, insulin and glucose treatment should be used. If the patient is also acidotic, they should be given an intravenous drip of sodium bicarbonate. If the drug is not controlled, emergency dialysis treatment should be initiated.

3.2 Refer to Table 6 for commonly used oral potassium lowering agents, including sodium polystyrene sulfonate, calcium polystyrene sulfonate, sodium zirconium cyclosilicate and patiromer. Sodium zirconium cyclosilicate can be used for potassium lowering therapy in acute hyperkalemia and for long-term management of chronic hyperkalemia.[134]

XIV. Metobolic Acidosis

1. Diagnostic Criteria

Clinically, metabolic acidosis is considered to be present when serum bicarbonate levels falls below the level of 22 mmol/l.[12]

2. Treatment

2.1 For the predialysis period, it is suggested that patients with serum bicarbonate concentrations <22 mmol/l should be treated with oral bicarbonate supplementation. The treatment may be initiated at a dosage of 500 to 1000 mg, 2 to 3 times daily. Dosage should be adjusted to keep serum HCO_3^- in the range of 22 to 26 mmol/l.[12,28,29]

2.2 High serum bicarbonate concentrations greater than 32 mmol/l are associated with increased risk of death irrespective of the level of kidney function.[12,28,29]

2.3 Dialysis is the effective way to correct metabolic acidosis in ESKD patients. Patients on hemodialysis experience exposure to a large fluctuation of the acid–base status with each dialysis episode. Bicarbonate profiling during hemodialysis or graded bicarbonate dialysate might minimize the large acid–base swing. It suggested that the concentration of HCO_3^- in the dialysate rangs from 30 to 40 mmol/l.[12,28,29,76,117]

Table 6. Comparison of oral potassium lowering drug properties

Medicinal property	Sodium polystyrene sulfonate	Calcium polystyrene sulfonate	Zircon cyclosilicate	Patiromer[a]
Site of action	Colon	Colon	Whole digestive tract	Colon
Selective	Nonselective, also binds calcium and magnesium	Selectivity, also bound to magnesium	Highly selective binding potassium	Selectivity, also bound to magnesium
Sodium content	1500 mg/15g	0	400 mg/5g	0
Onset of action	2–6 h	Not identified	1 h	7 h
Dosage and administration	15–30 g at a time, Once or twice daily	15–30 g daily, Divide into 2 to 3 doses	Use in adults (including elderly): Correction period: 10 g, tid Maintenance period: starting at 5 g/day, increase to 10 g/day or decrease to 5 g/every other day as needed; Treatment of hemodialysis patients: nondialysis daily dosing, starting at 5 g/day and adjusting at weekly intervals, up to 15 g once daily	8.4–25.2 g/d
Adverse reactions	Gastrointestinal adverse reactions, Edema, hypokalemia	Constipation, gastrointestinal adverse reactions (intestinal perforation, ileus), hypokalemia	Edema, hypokalemia	Gastrointestinal motility decreased, hypomagnesemia, hypokalemia

[a]Patiromer is not marketed in China yet.

XV. Patient Education

Due to the long-term management needs of CKD and the high incidence of predialysis patient complications, patients must inevitably become responsible for their own self-management. Clinicians should ensure that patients are knowledgeable of CKD-related complications and how to self-manage, and they should be encouraged to actively participate in the management activities of their disease. Doctor-patient communication and patient follow-up should be improved to help patients continuously enhance their ability to self-manage their disease and to develop "patient-centric" medical interventions.

SECTION 6 FUTURE RESEARCH DIRECTIONS

There are still many gaps in the management of CKD-PeriDialysis patients. These is the first guideline to be established in China, and the rest of the world, specifically for CKD-PeriDialysis patients. Based on the current research status, there are still many topics worth studying in the future, including the following:

I. Optimizing Risk Assessment Management

For Predialysis patients, risk prediction tools which quantify the risk of adverse outcomes need to be developed. Adverse outcomes may be a result of concomitant comorbidities, including cardiovascular disease, or from the rate of progression of renal failure, and death. Risk prediction tools will help to improve patient management to improve the survival of patients on dialysis.

II. Exploring the Social Benefits of Dialysis Models

Hemodialysis is the leading mode of dialysis worldwide, however, in some countries or regions, PD is preferred for health economic reasons. Further studies on the effects of the mode of dialysis on mortality and the health economic benefits should be carried out to guide patients on selecting the most appropriate treatment mode.

III. Explore the Impact of Different Policies on Patient Disease Burden and Treatment Outcomes

The impact of different policy factors on the disease burden and treatment outcome in patients, with consideration of local medical conditions and health insurance policies, should be researched to explore more suitable treatment strategies in the patient's local area.

IV. Explore the Treatment Plan and Treatment Target of CKD-Peridialysis

Based on the characteristics of hypertension and HF in patients with CKD during the peri-dialysis period, the correlation between different treatment targets and different clinical outcomes should be explored.

V. Establishing a Patient-centric Treatment Outcome Assessment Model

In addition to cardiovascular disease, renal failure, and death, the impact on quality of life, social function status, and hospitalization is also needed to help patients and physicians weigh-up and select the most appropriate treatment option.

VI. Establishing Multidisciplinary Collaborative Treatment

There are many comorbidities and contributing factors that influence disease progression in patients with CKD-PeriDialysis and, therefore, multidisciplinary department collaboration is required. Treatment decision models with multidisciplinary collaboration need to be explored to better manage patients and improve prognosis.

VII. Carrying Out Big Data-based Informatization Follow-up

In the context of big data, studies to establish standardized information and follow-up tools are needed to optimize patient management and improve patient outcomes.

APPENDIX

Experts Group on Chinese Guideline for the management of "CKD-PeriDialysis"

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DISCLOSURE

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