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Peritoneal Dialysis Guidelines 2019 Part 1 (Position paper of the Japanese Society for Dialysis Therapy)

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Abstract

Approximately 10 years have passed since the Peritoneal Dialysis Guidelines were formulated in 2009. Much evidence has been reported during the succeeding years, which were not taken into consideration in the previous guidelines, e.g., the next peritoneal dialysis PD trial of encapsulating peritoneal sclerosis (EPS) in Japan, the significance of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), the effects of icodextrin solution, new developments in peritoneal pathology, and a new international recommendation on a proposal for exit-site management. It is essential to incorporate these new developments into the new clinical practice guidelines. Meanwhile, the process of creating such guidelines has changed dramatically worldwide and differs from the process of creating what were "clinical practice guides." For this revision, we not only conducted systematic reviews using global standard methods but also decided to adopt a two-part structure to create a reference tool, which could be used widely by the society's members attending a variety of patients. Through a working group consensus, it was decided that Part 1 would present conventional descriptions and Part 2 would pose clinical questions (CQs) in a systematic review format. Thus, Part 1 vastly covers PD that would satisfy the requirements of the members of the Japanese Society for Dialysis Therapy (JSDT). This article is the duplicated publication from the Japanese version of the guidelines and has been reproduced with permission from the JSDT.

Keywords: Peritoneal dialysis, Optimal dialysis, Nutritional management, Peritoneal function, EPS, Peritonitis, Exit site

Chapter 1 Introduction
Key points

1. Peritoneal dialysis (PD) should be performed for a patient after sufficient information regarding hemodialysis (HD), PD, and kidney transplantation has been provided and consent has been obtained from the patient. The same information should be provided to all patients (Note 1).

2. Appropriate patient education and planned initiation should be undertaken in order to obtain the benefits of PD. Information relating to renal replacement therapy should be provided in patients with stage 4 (glomerular filtration rate [GFR] below 30.0 mL/min/1.73 m^2 or above 15.0 mL/min/1.73

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m²) chronic kidney disease [CKD]) accompanied by chronic decreased renal function (Note 2).

3. Dialysis initiation should be considered in patients with stage 5 CKD (GFR below 15.0 mL/min/1.73 m²) and who display clinical symptoms that are resistant to conservative treatment (Note 3).

4. Dialysis initiation should be considered in patients with GFR below 6.0 mL/min/1.73 m² (Note 4).

The four points mentioned above were written as the initiation criteria in the Peritoneal Dialysis Guidelines published in 2009 by the Japanese Society for Dialysis Therapy [1]. These same points will also be discussed here.

Note 1: A questionnaire survey based on the "Peritoneal Dialysis Guidelines" published in 2009 by the Japanese Society for Dialysis Therapy was conducted in 2011 [2]. Results showed that prior to initiation, 64% of patients received all the necessary information on HD, PD, and kidney transplantation; 23% were selectively provided information; and 13% were not provided with all the relevant information. These results showed that patients were informed to varying degrees and that bias existed.

Note 2: A similar recommendation regarding the provision of information related to renal replacement therapy was made in the "Maintenance Hemodialysis Guidelines: Hemodialysis Initiation" (2013) (Statement 3) by the Japanese Society for Dialysis Therapy [3] and the "CKD Stage G3b-5 Clinical Guidelines 2017 (2015 Expanded Edition)" (CQ 1) by sponsored research in the Japanese Agency for Medical Research and Development [4].

Note 3: Clinical symptoms that are resistant to conservative treatment and accompany decreased renal function are as follows: fluid retention (edema, pleural effusion, ascites), malnutrition, cardiovascular symptoms (breathing difficulties, shortness of breath, cardiac insufficiency, hypertension), renal anemia, electrolyte imbalance (hypocalcemia, hyperkalemia, hyponatremia, hyperphosphatemia), acid-base imbalance (metabolic acidosis), digestive symptoms (nausea, vomiting, anorexia), and neurological symptoms (impaired consciousness, convulsions, numbness).

The Japanese Society of Dialysis Therapy has stated in their "Maintenance Hemodialysis Guidelines: Hemodialysis Initiation" (2013) (Statement 6) that the initiation period should be decided when a patient's GFR is below 15.0 mL/min/1.73 m² [3].

The estimated GFR (eGFR), which uses the serum creatinine value, age, and sex, is used for evaluating renal function during stable periods. Evaluations with eGFR are also conducted in patients with stage 4 (GFR below 30.0 mL/min/1.73 m²) and 5 (GFR below 15.0 mL/ min/ 1.73 m²) CKD (Supplementary Provision 1).

GFR measurements using a 24-h urinalysis are conducted to the fullest extent possible for dialysis initiation (Supplementary Provision 2).

Note 4: The Japanese Society of Dialysis Therapy has stated in their Maintenance Hemodialysis Guidelines: Hemodialysis Initiation (2013) (Statement 7) that with regard to the timing of dialysis initiation, a "favorable prognosis was observed following hemodialysis initiation even when renal failure symptoms are observed if follow-up observations with conservative treatment are conducted until GFR < 8 mL/min/1.73 m². However, hemodialysis should be introduced until GFR 2 mL/min/1.73 m² from a post-dialysis prognosis standpoint, even with the absence of renal failure symptoms" [3].

The Japanese Society of Nephrology in their "Evidence-based CKD Clinical Guidelines 2013" (Until Dialysis Treatment Initiation, CQ2) also stated that "early initiation up to around eGFR 8-14 mL/min/1.73 m², where no uremic symptoms are observed, does not contribute to improved prognosis after the initiation of dialysis. Meanwhile, prognosis can worsen if this is not introduced up to eGFR 2 mL/min/1.73 m² even without symptoms" [5].

Residual renal function is an important consideration in continued treatment during PD. For this reason, PD, which is expected to maintain the residual renal function, should be initiated when renal function is still present, even if the patient is asymptomatic.

Explanation

A questionnaire survey was conducted in 2011 using the "Peritoneal Dialysis Guidelines" published in 2009 by the Japanese Society for Dialysis Therapy. This survey confirmed that information related to renal replacement therapy was provided, explanatory material was shared and standardized, non-physician staff members (particularly nurses) were already playing a large role, and eGFR calculations were being conducted at 90% of the facilities [2].

For these reasons, the 2009 "Peritoneal Dialysis Guidelines" have been used as the standard since then.

1. Information provision and consent acquisition

Appropriate clinical information regarding the initiation of dialysis is provided directly to the patient, as well as to the patient's family, guardians, and caregivers, as needed. Information provision and consent acquisition procedures should be conducted by teams composed of physicians, nurses, social workers, and clinical engineers. Prior to the initiation of dialysis, patients should be informed about the three treatment methods for renal replacement therapy during end-stage renal failure (i.e., HD, PD, and kidney transplantation), as well

as the benefits and drawbacks of each treatment, for consent acquisition. Additionally, it should be ensured that the patient has sufficient comprehension of all the treatment options available and are guided in their treatment selection (Supplementary Provision 3). Insufficient information related to end-stage renal failure treatment methods is currently being provided to patients in Japan, and information provision related to PD has a strong tendency to be limited to facilities that conduct PD [6]. Information should be equally provided, and cooperation with a dialysis facility that can conduct PD should be actively prioritized in cases where a patient, who is in a facility that cannot conduct it, requests that treatment.

Evaluation of the initiatives and performance related to the promotion of PD began with the Revision of Medical Fees for Financial Year 2018. In other words, an initiation period addition is calculated based on the documents created by related associations and other referenced materials after sufficient information regarding renal replacement therapy has been provided to the patient. Other additions are calculated when an institution shows performance related to PD guidance management or initiatives for kidney transplantation promotion.

Proposals on decision-making processes related to the commencement and continuance of maintenance HD were issued in 2014 in order to address end-stage dialysis non-initiation and suspension [7]. However, there were no such proposals related to PD. Conservative treatment other than renal replacement therapy may also be conducted.

2. Pre-initiation education and planned initiations

Pre-initiation education and planned initiations are conducted for PD. Reports have confirmed that PD should be introduced while residual renal function is still present so as to avoid initiation period complications and improve patient prognosis [8]. Active referrals to specialists and outpatient renal failure education are important as they help promote planned initiation of dialysis [9–12].

Patients who were referred to specialists at an early stage (roughly 6 months or more before initiation) tended to choose PD as their primary form of renal replacement therapy compared to those who were referred immediately prior to symptom onset [13, 14]. Reports have also indicated a strong correlation between pre-initiation patient education and PD selection [15].

Hospitalization due to catheter implantation and potential surgical complications are particular issues related to the planned initiation of dialysis. To address these issues, Japan uses a stepwise PD initiation method, which involves the insertion and implantation of the PD catheter prior to the onset of clinical symptoms and

initiation of PD as soon as the opportunity presents itself (Stepwise initiation of PD using the Moncrief and Popovich technique, SMAP method) [16, 17].

3. Dialysis initiation period

There is currently no comprehensive, evidence-based standard for the initiation of dialysis. This is thought to be because the pathology of end-stage renal failure patients is strongly affected by factors such as patients' primary disease, age, nutritional status, and complications. Currently, the most widely used standard for initiation of dialysis in Japan is the standard outlined by the clinical research project on renal failure by the Japanese Ministry of Health, Labour and Welfare in 1991 [18]. This standard details a comprehensive evaluation based on renal function, clinical symptoms, and the extent of daily life disabilities. The standard has been validated using patients' prognoses 2 years after the initiation of dialysis and follow-ups regarding complications [18]. Furthermore, this standard considers both the elderly and children. However, it only considers initiation of HD, and there are no analyses for PD. Meanwhile, the United States of America initiation standards are set at CKD stage 5 (GFR below 15 mL/min/1.73 m^2), regardless of HD or PD [19]. Europe has also set CKD stage 5 as the standard, recommending that the initiation of dialysis and surgery preparations begin when renal failure symptoms appear and patients' nutritional status worsens [20]. Considering the current initiation standards across the world, we recommend that Japan also use GFR as the standard for evaluation methods of renal function. We also recommend that dialysis be introduced at an appropriate period to maintain and guarantee a favorable nutritional status and high quality of life (QOL) of patients [21–24]. Initiation of dialysis should not be delayed, from a patient prognosis standpoint, in cases where treatment-resistant clinical symptoms appear [25].

4. Examples when GFR is below 6.0 mL/min/1.73 m^2

The maintenance of residual renal function [26, 27], favorable QOL, and high satisfaction [28, 29] have been indicated as medical advantages of PD (Supplementary Provision 4). Meanwhile, medical justifications for establishing initiation standards from only a renal function perspective are not always sufficient in cases where patients are appropriately managed without presenting clinical renal failure symptoms [30–32]. However, there is a strong correlation between decreased renal function and worsening nutritional status [33, 34]. The residual renal function after the initiation of PD has a large influence on patient prognosis [35, 36]. Therefore, cases for

which initiation of PD is planned should not be left until a later stage. Initiation of dialysis should be considered when the GFR is below 6.0 mL/min/1.73 m^2, even in cases where subjective and/or objective symptoms are not observed.

During prospective observational studies, patient groups in which PD was introduced at an eGFR of 5.0–10.0 mL/min/1.73 m^2 showed significantly more favorable prognoses than groups in which it was introduced at an eGFR below 5 mL/min/1.73 m^2 and above 10 mL/min/1.73 m^2 [37]. Meanwhile, randomized controlled trials (RCTs) have reported that patients who underwent planned PD initiation showed no significant differences in prognoses between early-stage (eGFR 10–14 mL/min/1.73 m^2) and late-stage (eGFR 5–7 mL/min/1.73 m^2) initiation groups [38].

Supplementary Provision 1

The Japanese equation is set according to the estimated equation by the Japanese Society of Nephrology [39]. This equation should not be used for evaluating pediatric renal function (please refer to "Initiation in Pediatric Patients").

Supplementary Provision 2

Currently, there is insufficient evidence on the validity of evaluating the eGFR mentioned above during the dialysis initiation period. Evaluations are conducted with measured GFR to the fullest extent possible for the initiation of dialysis. The Japanese Society for Dialysis Therapy in their "Maintenance Hemodialysis Guidelines: Hemodialysis Initiation" (2013) (Statement 2) recommends measurement-based evaluations such as the inulin clearance test, 24-h-urinalysis-based creatinine clearance, and the sum of creatinine clearance and urea clearance (Ccr + Curea) divided by 2 for accurate evaluations of renal function during the dialysis initiation period [3].

Serum creatinine values or endogenous creatinine clearance is used in the authorization standards for renal dysfunction-related physical disability certificates, and from April 2018 onwards, eGFR is also applicable in level 3 and 4 determinations.

Supplementary Provision 3

A manual ("Selection and Conditions of Renal Failure Treatment" (2018 Edition)) was jointly issued by the Japanese Society of Nephrology, Japanese Society for Dialysis Therapy, Japan Society for Transplantation, Japanese Society for Clinical Renal Transplantation, and the Japanese Society for Peritoneal Dialysis to explain renal replacement therapy during end-stage renal failure.

Supplementary Provision 4

Given the advantages of PD, a PD-first policy has been advocated, in which PD is selected as the first choice of treatment for end-stage renal failure [40]. Given the realities in Japan, our committee has defined this concept as "a thought process that preferentially considers PD in patients with residual renal function in order to sufficiently take advantage of the benefits of PD."

Residual renal function refers to renal function following the initiation of dialysis and is clinically defined as daily urine volume exceeding 100 mL.

Initiation in pediatric patients
Key points

1. Sufficient information related to PD, HD, and kidney transplantation should be provided to the patient and their family before renal replacement therapy is initiated. Additionally, sufficient time should be allowed to consider the most appropriate treatment. Referral to a specialized facility may be required.
2. The estimated glomerular filtration rate (eGFR) for children is used to evaluate renal function, which is a criterion for initiation timing.
3. Dialysis should be considered at an eGFR level of 10-15 mL/min/1.73 m^2. The initiation timing should be decided after considering complications such as growth or psychomotor disorders.

Explanation

1. Preparation for initiation

Children and their guardians should be provided with comprehensive information regarding dialysis before obtaining their informed consent. Referrals to specialized facilities are advised for adult patients with CKD-3 (eGFR 30–60 mL/min/1.73 m^2), when various complications begin to appear, or at an eGFR of 30 mL/min/1.73 m^2 at the latest [41]. In pediatric patients (Definition of Japanese pediatrics is under 15 years old.), a clinical team with sufficient knowledge should provide information on PD, HD, and kidney transplantation and take sufficient time to consult with children and their guardians before making treatment decisions. In cases of serious complications other than renal failure, the patient and guardians should consult with several different medical professions so that they are fully informed about the best treatment option to choose. The "Guidelines for discussion about treatment for children with serious illnesses" [42] and "Proposals for the decision-making process relating to the commencement and continuance of

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maintenance hemodialysis" [43] should be referred to in such cases.

Irreversible complications such as those related to growth or social development should be considered when deciding the initiation timing in children. It is important for patients to consider long-term treatment options, including kidney transplantation, and to be referred to a pediatric renal disease specialist at an early stage of CKD. PD is often the preferred treatment option for children due to the many advantages it confers [44], including treatment at home, which is essential for acquiring social skills; daily dialysis, which allows nutritional and fluid uptake essential for growth; and nighttime dialysis, which allows for school attendance and extracurricular activities. PD is almost exclusively used for low-weight children, with 87% of children with renal failure being started on PD under the age of 5 [45].

2. Evaluation methods of renal function and suitability

Renal function in children is evaluated using the eGFR. In Japan, the three equations for eGFR in children include Cr [46–48], CysC [49], and β2MG [50]. Special care must be taken depending on the patient's age and physique (Supplement).

There is no absolute consensus regarding the appropriate renal function-based initiation timing for PD in children [51, 52]. There are no CQs about the standard initiation timing in evidence-based Clinical Guidelines for CKD 2013 and 2018, and the section on children in the Maintenance Hemodialysis Guidelines [53] states that initiation of dialysis should be considered in children when the GFR is below 10 mL/min/1.73 m^2, even if asymptomatic. Meanwhile, in international pediatric initiation standards, the Kidney Disease Outcomes Quality Initiative (K/DOQI) states that dialysis should be considered at an eGFR of 9–14 mL/min/1.73 m^2 and started at 8 mL/min/1.73 m^2 [54], with the initiation at a higher eGFR if the patient exhibits malnutrition, growth disorders, or other complications that cannot be medically controlled [54]. The European pediatric PD working group states that dialysis should be initiated at 10–15 mL/min/1.73 m^2 if no symptoms are observed [55]. Generally speaking, dialysis is initiated at an earlier stage than in adult patients after any potential complications have been considered.

3. Absolute indications and relative indications

Absolute indications of dialysis are serious uremic symptoms, such as neurological complications, hypertension that cannot be controlled by antihypertensive drugs, excessive fluid-induced pulmonary edemas that do not respond to diuretics, pericarditis, hemorrhagic complications, and refractory nausea or vomiting [51]. There is no consensus on the appropriate renal function-based initiation timing in children who do not present absolute dialysis indications [51, 52]. Instead, comprehensive evaluations are conducted based on renal function and symptoms. Relative indications include mild uremic symptoms such as fatigue, reduced cognitive function, and decreased QOL in school life, as well as hyperkalemia, hyperphosphatemia, malnutrition, and growth disorders. Growth disorders are included as an important characteristic category of clinical symptoms in the decision-making standards for children. Growth and development are prioritized over renal function in infants [56].

Supplement

Estimated GFR formula in Japanese children The equation includes Cr (mg/dL), CysC (mg/L), β2MG (mg/L), and height (m). Care must be taken as inaccurate values may lead with Cr eGFR, which uses height as a physique indicator, when the patient's muscle mass varies significantly from the standard physique; CysC eGFR during thyroid dysfunction or steroid treatment; and β2MG eGFR when the patient has an inflammatory disease.

Cr eGFR [46–48]

$$eGFR_{Cr}\ (mL/\ min/1.73\ m^2) = (110.2 \times standard\ Cr/patient\ Cr + 2.93) \times R$$

*Standard Cr (mg/dL)

$$Male:\ Standard\ Cr = -1.259 \times Height^5 + 7.815 \times Height^4 - 18.57 \times Height^3 + 21.39 \times Height^2 - 11.71 \times Height + 2.628$$

$$Female:\ Standard\ Cr = -4.536 \times Height^5 + 27.16 \times Height^4 - 63.47 \times Height^3 + 72.43 \times Height^2 - 40.06 \times Height + 8.778$$

*R: 2 years or older…R=1,

Aged 3 months to 23 months…R = 0.107 × In (Months) + 0.656

CysC eGFR [49]

$$eGFR_{Cys}\ (mL/\ min/1.73\ m^2) = 104.1/Cys\text{-}C - 7.8$$

β2MG eGFR [50]

$$eGFR_{β2MG'}\ (mL/\ min/1.73\ m^2) = 149.0 \times 1/β2MG + 9.15$$

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Chapter 2 Optimal dialysis
Key points

1. There is no clear definition established for optimal PD.
2. A total $Kt/V \geq 1.7$, including both peritoneal and residual renal function, was recommended for solute removal of urea as an indicator. However, merely increasing the efficiency of small solute removal without considering a patient's general condition does not necessarily reduce the mortality risk.
3. The residual renal function is an important prognostic factor. A strong correlation between ultrafiltration failure and mortality is observed in PD patients with anuria, and appropriate management of body fluid volume is important.
4. β_2-microglobulin (β_2-MG) has a strong impact on prognosis, but its concentration levels correlate with the residual renal function. Regulating this with PD prescription is difficult.
5. The combined therapy of PD and HD (PD + HD) is efficacious in removing solutes, especially those larger than β_2-MG.

Explanation

There is currently no clear definition for the optimal dialysis method, so the guideline classifies this into the following three categories: (1) optimal dialysis from the perspective of substance removal and ultrafiltration, (2) optimal dialysis from the perspective of circulatory dynamics, and (3) optimal dialysis during combined therapy. Details of each procedure are summarized below.

(1) Optimal dialysis from the perspective of solute removal and ultrafiltration (includes β_2-MG, acid-base status)

(A) Mass transfer in the peritoneum

Key points

1. The primary mechanism of PD is a molecular diffusion-based mass transfer and osmotic flow-based surplus water removal.
2. Various numerical models have been utilized for PD analysis, and its mechanisms have been clarified.

Explanation

In PD, the capillary vessels in the visceral and parietal peritoneum serve as semi-permeable membranes and correspond to the hollow fibers found in dialyzers used in HD [57].

1. Diffusion, osmosis, and convection in the peritoneum

If only solvents (i.e., water) can pass through a semi-permeable membrane with no solute, then fluid on the lower-concentration side will flow into the higher-concentration side over time through osmosis. The minimal amount of pressure needed to stop this phenomenon is referred to as the osmotic pressure. If some solutes can pass through the semi-permeable membrane, then molecular diffusion based on the concentration gradient from the high- to low-concentration side is generated. Water can be moved in the same direction as molecular diffusion if positive pressure is applied on the fluid on the higher-concentration side or if negative pressure is applied on the fluid in the lower-concentration side. This water movement is associated with solutes and is generally referred to as filtration. The migration phenomenon that accompanies fluid flow is referred to as convection; this filtration through the membrane is also a form of convection.

HD conducts filtration (ultrafiltration) by applying negative pressure on the side of the dialysis fluid, but PD uses a fluid that is hypertonic compared to bodily fluids and conducts ultrafiltration through osmotic pressure differences. For this reason, PD uses a variety of dialysis fluids with different osmotic pressures. There are also routes through which minimal amounts of dialysis fluid are reabsorbed into the body through the lymph ducts. A variety of numerical models have been proposed to evaluate peritoneum permeability.

2. Classic model and the three-pore model

In the first PD model by Henderson, the peritoneum was homogeneous and it was assumed that only molecular diffusion would occur [58]. Most transport phenomena across the peritoneal membrane for solutes smaller than β_2-MG could be explained by a classic mass transfer model, assuming that the peritoneum consists of a single pore type. However, this precludes the permeability of any macromolecules that exceed the size of albumin, which has a molecular weight (MW) of 66,000. Rippe et al. proposed a two-pore model, which assumed that there were two kind of pores in the peritoneum [59, 60]. However, it was later shown that this model could not explain the mechanism of ultrafiltration. Thus, Rippe et al. devised and proposed the three-pore model [60], which assumed that there was a third pore type called the ultra-small pore that only managed water transport across the peritoneum. This ultra-small pore represented

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the cell-permeable water pathway (aquaporin 1 [61]) and is also called a cell pore.

(B) Solute removal and clearance

Key points

1. Molecular diffusion is the primary mechanism for solute removal in PD.
2. The realistic recommended dialysis dose in PD is set as a total weekly *Kt/V* for urea ≥ 1.7. However, merely changing this value does not affect prognosis.

Explanation

Molecular diffusion is the primary mechanism for solute removal in PD. Only solutes up to a MW of around 3000 could be filtered through HD when CAPD was proposed in the late 1970s. As such, further attention was given to PD, which can remove larger solutes. However, the super-high-flux (former IV-type and former V-type in the Japanese reimbursement system) dialyzers currently used for over 90% of patients in Japan can remove 200–300 mg of β_2-MG with 4 h of HD. In contrast, around 20 mg of β_2-MG is removed with standard CAPD in 1 day. HD is over 5 times more efficient when compared over 2 days. Therefore, PD is currently not considered to be superior to HD in terms of removing larger solutes.

By rearranging the definition of kidney clearance in living bodies, PD clearance K_P is defined as follows:

$$K_P = \frac{C_D \times V_D}{C_P \times t} \tag{1}$$

where C_D is the dialysis fluid concentration [mg/mL], C_P is the plasma concentration [mg/mL], V_D is the dialysis fluid drainage amount [mL], and t is the dialysis fluid storage time [min]. All four factors on the right-hand side change with time. Therefore, K_P itself varies considerably with time.

1. Importance of optimal dialysis

Decisions on whether a sufficient dialysis dose is provided are based on the following criteria:

(a) No treatment (dialysis)-related complications have occurred
(b) General condition is favorably maintained
(c) Diagnostic criteria for prognosis are within the favorable range

However, even if it appears that conditions (a)–(c) are satisfied, long-term PD can lead to advanced deterioration of the peritoneum, and encapsulating peritoneal sclerosis (EPS) can occur after the termination of PD. In other words, needlessly continuing PD can be harmful. The conditions mentioned above explain why an optimal dialysis method cannot be clearly defined.

A strong negative correlation is observed between the residual renal function and blood β_2-MG concentration in PD patients. In other words, removal of larger solutes that exceed the size of β_2-MG is dependent on the residual renal function, and the removal through PD has proven to be difficult. With this in mind and using the loss of the residual renal function as a boundary, we need to consider switching the treatment from PD to HD.

1.1. Weekly *Kt/V* for urea (*Kt/V*)

Kt/V is a non-dimensional dialysis dose defined as the product of urea clearance (*K*) and treatment time (*t*) divided by the patient's total body fluid volume (*V*). Results of the CANUSA study recommended a total weekly *Kt/V* for urea of 2.0–2.1, which combines both the residual renal function and the peritoneum [62, 63]. Generally, $C_D/C_P \approx 1.0$ is achieved for urea if the dialysis fluid is indwelled for over 4 h. If the patient is experiencing anuria, the K in Eq. (1) is replaced by the PD clearance K_P, making the following equation self-evident:

$$K_P \cdot t \approx V_D \tag{2}$$

Typically, $V_D \approx 9.0$ L/day ≈ 63.0 L/week, so if the body fluid volume of a 60-kg patient is set as $V \approx 36.0$ L, a weekly $K_P t/V$ is:

$$\frac{K_P t}{V} = \frac{V_D}{V} \approx \frac{(63.0)}{(36.0)} = 1.75 \tag{3}$$

In other words, it is challenging to achieve *Kt/V* ≥ 2.0 with PD alone. Additionally, the ADEMEX study showed that no changes in prognosis were observed even if *Kt/V* is increased on purpose [64]. Moreover, data from Hong Kong showed that favorable prognoses were observed even at *Kt/V* ≤ 2.0 [65]. Currently, a total *Kt/V* ≥ 1.7 is recommended as a realistic value [66–68].

1.2. Weekly creatinine clearance (*Ccr*)

Ccr is normalized with a Westerner's body surface area (peritoneal surface area) of 1.73 m^2 when compared to standard values across the world. *Ccr* = 60 L/week/1.73 m^2 is used as a target value for PD [62], but subsequent analyses supported a formerly used value of 45 L/week/1.73 m^2 [69]. However, creatinine concentrations are also

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generally high in patients whose muscle mass is assured. Analysis of 4 years of statistics from the Japanese Society for Dialysis Therapy (JSDT) showed an inverse correlation between mortality risk and creatinine concentration [70]. Based on these facts, *Ccr* is not recorded as an indicator of the optimal dialysis in the current guidelines.

2. *Kt/V* for urea and prognosis

Reports have indicated decreases in mortality risk with increased *Kt/V* in HD [71]. However, the HEMO study published in 2002 [72] showed no statistically significant differences in prognosis between groups with a single pool *Kt/V* of 1.32 and 1.71. Comparisons between the 2-year survival rates in 965 PD patients separated into two groups using the K/DOQI guideline [63] target *Ccr* = 60 L/week/1.73 m^2 (total *Kt/V* = 2.13) and those who maintained *Ccr* = 45 L/week/1.73 m^2 (total *Kt/V* = 1.62) showed no statistically significant differences (ADEMEX study [64]). In other words, simply increasing the small solute removal efficiency in both HD and PD without considering the patient's general condition did not reduce mortality risk.

Residual renal function, which was clarified with the NECOSAD research [73], is another important prognostic factor. Additionally, the EAPOS research, which focused on APD patients with anuria [74], indicated that there was a strong correlation between ultrafiltration failure and mortality rate increase.

3. Methods that increase dialysis dose

The removal efficiency of larger solutes in PD is almost entirely unrelated to the amount of dialysis fluid and is dependent on the residual renal function. Methods that combine PD and HD (PD + HD combined therapy) are efficacious in improving the removal of these solutes. Increasing the amount of dialysis fluid can increase the dialysis dose for small solutes but increasing the number of dialysis fluid exchanges during the day is not practical. The only way to achieve this is through APD, which can actively exchange dialysis fluid while the patient is asleep at night.

(III) Water removal

Key points

1. Ultrafiltration in PD is conducted by establishing an adequate osmotic pressure difference between the dialysis fluid and body fluid (blood).
2. Ultrafiltration failure can be based on catheter abnormalities or increased peritoneal permeability.

Ultrafiltration can also be dramatically improved by using dialysis fluid with macromolecular dextrin (icodextrin) as an osmotic agent.

Explanation

1. Ultrafiltration and selection of dialysis fluid

Ultrafiltration in PD is conducted by establishing an adequate osmotic pressure difference between the dialysis fluid and body fluid (blood). Glucose is used as an osmotic agent because it is cheap, has no biological toxicity within the physiological concentration range in the bloodstream, and serves as a source of energy after absorption. There are no significant differences between the dialysis fluid used in PD and HD, except that the former does not include K$^+$ and uses lactic acid as a buffer (bicarbonate has also recently been used). However, each dialysis fluid manufacturer prepares three fluid types with different sugar concentrations, as the PD dialysis fluid induces ultrafiltration through osmotic pressure differences. The osmotic pressures of each of these are around 460, 400, and 360 mOsm/kg; these are referred to as "high-concentration fluid," "moderate-concentration fluid," and "low-concentration fluid," respectively. As is clear from its intended use, even the "low-concentration fluid" is hypertonic compared to the body fluid (approximately 300 mOsm/kg), and continuous glucose exposure to the peritoneum could promote peritoneal degradation. This is exacerbated with higher sugar concentrations; currently, the high-concentration fluid is not used in Japan, and the prescription of moderate-concentration fluid is limited.

Heat sterilization accompanies the caramelization of glucose when the dialysis fluid is neutralized, and glucose degradation products (GDPs) are produced. In the past, an acidic solution with a pH of around 5.0–5.5 was used as the dialysis fluid to avoid this degradation reaction. However, there were concerns regarding GDP toxicity and its non-physiological nature due to its low pH. Neutralized dialysis fluids with minimal GDPs are currently being used in Japan.

2. Causes of ultrafiltration defects and countermeasures

Ultrafiltration defects involve cases of catheter abnormalities and cases based on increased peritoneal permeability. The following reasons can be cited in case of the former, which are then addressed as follows:

(a) Catheter misplacement
(b) Omentum entanglement with a side hole

(c) Excessively tightened catheter suture in the abdominal wall
(d) Kinking of the catheter or connection tube

The following countermeasures can be conducted in case of the latter:

(a) Use of a higher concentration of dialysis fluid
(b) Frequent exchanges of dialysis fluid
(c) Use of macromolecular dextrin (icodextrin) products
(d) Implementation of peritoneal resting (short-term, medium-term, long-term)

The peritoneal glucose exposure amount increases with the use of a higher concentration of dialysis fluid (a), which can further promote peritoneal permeability. The frequent exchange of dialysis fluid (b) can be successful if an APD cycler is used and the dialysis fluid is exchanged over a short period at night. The use of macromolecular dextrin products (c) is limited to specified dialysis fluid manufacturers, so this cannot be applied for all patients. Furthermore, reports have indicated that the long-term use of icodextrin dialysis fluid (limited to cases of once per day) has gradually resulted in the loss of ultrafiltration [75], so attention must be taken. The implementation of peritoneal resting (d) is not necessarily efficacious for all patients, either; however, there have been many reports on this method, with the oldest going back to the 1990s [76–81].

(IV) Acid-base equilibrium

Key points

1. Neutralized dialysis fluids are primarily used in Japan.
2. There are no substantial in-treatment changes in pH in CAPD, and values are confined to a relatively narrow normal range.

Explanation

1. Dialysis fluid pH and buffer (alkaline agent)

As previously mentioned, acidic heat-sterilized dialysis fluid was used in the past. However, reports have indicated that even if dialysis fluid with a pH of 5.2 is retained in the abdominal cavity, its pH value increases to over 6.5 within 15 min [82]. This is due to the influence of residual liquid, which had not drained during the fluid exchange. Furthermore, the dialysis fluid is only 2 L compared to over 30 L of the total body fluid. However, there were concerns regarding this brief peritoneal

deterioration due to non-physiologic pH dialysis fluid exposure with each infusion. The utilization rate of neutralized dialysis fluid has rapidly increased in Japan since its introduction to the market in 2000. Low-GDP neutralized dialysis fluid is primarily used, with the exception of some icodextrin dialysis fluids. Collaborative multi-facility research, which evaluated neutralized dialysis fluids, reported no changes to peritoneal fibrosis markers but showed improvements in mesothelial cell markers [83]. Pentosidine also decreased with neutralized fluid use, but its removal takes time, so it should ideally be used at the early stage of initiation. Based on these findings, the necessity of neutralized fluids in the long-term use of PD has not been internationally proven, but it should be recommended as a finding from Japan.

Many PD fluids include lactate as a buffer, but high lactate concentrations are considered non-physiologic. Plasma bicarbonate (HCO_3^-) increases over time in PD patients, and there have been concerns of excessive acidosis correction or alkalosis-based vascular calcification risk. Based on these aspects, dialysis fluids with reduced amount of lactate or those with bicarbonate have been developed.

2. Acid-base balance correction in body fluids

Metabolic acidosis is the pathology of renal failure, so alkaline agent (lactic acid)-based acidosis correction is essential. Compared to intermittent treatments such as HD, where pH can vary considerably, CAPD results in minimal changes in pH and is confined to a relatively normal range. Albumin synthesis from amino acids in the liver is inhibited in the acidic pH range of body fluids. Clinicians have often indicated the superior quality of CAPD because of its acid-base balance correction effects [84, 85].

(2) Optimal dialysis from the perspective of circulatory dynamics

(A) Blood pressure management

Key points

1. The most important general principle of antihypertensive therapy is the optimization of "dry weight." Antihypertensive medication should be considered in cases where achievement and maintenance of "dry weight" do not result in blood pressure reduction.

2. The relationship between blood pressure and prognosis is represented by the so-called "reverse epidemiology." However, care must be taken as this is the result of an observational study and has no intervention-based evidence.
3. The objective of blood pressure management is to maintain systolic and diastolic blood pressure (DBP) below 140 and 90 mmHg, respectively. Special care must be taken to ensure that systolic blood pressure (SBP) is excessively reduced below 110 mmHg.
4. Body fluid volume (extracellular volume) overload is the most important cause of hypertension.
5. Renin/angiotensin/aldosterone inhibitors and loop diuretics should be considered for antihypertensive medication.
6. Blood pressure should be controlled with consideration for circadian, weekly, and seasonal variabilities of home blood pressure.

Explanation

1. Epidemiology and pathology

The FY 2016 Statistics collected by the Japanese Society for Dialysis Therapy indicated that a significant cause of death among dialysis patients was attributed to cardiovascular disorders such as cardiac insufficiency, cerebrovascular diseases, and myocardial infarctions, with 36.1% of patients being affected [86]. Hypertension is a significant risk factor for arteriosclerosis, which causes these diseases, and its prevalence at the time of dialysis initiation is between 80 and 90%. Therefore, it is thought to be closely related to patient prognosis. Compared to HD patients, PD patients have a low frequency of hypertension or left ventricular hypertrophy (LVH) and consequently have fewer cases of severe arrhythmia [87]. However, contributing causes to hypertension in HD patients include (a) body fluid volume (extracellular volume) overload, (b) renin-angiotensin system abnormalities (inappropriate angiotensin II reactivity to volume load), (c) increased sympathetic nerve activity, (d) endothelium-dependent vasodilation disorders, (e) uremic toxins, (f) genetic factors, and (g) erythropoietin. In particular, body fluid volume overload has been cited as the primary contributory cause, and reports have indicated that its correction has resulted in controlled blood pressure levels in over 60% of patients [62, 88–90]. In other words, the most important general principle of antihypertensive therapy in dialysis patients, including those on PD, is the optimization of "dry weight." Antihypertensive medication should be considered in cases where achievement and maintenance of "dry weight" do not result in blood pressure reduction.

The prevalence of hypertension in PD patients is between 69 and 88%. However, there are several different definitions of hypertension. Hypertension prevalence was 88% when hypertension was defined as an SBP of over 140 mmHg or a DBP of over 90 mmHg or when antihypertensive drugs were administered [91]. On the other hand, hypertension prevalence was 69% when hypertension was defined as having blood pressure values exceeding 140/90 mmHg during the day or 120/80 mmHg at night [92] over 30% of the time during 24-h ambulatory blood pressure monitoring (ABPM).

Prognosis based on blood pressure levels in PD patients is represented by "reverse epidemiology," [93]. The total mortality rate significantly increases when blood pressure level decreases below the control SBP value of 111–120 mmHg. However, no significant increases in the total mortality rate were observed even if the SBP levels exceeded the control. A virtually identical trend was also observed in HD patients [94].

2. Treatment
2.1. Target blood pressure

It is well-known that hypertension results in poor prognosis due to its ability to cause cardiovascular complications in the general population and in those with CKD. However, reports have indicated that the relation between blood pressure and prognosis in PD patients represents the so-called "reverse epidemiology," as described above [93]. Regarding the relationship between mortality and blood pressure, prognosis also improves as blood pressure increases in the early stages of PD initiation (within 1 year). However, this relationship was not apparent in patients who were waiting for kidney transplants and had dialysis initiated within the previous 6 months [95]. The same study also showed that prognosis worsens with an increase in blood pressure 6 years after dialysis initiation [93]. These observational studies show that it is challenging to set a target blood pressure.

No research has directly shown improved prognosis in PD patients with antihypertensive therapy. However, antihypertensive therapy has improved prognosis in the general population and in those with CKD [96]. An ideal blood pressure level should always be maintained below 140 mmHg (SBP) and below 90 mmHg (DBP). These statements were shared by the full joint review conducted by the European Renal Association (ERA-EDTA), the European Society of Hypertension (ESH) [97], and the International Society for Peritoneal Dialysis (ISPD) [98], with all proponents making similar recommendations. (In the current guidelines of JSH2019 and/or CKD2018, the target blood pressure has been modified according to the age (under 75 years or older), presence or absence of proteinuria and diabetes.)

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The previously mentioned observational studies [93] also reported worsened prognosis when the SBP was below 110 mmHg. CKD research in Japan has shown that cardiovascular events increase and prognosis worsens when the SBP falls below 110 mmHg [99]. The same is thought to apply to PD patients, and special care must be taken when attempting to excessively lower blood pressure.

2.2. "Dry weight" management

Body fluid volume (extracellular volume) overload is the most important cause of hypertension also in PD patients [100, 101]. Systematic reviews of body fluid analyses using bioimpedance analysis (BIA) were performed, where dry weight was calculated, and the relationship between total mortality and blood pressure was determined. These reviews showed that the total mortality rate did not improve, but significantly favorable control of the SBP was obtained [102].

Reports have also indicated that decreases in residual renal function (RRF) are rapid, regardless of whether body fluid volume overload is transient or constant [103]. Excess body fluid volume continues to decrease RRF, and it is thought that hypertension becomes more likely as a result.

Reports have indicated that there is a relationship between hypertension and the high transport (i.e., peritoneal permeability is increased) in peritoneal function. This is thought to be because ultrafiltration failure stems from high transport, which results in excess body fluid volume, increased frequency of hypertension during the day and night, and increased left ventricular mass index (LVMI) [104]. The frequency of bodily fluid overload is higher in PD patients than in HD patients, and as a result, the frequency of antihypertensive agent administration is higher in PD patients as well [105]. Increased duration of PD also induces excess bodily fluid through ultrafiltration failure, which worsens blood pressure control [106, 107].

2.3. Selection of antihypertensive medications

Maintenance of urine volume in PD patients with RRF is important from a blood pressure management perspective. There were no statistically significant differences in RRF maintenance between the groups that used furosemide and those that did not. However, the urine volume and urinary Na excretion amount were both elevated in the former group [108]. Reports have indicated that tolvaptan not only increases the urine volume but also increases the urinary Na excretion and improves RRF [109]. (The patients' background of reference [53] is basically heart failure with preserved ejection fraction

(HFpEF).) Reports in PD patients with cardiac failure have also indicated improved RRF with tolvaptan. Tolvaptan was reported to decrease both extracellular water (ECW) and intracellular water (ICW), and to improve body fluid control without occurrence of hyponatremia [110]. Reports on mineralocorticoid receptor antagonists (MR antagonists) such as spironolactone showed preventative effects against decreasing left ventricular ejection fraction and cardiac hypertrophy [111].

RRF maintenance is important when considering the prognosis of PD patients. Reports on renin/angiotensin inhibitors indicated that there were no differences in antihypertensive effects from angiotensin-converting enzyme inhibitor (ACEI) ramipril [112] and angiotensin receptor blocker (ARB) valsartan [113], compared to placebos. However, they had a significant effect on RRF maintenance. On the contrary, another report has indicated that ACEIs and ARBs had no significant effects on RRF maintenance and the elapsed time up to anuria [114]. Therefore, further research is required.

Ultrafiltration is conventionally conducted with high glucose concentration PD dialysate injections under conditions of body fluid volume overload. However, Japan does not use high glucose concentration PD dialysate as this worsens the risk of EPS onset. Both SBP and DBP showed statistically significant decreases when icodextrin was used instead of moderate glucose concentration dialysate [115].

2.4. Blood pressure variability

Night-time hypertension in PD patients is often represented by non-dipper type blood pressure variations [116, 117]. There is a high prevalence of early-morning hypertension as well [118]. Increased body fluid volume is considered to be one of the causes. Increase in ultrafiltration is accompanied by a decline in blood pressure [115].

It is obvious that PD patients have less blood pressure variations over 1 week compared to HD patients who need to receive short-term ultrafiltration at regular intervals. However, this has only been proven in a small number of patients [119]. Early-morning blood pressure in HD patients before 2-day interval dialysis is extremely high and is associated with a higher mortality rate. However, these types of changes are not evident in PD patients because PD is continuous dialysis [120, 121].

With regard to seasonal variation, blood pressure decreases during the warmer seasons and increases during the colder seasons [122].

Therefore, prevention of cardiovascular diseases must involve blood pressure control while considering intraday, daily, weekly, and seasonal variations of blood pressure.

(B) Body fluid volume management (maintenance of optimal weight "dry weight")

Key points
It is important to avoid body fluid volume (extracellular fluid volume) overload and maintain an optimal "dry weight."

Explanation
As shown in the NECOSAD study, the residual renal function regulates prognosis and is an important factor [73]. The EAPOS study [74] on APD patients with anuria also indicated strong correlations between ultrafiltration failure and increases in mortality rate, which highlights the importance of "dry weight."

1. Evaluation methods

As shown above, optimal weight is an important element in PD patients; however, similar reports have stated that patients with body fluid overload in Japan also comprised over 30% of cases that required PD [123]. BIA is a favorable indicator for determining "dry weight" [102], but this is not currently used in all facilities. Furthermore, different frequency bands may be used depending on the device, ICW may vary according to physical exhaustion, and whether the absolute value evaluations can be applied to clinical settings is unclear. It is thought that this should be used as a reference and changes over time should be observed [124].

There are conventional methods for determining dry weight in HD [88], which is clinically determined using the following evaluations in PD: (a) No peripheral edema is present during a physical examination, (b) no pleural effusion or pulmonary congestion is present during chest X-ray, and the cardiothoracic ratio is below 50% for males and 53% for females, (c) atrial natriuretic peptide (ANP) concentration is between 50 and 100 pg/mL, and (d) inferior vena cava diameter and respiratory changes {evaluated using the diameter of the expiratory inferior vena cava (IVCe) and the diameter of the inspiratory inferior vena cava (IVCi). IVCe between 14 and 20 mm and collapsibility index = (IVCe − IVCi) / IVCe ≥ 0.5 is considered normal} are used as references, but these are also used when observing changes over time [125].

2. Treatment methods

There are no specific body fluid volume management therapies in PD patients. The detail of therapy is discussed in the section "Blood pressure management." However, the salt intake amounts outlined by the Japanese Society of Nephrology using the PD ultrafiltration volume and urine volume should be targeted and maintained. Salt intake can be estimated as [ultrafiltration volume (L) × 7.5 g] + [0.5 g per 100 mL of residual renal urine volume] or 0.15 g/kg/day with an upper limit of 7.5 g in cases where the urine volume measurement is difficult [126]. Please refer to "Chapter 3 Nutritional management" for further detail.

(3) Optimal dialysis in combination therapy (combined PD + HD therapy)

Key points

1. Combination therapy is a treatment method that improves insufficient dialysis (solute removal deficiency over hydration) in PD-only treatment.

(A) Combined PD + HD therapy (definitions, current status, objectives)

Key points

1. Combined PD + HD therapy incorporates HD once every 1–2 weeks.
2. As of December 31, 2016, over 20% of patients use combination therapy in Japan.
3. Supplementing PD-only therapies with HD therapy in patients with insufficient solute removal or over-hydration is important.

Explanation

1. Definition and current status

Combined PD + HD therapy is a treatment method that adds HD during PD therapy about once every 1–2 weeks [127].

Combined PD + HD therapy has been implemented since the 1990s, but HD service fee requests were not recognized at the time, and it was not widely used [128]. Cases that utilized combined PD + HD therapy increased after the artificial kidney (HD/HDF) calculation/demands for a frequency of once a week in PD patients were authorized in April 2010. Statistical surveys conducted by the Japanese Society for Dialysis Therapy in 2016 indicated that there were 1831 cases in which combined PD + HD therapy was implemented, which was over 20% of all PD cases (total PD patient number 9021). Therefore, it is clear that combined PD + HD therapy has become an established treatment method. When evaluating combination conditions by PD history, 3.4% of patients with a PD history of less than 2 years

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used this therapy, whereas 53.1% of those with over 8 years of PD history have used it, indicating that the number of patients who use combination therapy increases over time. Decreased or no residual renal function (RRF), accompanied by extended PD duration and decreased solute and water removal volume due to deteriorated peritoneal function, has been thought to cause this. The majority of patients (over 80%) combine HD with PD at a frequency of once per week [86].

2. Objectives of combination therapy

The objectives of combined PD + HD therapy are to improve insufficient solute removal and overhydration. PD retains dialysis fluid within the abdominal cavity and is a renal replacement therapy that corrects abnormalities of body fluid composition and volume in renal failure patients through diffusion-based solute removal and osmosis-based ultrafiltration. However, there are limits to the volume of dialysis fluid that can be stored within the abdominal cavity, as well as the time and frequency that can be stored in a single day (24 h). There are also limits to the removal of uremic solutes. For these reasons, the commencement of PD therapy from the point where RRF is present is recommended to sufficiently assure solute removal volume [66]. Solute and water removal with PD therapy while RRF is still present is the sum of contributions from PD and RRF. However, after commencing PD therapy, RRF declines and disappears over time. Solute removal will depend entirely on PD therapy, and the amount of solute removal will decrease. Combination therapy with HD as a supplement for solute removal is becoming an effective strategy for cases where PD therapy was started after the loss of RRF or where RRF was lost following long-term PD therapy. As of December 31, 2006, the most common reason for withdrawing from PD therapy in Japan was peritonitis (27.7%), followed by ultrafiltration failure (15.5%) and dialysis deficiencies (13%). Therefore, insufficient solute removal and ultrafiltration failure were the most common reasons for PD therapy withdrawal. These survey results also show the importance of combining PD with HD to supplement ultrafiltration failure and insufficient solute removal as a measure for prevention of PD withdrawal [129].

(B) Calculation of solute removal volume in combination therapy

Key points

There is no unified calculation method for determining solute removal in combination therapy.

Explanation

1. Calculation of solute removal volume in combined PD + HD therapy

It was previously mentioned that an objective of combined PD + HD therapy was to supplement insufficient solute removal. The calculation of solute removal volume is important when discussing the adequate dialysis dose during combined PD + HD therapy. PD is a continuous therapy method in cases where RRF is still present, so RRF-based creatinine (CCr) and urea (CUn) clearance can be simply added to PD-based CCr and CUn. Meanwhile, CCr and CUn from the intermittent therapy method (HD) cannot be simply added to RRF- and PD-based CCr and CUn. For these reasons, there have been attempts to evaluate dialysis doses during combined PD + HD therapy and calculate solute removal to compare the solute removal volume in PD + HD cases to other modes of therapy (PD only, HD only). Kawanishi et al. calculated the solute removal volume based on PD effluent, HD dialysate [130], and combined PD + HD therapy using equations such as equivalent urea renal clearance (EKR) [131]. Calculations based on EKR are simple because PD effluent and HD dialysate are not collected but are limited in their criteria. Furthermore, it can overestimate the solute removal volume in certain cases [131]. Yamashita et al. examined PD effluent, HD dialysate, and 24-h urine and reported that the concentration of solutes in these fluids was used to calculate the total solute removal volume, which in turn was used to determine a concept called "the clear space." This was deemed to be a useful indicator of solute removal during combined PD + HD therapy and as a comparative metric with other treatment methods [132].

As stated above, there is no consensus regarding the calculation of dialysis dose during combination therapy and no unified solution. However, it is impossible to discuss issues relating to target dialysis doses in combined PD + HD therapy without a standardized calculation method of dialysis dose. Additionally, various clinical research-based analyses are also impossible. We anticipate unified solutions on the calculation methods of solute removal volumes during combined PD + HD therapy in the future.

(III)Effects of combination therapy

Key points

1. Circulatory dynamics can be improved with combination therapy. Achievement of an optimal "dry weight" is possible.

2. The effects of combination therapy include the following:
   – Improved blood pressure
   – Decreased serum β_2-MG concentration
   – Decreased serum creatinine concentration
   – Improved anemia
   – Decreased blood CRP concentration
   – Increased PD-based ultrafiltration, increased CCr
   – Maintenance of serum albumin concentration

Explanation

1. Body fluid/circulatory dynamics management in combined PD + HD therapy

Body fluid management is unstable in PD patients compared to that in HD patients because of the dependence on urine volume in cases where water removal is conducted through ultrafiltration of the peritoneum or when RRF is present. Reports have indicated a high mortality rate in high transporters, which is often a sign of ultrafiltration failure in PD patients [133], with 55% of PD withdrawals being due to failure in controlling body fluid [134]. In such cases of ultrafiltration failure and excess bodily fluid conditions, combining PD with HD assures ultrafiltration and is efficacious in the maintenance of suitable body fluid conditions where edema and hypertension are not present. An analysis of 53 patients who transitioned from PD-only therapy to combined PD + HD therapy by Matsuo et al. showed that combined PD + HD therapy resulted in decreased bodyweight (P < 0.01), SBP (P = 0.03), administered antihypertensive agent dose (P < 0.01), and atrial natriuretic peptides (ANP) in the blood and that combining with HD is efficacious in controlling body fluid volume [135]. Reports have indicated that water removal from HD-based ultrafiltration, as well as PD-based effluent volume, increased. Analyses done by Suzuki et al. involving 7 patients who underwent combined HD once a week with PD therapy showed that the effluent volume increased from an average of 890 to 1150 mL/day [136]. The mechanisms by which PD-based effluent volume improved by combining with HD are not clear, but it is assumed that body fluid/circulatory dynamics management became easier with combined PD + HD therapy.

With combined PD + HD therapy, the achievement of dry weight, which is difficult with PD-only therapy, becomes possible due to guaranteed ultrafiltration from HD implementation. However, the dry weight is only achieved for the day when HD is conducted, and the long-term clinical effects of this are unclear.

2. Effects of combined PD + HD therapy

The reported effects of combined PD + HD therapy were mentioned in the key points [135–137]. As mentioned previously, reports on improved circulatory dynamics caused by combined PD + HD therapy include decreased body weight (potentially due to improvements of overhydration), SBP, antihypertensive agent administration, and blood ANP concentrations. Reports on solute removal by Matsuo et al. indicate decreased serum β_2-MG concentration and serum creatinine concentration [135]. Dialyzers with high β_2 microglobulin (β_2-MG) removal performance (β_2-MG clearance of over 50 mL/min) have been increasingly used following the functional classification of dialyzers in 2006. The removal performance [138] is thought to be due to increased β_2-MG removal from combining with HD. Matsuo et al. also reported increased hemoglobin concentration (average increased from 8.2 to 10.7 g/dL) and decreased erythropoietin dose used (average decreased from 5800 units/week to 4556 units/week) [135]. Hemoglobin value comparisons between the four treatment method categories of "HD (F) only," "HD (F) only - PD catheter present," "PD only," and "PD + HD combined" in statistical surveys conducted by the Japanese Society for Dialysis Therapy in 2009 showed that hemoglobin values were the highest in the "PD + HD combined therapy" category for both males and females (average values of 10.8 g/dL and 10.5 g/dL for males and females, respectively) [71]. Improved anemia effects were also maintained with the combined PD + HD therapy. The mechanisms for decreased erythropoietin dose and increased Hb values in combined PD + HD therapy are unclear. However, increased solute removal due to the combination with HD is thought to be the cause [139]. CRP as an inflammation marker is thought to be a risk factor for worsening dialysis-related complications and malnutrition. However, reports have also indicated decreased CRP concentrations as a result of combined PD + HD therapy (average decrease from 0.5 to 0.2 mg/dL) [135]; improved nutritional status and the prevention of the onset of complications such as arteriosclerosis are also expected from this therapy. Suzuki et al. [136] and Kawanishi et al. [137] reported increased ultrafiltration rate with combined PD + HD therapy. Additionally, Suzuki et al. reported increased CCr due to PD [136]. Increased ultrafiltration is thought to be due to improvements in increased peritoneal permeability. It is thought that solute permeability is generally controlled and that solute removal decreases if peritoneal permeability is improved (controlled). However, as mentioned in "Solute removal and clearance," PD therapy clearance K_P is set as the product of C_D (solute concentration in effluent) and V_D (volume in effluent). As such, K_P can increase by supplementing decreased solute permeability in the peritoneum with increased ultrafiltration (i.e., V_D

increasing even if C_D decreases). The increased CCr in PD reported by Suzuki et al. was thought to be due to an increase in ultrafiltration (V_D) from improvements in increased peritoneal permeability, supplemented by decreased creatinine concentration (creatinine C_D) in PD effluent due to improved peritoneal permeability increases (i.e., decreases). Moreover, analyses by Ueda et al. on patients who underwent combined PD + HD therapy since the initiation of dialysis reported that combined PD + HD therapy maintained statistically significant serum albumin concentrations compared to PD-only patients. Transitioning to combined PD + HD may be one alternative treatment strategy for patients with decreased (or decreasing) serum albumin concentrations during PD-only therapy [140].

The effects of combined PD + HD therapy have been explained here. There are many reports wherein combined PD + HD therapy has been proven to be a favorable treatment modality compared to PD-only therapy. Unfortunately, there are relatively few research reports on these effects, and we look forward to future analyses and investigations based on prospective observational studies and randomized controlled research on multiple patients.

(IV) Optimal dialysis in combined PD + HD therapy

Key points

1. Establishing solute removal volume in combination therapy is currently difficult.
2. Optimal dialysis should be determined based on the clinical inspection values and physical examination findings.
3. There is no edema or hypertension with regard to circulatory dynamics, and a suitable body fluid condition is maintained.
   No hypertension (blood pressure below 140/90 mmHg)
   No pulmonary congestion in chest X-rays
   The cardiothoracic ratio is below 50%
4. Inspection results reveal the following:
   Hb concentration between 10 and 12 g/dL is maintained
   Serum β_2-MG below 30 mg/L is maintained
5. No symptoms of renal failure such as malnutrition or anorexia

Explanation

1. Optimal dialysis indicators in combined PD + HD therapy

The solute removal volume and solute removal efficiency due to combined PD + HD therapy should be considered when discussing optimal dialysis during dialysis therapy. However, as previously mentioned, calculation methods for the solute removal volume in combined therapy have not been standardized either in Japan or overseas. As such, the optimal dialysis of combined PD + HD therapy can only be discussed in terms of the clinical inspection values and physical examination findings of the present therapy method. The "Adequacy of Peritoneal Dialysis" chapter in the Peritoneal Dialysis Guidelines published by the Japanese Society for Dialysis Therapy in 2009 recommended "maintaining a value of 1.7 for weekly urea Kt/V in combination with residual renal function" for the dialysis dose. The guidelines also recommend that the patient should "change prescriptions or therapy methods in cases where renal failure or malnutrition symptoms appear, regardless of whether the patient is conducting optimal dialysis (i.e., Kt/V is maintained at 1.7)" [66]. In other words, "a weekly urea Kt/V of 1.7" is a necessary condition, and the "absence of renal failure symptoms and malnutrition" is a sufficient condition. The clinical inspection values and physical examination findings are important in addition to the dialysis dose. In addition, the clinical inspection and physical examination findings of combined PD + HD therapy are advocated as indicators for optimal dialysis in the clinical guidelines published by the Japanese Society for Dialysis Therapy and are designated as "appropriate dialysis indicators for combined PD + HD therapy," similar to those in PD- and HD-only therapy. Transitioning from PD-only therapy to combined PD + HD therapy or changing the prescriptions in PD + HD therapy should be investigated to maintain the following physical examination findings and inspection values as optimal dialysis indicators for combined PD + HD therapy.

1.1. Edema and hypertension are absent, and suitable body fluid conditions are maintained [66, 141, 142].

No hypertension (blood pressure below 140/90 mmHg)
No pulmonary congestion present in chest X-rays
Cardiothoracic ratio below 50%
The objectives of combined PD + HD therapy are to improve solute removal deficiencies and excess moisture. As such, the physical examination of body fluid conditions deemed optimal in PD- and HD-only therapy and target blood pressure are indicators that should be achieved during combined PD + HD therapy. A target blood pressure value of "below 140/90 mmHg" is set for patients who undergo combined PD + HD therapy, given that in the "Japanese Society for Dialysis Therapy

Guidelines for Management of Cardiovascular Diseases in Patients on Chronic Hemodialysis," it is stated that "in patients under stable long-term maintenance dialysis with no impairment of the cardiac function, we suggest the target of antihypertensive treatment should be blood pressure > 140/90 mmHg before dialysis at the beginning of the week" and mentioned "below 140/90 mmHg" as a target value in the section "Blood pressure management." Furthermore, most patients undergoing combined PD + HD therapy have high levels of overhydration prior to HD, and similar to when conducting PD, blood pressure should be managed to "below 140/90 mmHg" prior to HD. Body fluid condition and blood pressure management are based on appropriate salt and water intake, and depending heavily on ultrafiltration during HD implementation should be avoided. Thus, setting an upper limit of 15 mL/kg/h for the ultrafiltration rate during a single HD session is ideal, and correcting excess bodily fluid with sudden ultrafiltration should be avoided.

1.2. Maintain a pre-HD Hb concentration between 10 and 12 g/dL

The 2015 Japanese Society for Dialysis Therapy Guidelines for Renal Anemia in Chronic Kidney Disease recommended that "target Hb levels that should be maintained for adult peritoneal dialysis (PD) patients are between 11 and 13 g/dL." However, there is no target Hb value mentioned in relation to combined PD + HD therapy. In cases of combined PD + HD therapy, blood is concentrated during HD implementation due to ultrafiltration; prognosis is most favorable when Hb levels are between 11 and 12 g/dL during HD-only therapy cases, and the mortality risk increases when these levels are above 12 g/dL [143]. The target Hb levels in patients with combination therapy were set between 10 and 12 g/dL since. Low erythropoiesis-stimulating agent (ESA) reactivity in PD-only therapy is defined as cases where the remaining kidney function and PD therapy total Kt/V is maintained above 1.7, and the target hemoglobin concentration is not achieved with weekly administrations of 6000 units of rHuEPO or 60 μg of Darbepoietin [144]. This type of low reactivity should be considered for combined PD + HD therapy as well, and the achievement or maintenance of target hemoglobin levels through combination therapy is ideal. The presence of iron deficiencies or inflammation should be investigated, and analyses on the prescription content of HD should be conducted if target hemoglobin concentrations are also not achieved in combined PD + HD therapy even after the administration of 6000 units of rHuEPO or 60 μg of Darbepoetin.

1.3. Maintain a pre-HD serum β_2-MG level of below 30 mg/L

Serum β_2 microglobulin (serum β_2-MG) is a causative agent of dialysis amyloidosis. There are limits to the removal volume of β_2-MG in PD, but this can dramatically increase by combining with HD. Serum β_2-MG concentration is thought to reflect middle molecule removal conditions to some extent, and reports have indicated improved prognosis when serum β_2-MG is maintained at a level below 30 mg/L [132, 141, 145]. In patients undergoing combined PD + HD therapy, attention should be paid to their serum β_2-MG concentration levels. The prescription content of their combined HD therapy should be analyzed if serum β_2-MG concentration increases are observed.

1.4. Absence of renal failure symptoms such as malnutrition or anorexia

Combined PD + HD therapy is conducted to supplement insufficient solute removal. Therefore, the goal of this therapy is to eliminate insufficient solute removal-based renal failure symptoms such as anorexia, and symptoms should be addressed even during combined PD + HD therapy if these renal failure symptoms are observed by increasing the dialysis dose [66, 141]. Furthermore, transitioning to combined PD + HD therapy should be considered in cases where decreased serum albumin concentrations are observed during PD-only therapy with the objective of maintaining these concentrations [140].

(E) Protective peritoneal effects due to combined PD + HD therapy

Key points
Reports have indicated possible improved peritoneal function due to combination therapy. However, there is no concrete evidence of this.

Explanation
The time period during which the peritoneum is not exposed to dialysis fluid has conventionally been thought to influence peritoneal function as a dialysis membrane, and reports have indicated that peritoneal function improved after long periods in which the peritoneum was not exposed to dialysis fluid (i.e., "peritoneal resting") [146].

HD therapy is conducted once every 1–2 weeks during combined PD + HD therapy, but the implementation of PD during these HD implementation days is not authorized by the insurance system in Japan. There is a period during PD + HD therapy where PD therapy is not

conducted, or in other words, a 1–2-day period during which the peritoneum is not exposed to PD fluid. Matsuo et al. reported that D/P Cr, which is an indicator of peritoneal permeability, significantly decreased following 1 year of combination therapy [135]. Analyses by Moriishi et al. on patients undergoing combined PD + HD therapy reported that D/P Cr significantly decreased in the high-average peritoneal function group and tended to decrease in the low and low-average peritoneal function groups [147]. Comparative analyses on cell activity with peritoneal resting models using human peritoneal mesothelial cells by Tomo et al. confirmed that peritoneal mesothelial cell activity improved with 24 h of peritoneal resting and that 1–2-day PD suspension periods may affect the peritoneal membrane tissue [148].

However, these clinical analyses focus only on D/P Cr, with measurement methods varying according to each study and no histological examinations conducted. Fundamental research also lacks the establishment of animal models.

There is no consensus on whether peritoneal function is improved with peritoneal resting at a frequency of 1 day per week during combined PD + HD therapy. This should be researched in the future.

1. Notable points during combined PD + HD therapy

Key points

1. Maintain HD quality during combined PD + HD therapy
2. Avoid excessive ultrafiltration due to HD
3. Use a high-performance membrane dialyzer
4. Use purified dialysis fluid

Explanation

The method by which HD is implemented is critical during combined PD + HD therapy. Combined PD + HD therapy is often used to supplement solute or water removal in patients with decreased or absent RRF. Moreover, it can also be used to further enhance solute removal in patients whose RRF is relatively maintained. The maintenance of RRF and urine volume should be a priority in these types of patients, and sudden HD-induced ultrafiltration should be avoided. Any decreases in blood pressure should be closely monitored. Furthermore, high-performance dialyzer usage for HD is standard practice in Japan, and its use is also recommended by the Japanese Society for Dialysis Therapy in their "Clinical Guideline for Maintenance Hemodialysis: Hemodialysis Prescription" [141]. High-performance dialyzers should also be used in combined PD + HD therapy. The back-filtration of dialysis fluid when using these high-performance dialyzers is essential. Decreased

RRF can occur as a result of pyrogen influx in the bloodstream, and inflammation due to back-filtration in cases where the biological contamination of dialysis fluid is present. HD must be conducted with purified dialysis fluid, and care must be taken to maintain RRF [149–151].

Optimal dialysis in pediatric patients
Key points

1. The target dialysis dose in children should exceed the target dialysis dose of adults.
2. Appropriate body fluid management is essential for cardiovascular and long-term prognosis.
3. Age, sex, and physique must be considered in children to set up DW and to determine standard hypertension values.
4. The efficacy of combined PD + HD therapy in children is unclear.

Explanation

1. Optimal dialysis from the perspective of substance removal and ultrafiltration

There is no clear definition of the optimal PD method in children. However, children-specific outcomes such as growth and development need to be considered, in addition to the survival rate, renal failure complications, and QOL effects, all of which are considered in adults. A high protein intake volume requirement per unit body weight and nitrogen dynamics are prioritized in children for their growth, so total weekly urea Kt/V is used as an indicator for small solute removal. Exceeding the dialysis dose recommended in adults was set as the target for children undergoing HD due to the considerations mentioned above, and there is a consensus that substance removal during pediatric dialysis needs to exceed that of adults [152]. However, there is no clear target value of the total weekly urea Kt/V. The Japanese Society of Pediatric Dialysis has set the target total weekly urea Kt/V as 2.5 (3.0 in infants) for pediatric PD [153], and K/DOQI has set this as 1.8 in combination with remaining renal function [54]. Mortality rates in pediatric PD patients are lower than in adult patients; many patients transition into kidney transplantation, making large-scale research that uses mortality or cardiovascular events as outcomes similar to those used in adults difficult when trying to validate these target values. Meanwhile, reports have indicated correlations between cardiac function, Ca/P values, anemia, FGF23, and total weekly urea Kt/V [154–156]. However, the number of patients studied is small, and there is insufficient evidence to confirm this. Reports on growth have indicated

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that remaining renal function is more important than the total weekly urea Kt/V [157, 158], and the influence of remaining renal function in children is considerable. There is currently no clear evidence that increased small solute removal results in improved prognosis. Thus, the target total weekly urea Kt/V value is a minimal treatment target and should be considered as one of the indicators of optimal dialysis.

2. Optimal dialysis from the perspective of circulatory dynamics

The cause of death in 38% of pediatric PD cases in Japan can be attributed to cardiovascular diseases, and the cause of transitioning from PD to HD treatment in 21% of cases can be attributed to ultrafiltration failure [159]. For these reasons, the optimization of circulatory dynamics is important in children. DW setup similar to that with HD is conducted based on the blood pressure, cardiothoracic ratio, echo-based inferior vena cava diameter, body composition measurements using a bioimpedance analysis, and ANP/BNP, in order to optimize body fluid volume. Blood pressure, cardiothoracic ratio, and body fluid volume can vary according to age, so both age and physique need to be considered [152]. Hypertension is an important finding that indicates excess body fluid. Although there are no large-scale pediatric studies that used mortality or cardiovascular events as outcomes, there have been studies that have used LVH or the internal carotid artery intima-media thickness as midterm outcomes. Hypertension was an independent predictive factor for LVH in pediatric PD and HD patients [160–162]. Elevated DBP value in pediatric PD patients was also an independent predictive factor for the internal carotid artery intima-media thickness in pediatric PD patients [163]. The importance of hypertension treatment has been recognized, but antihypertensive target values in pediatric PD patients have not yet been set; currently, values specified by the Japanese Hypertension Treatment Guidelines [164] and the Pediatric Hypertension Determination Standards are used as targets.

3. Optimal dialysis in combined therapy (combined PD + HD therapy)

There are no aggregate reports on combined PD + HD therapy in children. Assurance and maintenance of the vascular access necessary for HD in low-body-weight children are challenging. We anticipate further studies on adolescent patients in the future.

Chapter 3 Nutritional management

(1) Malnutrition in PD patients

Key points

1. Malnutrition is a factor that influences prognosis and QOL in dialysis patients.
2. There are currently no systematic reviews on the nutrition of PD patients.
3. PD patients are likely to present excess body fluid and malnutrition.
4. Patients are likely to experience enhanced catabolism due to protein loss during dialysis with subsequent malnutrition.
5. Nutritional management of PD patients should pay attention to weight loss and emaciation, as well as avoid insufficient dialysis due to decreased residual renal function.

Explanation

Malnutrition is a factor that significantly influences prognosis and QOL in maintenance dialysis patients, including those on HD and PD. The frequency of severe malnutrition cases is up to 10% and that of mild to moderate cases is between 30 and 60%, whereas around 30% shows no malnutrition [165–169]. Malnutrition in CKD patients can be caused by either insufficient energy intake from proteins or chronic inflammation, although most cases are a combination of the two [170, 171]. The current guideline for the nutritional management of CKD patients on HD is based on one existing systematic review [172]. However, there are yet no systematic reviews on the nutrition of PD patients.

One-third of PD patients present excess body fluid conditions, with or without symptoms [173], and this fluid retention itself can induce malnutrition [174, 175]. Furthermore, protein leakage from the blood vessels into the PD dialysate during dialysis has been shown to promote catabolism and induce malnutrition. It has generally been considered that obesity in HD patients worsens prognosis, whereas in PD patients, reports have indicated that it is weight loss or emaciation that worsens prognosis [176]. There are only a few reports of sarcopenia and frailty in PD patients, which has become a topic of increasing interest in recent years. However, these conditions seem to have significant effects on prognosis and QOL, similar to HD patients [177, 178]. Additionally, long-term PD is known to cause a decrease in residual renal function, and PD-only treatment is known to further worsen the patients' nutritional status due to insufficient dialysis [179–181]; thus, care must be taken regarding body weight changes, as well as dialysis efficiency, which should include residual renal function.

(2) Nutritional management in PD patients

(A) Total energy intake

Key points

1. Total energy intake is set at a value of 30–35 kcal/kg/day for standard bodyweight (body mass index (BMI) = 22 kg/m^2) and adjusted according to age, sex, and physical activity level.
2. The total energy amount in PD patients should consider the amount of energy absorbed from the peritoneum in addition to energy absorbed from food.
3. Continuous glucose loads can induce triglyceride increase and low high-density lipoprotein (HDL) cholesterolemia. Care must be taken regarding increased body fat and the onset of cardiovascular complications.
4. An energy intake of 30–32 kcal/kg/day is generally considered suitable for patients with diabetic nephropathy, but appropriate energy levels should be set after evaluating the nutritional status of patients individually.

Explanation
A standard bodyweight with a body mass index (BMI) of 22 is used when calculating the total energy intake amount (dietary energy intake amount + peritoneal energy absorption amount).

Standard bodyweight (kg) = Height (m)^2 × 22

Total energy intake is set at 30–35 kcal/kg/day for the standard bodyweight and is individually adjusted using the patient's age, sex, and physical activity level [182]. The total energy amount in a PD patient is calculated from the amount of energy taken in through diet along with the amount of energy absorbed through the peritoneum. The amount of energy absorbed through the peritoneum is influenced by the PD dialysate glucose concentration, total PD dialysate amount used, retention time, and peritoneal function. For example, the peritoneal energy intake amount is approximately 70 kcal when 2 L of 1.5% glucose concentration PD dialysate is retained for 4 h, 120 kcal when 2 L of 2.5% glucose concentration PD dialysate is retained for 4 h, and 220 kcal when 2 L of 4.25% glucose concentration PD dialysate is retained for 4 h [183]. Furthermore, reports have indicated that continuous glucose loading can result in triglyceride increase and low HDL cholesterolemia, as well as increased body fat and cardiovascular complication risk [184–186]. There has also been an increasing number of patients with diabetic nephropathy, and for these

patients, 30–32 kcal/kg/day [187] is considered appropriate as they exhibit obese tendencies at energy intake levels of 35 kcal/kg/day. However, ideally, the nutritional status of each patient should be evaluated, and an appropriate energy intake amount established individually.

Currently, icodextrin-based dialysates are on the market, in addition to glucose dialysates that use glucose as an osmotic agent. Icodextrin is manufactured and refined through the hydrolysis of corn starch and is structurally a glucose polymer. Icodextrin-based dialysates, which have a much larger molecular mass than glucose, are used for CAPD. Given their large molecular weight, these substances are slowly absorbed into the body through the lymph system, with only 20% and 34% absorbed after 8 and 12 h of retention time, respectively, thereby maintaining an even osmotic pressure gradient over a long retention period. Calculations show that 150 kcal of energy is absorbed when 2 L of icodextrin is retained for 8 h [188]. Therefore, icodextrin-based dialysates have superior ultrafiltration capabilities over conventional glucose dialysates. We anticipate that icodextrin-based dialysates would be more efficient in patients with diabetes, given their absence of glucose loading. Prospective analysis trials that have used icodextrin-based dialysate as a retained dialysate have indicated improved lipid metabolism effects due to reduced glucose loading [189].

(B) Protein intake amount

Key points

1. Protein and albumin loss into the PD dialysate is thought to be about 10 g and 2–4 g per day, respectively.
2. Protein intake amount is thought to be related to prognosis and onset of cardiovascular events. The ideal protein intake amount is set at 0.9–1.2 g/kg/day assuming suitable energy intake. However, this needs to be evaluated and adjusted based on multiple nutritional indicators.

Explanation
Protein and albumin loss into the dialysate in PD patients is considered to be approximately 10 g and 2–4 g per day, respectively. However, PD prescriptions can influence the amount lost, with increases in the exchanged PD dialysate resulting in increased protein and amino acid loss [190, 191]. A protein intake amount of over 1.2 g/kg/day for a standard body weight is set as the target in order to replenish these losses [192, 193], with the strain on the residual kidney being considered. So far, there is no clear, standardized protein intake amount that applies to all patients. The regression line between

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normalized protein nitrogen appearance (nPNA) and %creatinine generation rate (%CGR), which is a muscle component indicator, in the protein intake amount data of 100 PD patients in Japan showed an intersection point between an nPNA value of 0.9 g/kg/day and %CGR value of 100% [194]. This indicates that the protein intake amount in PD patients with a favorable nutritional status is 0.9 g/kg/day. Furthermore, there was only one patient in this analysis that had an nPNA value of over 1.2 g/kg/day, which points to the fact that the protein intake amount of PD patients in Japan is probably significantly lower than in other countries. There are reports that indicate that the amount of protein intake is related to the prognosis and onset of cardiovascular events [195, 196], with levels below 0.8 g/kg/day thought to increase the risk. However, it is thought that this observed favorable prognosis is due to the protein being adequately absorbed and assimilated as a protein in the body, rather than the intake amount itself directly influencing prognosis. In this sense, the protein intake amount should not be the sole basis for dietary guidance, but rather, the evaluation with multiple indicators such as serum albumin levels, lean body mass, and a protein index score [197] would be more effective. In conclusion, the ideal protein intake amount in PD patients in Japan should be 0.9–1.2 g/kg/day, in the premise of a suitable energy intake. However, this needs to be adjusted after evaluating multiple nutritional indicators.

(III) Dietary salt intake amount

Key points

1. Salt intake management is vital in PD patients who are susceptible to excess bodily fluid issues.
2. The target salt intake amount is to be based on PD ultrafiltration and urine volume and calculated as [ultrafiltration volume (L) × 7.5 g] + [0.5 g per 100 mL of remaining renal urine volume], but this should be considered as 0.15 g/kg/day in actual clinical settings, with an upper limit of 7.5 g.

Explanation

Over 30% of the PD patients are affected by dominant or non-dominant excess body fluid conditions [123]. This highlights the importance of dietary salt intake guidance because excess body fluid conditions due to excessive intake of dietary salt or water are thought to induce hypertension and be a risk factor for cardiovascular complications [198]. Furthermore, potential excess body fluid can make the protein intake amount become insufficient and is recognized as a factor in malnutrition [174, 175, 199]. According to the Japanese Society of Nephrology guidelines, the salt intake amount of PD patients is

set as [ultrafiltration volume (L) × 7.5 g] + [0.5 g per 100 mL residual renal urine volume] [200], which is recommended based on its balance with the removal amount. Thus, patients who have completely lost residual renal function should have an upper dietary salt intake limit of 7.5 g per day per 1 L of PD ultrafiltration. In actual clinical settings, this upper limit of 7.5 g should be considered as the target dietary salt intake amount for 0.15 g/kg of body weight. This limit should be reduced to less than 6 g per day in patients with hypertension but should be re-adjusted if it causes malnutrition. With regard to the lower limits, there have been retrospective research reports by Dong et al. conducted on 305 PD patients who had daily dietary salt intake amounts ranging from 1.93 to 14.1 g [201]. Patient groups with low intake amounts divided by a third (average of 3.58 g/day) had significantly higher total and cardiovascular mortality rates, so it is thought that a daily intake of at least 3 g is necessary. Automatic PD research in Europe reported favorable prognosis in anuria patients with over 750 mL of ultrafiltration [202], which corresponds to a salt intake amount of 5.6 g. However, frequent exchange using automatic dialyzers can result in reduced sodium (Na) removal, so measurements of Na removal amount are ideal [203]. In conclusion, dietary salt intake amount guidelines need to consider the urine volume and ultrafiltration amount for individual patients.

(3) Evaluation and guidance intervention

(A) Evaluation of nutritional status

Key points

1. Nutritional care management methods are used for evaluating the nutritional status of patients. Nutritional screening, assessment, and care plans should be used to determine, implement, and re-evaluate the optimal nutrition for individual patients.
2. Nutritional evaluations should include both the regular evaluation of the dialysis dose and the individual evaluation of each patient's condition to properly implement nutritional management.

Explanation

Reports have indicated that there is a strong positive correlation between PD patients' survival rate, prognosis, PD initiation timing, and nutritional status during dialysis implementation [204, 205]. Therefore, the evaluation of nutritional status should be determined while comprehensively evaluating subjective nutrition evaluations,

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body measurements, body component analysis, and blood chemistry assessments. It is also important to ensure, during nutritional status evaluations, that muscle mass does not decrease over time. The K/DOQI guidelines [206] indicate the evaluation criteria and frequency, with the presence of anemia, as well as the evaluation of potassium, calcium, and phosphorus, as being important. However, many of the existing studies have been conducted on HD patients, with only a few on PD patients. Furthermore, regular dialysis dose evaluation based on collection of 24-h PD drainage fluid and 24-h urine volume is important for monitoring the nutritional status of PD patients. Nutritional evaluations should be conducted at least once every 6 months while taking into consideration possible changes over time. Regular body measurements and body composition analyses can also be beneficial.

1. Nutritional screening
   1.1. Subjective Global Assessment (SGA)

As part of the SGA, body weight changes, dietary intake conditions, and the presence of digestive symptoms such as nausea, vomiting, anorexia, and diarrhea are comprehensively scored. Reports have indicated its effectiveness in the nutritional management of PD patients [207–210].

   1.2. Other screening methods

Other screening methods include the malnutrition universal screening tool (MUST) and the mininutritional assessment (MNA). Each facility can select which screening method is suitable.

2. Nutritional assessment
   2.1. Body measurements

Body measurements are important for evaluating nutritional status. Regular height, body weight, BMI, arm circumference (AC), and triceps skinfold thickness (TSF) measurements can be used as nutritional status indicators. The AC and TSF are used to calculate the arm muscle circumference (AMC) and area (AMA). These measurements allow for the simple, straightforward, and indirect estimation of muscle and fat content in the body [211]; however, it should be taken into consideration that they can be influenced by extracellular fluid volume. These indicators have also recently been related to systematic nutritional status or prognosis [202–213].

   2.2. Body component analysis methods

The body component analysis methods that currently have the most reproducibility and are recognized as efficient in evaluating the protein content in PD patients are dual-energy X-ray absorptiometry (DEXA) [214, 215] and bioelectrical impedance analysis (BIA) [216, 217]. AMC and TSF are known to be somewhat correlated to DEXA and BIA results [215]. Measurements for BIA must be taken after PD dialysate drainage.

   2.3. Blood chemistry assessment

Serum albumin and pre-albumin are used for blood chemistry analysis to evaluate nutritional status. Serum albumin values are representative prognostic factors in patients with end-stage renal failure [216]. However, a wide range of factors influences serum albumin values in PD patients, including inflammation, loss of albumin into the dialysis fluid, and body fluid management conditions. Thus, serum albumin is not the most suitable indicator of the body protein amount and nutritional status [212, 218, 219]. For these reasons, the geriatric nutritional risk index (GNRI) [220], which is frequently used in HD patients, is not very useful as a screening tool in PD patients [221]. Reports have indicated that there is a weak negative correlation between albumin and acute reactive protein concentration in the blood [222], while prealbumin has not yet been clearly shown to be an appropriate biochemical indicator for evaluating the nutritional status of PD patients. Low nutritional status accompanying inflammation is a pattern of malnutrition observed in patients with kidney failure, whereas C-reactive protein (CRP) is important for finding the causes of malnutrition. CRP has been recognized as a predictive factor of mortality risk in PD patients [223, 224].

   2.4. Evaluation of the protein intake amount

The conventional procedure for the evaluation of the protein intake amount is based on interviews with patients. However, considerable training is required for the nutritionists to record, in detail, the individual diet content and intake, as well as to analyze them accurately. Other indices often used include the protein catabolic rate (PCR) (for example, based on the Randerson equation), which is calculated by analyzing 24-h urine collection and total 24-h PD dialysate drainage. Furthermore, reports have indicated that normalized PCR (nPCR), which is normalized based on each patient's individual body weight, is an even more efficient evaluation method of nutritional status compared to PCR [225].

   2.5. Evaluation of dialysis dose

To detect patients' possible malnutrition status due to inadequate dialysis earlier, regular evaluation of PD efficiency, residual renal function, and peritoneal function should be conducted.

(B) Nutrition intervention

Key points

1. Once the deterioration of malnutrition status is detected, the underlying cause needs to be examined so that countermeasures can be implemented promptly.
2. Clinical treatment conducted by a multidisciplinary team is an effective way to implement nutrition intervention methods.

Explanation

Malnutrition in PD patients can be attributed to factors such as nutritional intake deficiencies, nutrient loss into the dialysis fluid, chronic inflammation, and worsening uremia due to inadequate dialysis. Once deterioration of the malnutrition status is detected, the underlying causes need to be examined so that countermeasures can be implemented promptly. The fundamental pathology of malnutrition resulting from nutrient intake deficiency is energy intake deficiency, thus a suitable nutrition guideline is important [226]. Oral administration of a high-energy liquid diet is useful for patients with severe malnutrition. Meanwhile, along with the aging of the dialysis patients, sarcopenia as previously mentioned has also become a compelling issue, and suitable exercise therapy, in addition to nutritional management, is necessary for both matters. Nutrition intervention is thought to have minimal effects for malnutrition accompanying inflammation, and treatment of the primary disease that causes the inflammation is prioritized. A system that evaluates and introduces nutrition more effectively while also considering the patients' background (e.g., family/social support, patient's ADL, and economic situation) and specific characteristics of dialysis therapy should be constructed. Although there are already nutritional management and nutrition guideline policies for HD patients [227], there are only few reports regarding PD; however, we can suggest nutrition intervention methods for PD patients using HD cases as a reference.

1. Dialysis initiation period
    1.1. Thorough nutritional education at the initial stage

Nutritional education during the dialysis initiation period is important for achieving a stabilized lifestyle with dialysis. Diet management should be adjusted between the pre-dialysis and dialysis initiation periods, with nutrition consultations that evaluate the appropriate salt intake, protein control, and energy intake. Patients should be able to recognize the key methods for selecting foods and ensure that the recommended nutritional intake amounts are met. Patients should also be made aware of the importance of nutritional management and dietary therapy. During PD, patients must also pay attention to possible hypokalemia because potassium is excreted.

1.2. Body composition measurements, residual renal function, and peritoneal function evaluation

The optimal weight for PD patients, which corresponds to the dry weight in HD patients, is not always easily determined. Regular body composition measurements, weight check-ups, physical examinations, and imaging examinations are useful for evaluating body fluid balance and assuring that it is appropriately maintained. Patients who have excess body fluid levels should undergo salt intake evaluation and receive consultation, and the possible need for changes to the oral treatment and dialysis prescription should be considered. Evaluation of the residual renal function through 24-h urine collection analysis and/or evaluation of peritoneal function based on the peritoneal equilibration test (PET) is necessary for appropriately determining the dialysis efficiency, and such evaluations should be regularly conducted (every 6–12 months). Patients' PD prescription or dialysis method should be changed if decreased dialysis efficiency is suspected to be causing malnutrition.

2. Dialysis maintenance period
    2.1. Self-monitoring recommendations based on continuous nutritional guidance

Regular re-evaluations of patients' nutritional status should be conducted, and any abnormalities should be identified in the creation and implementation of nutritional screening, assessment, and planning. Continuous consultation that establishes plans based on these evaluations should be created and implemented until improvement is observed. Background factors in daily life, such as home and work environments, need to be considered when evaluating the observed improvements in dietary habits. The consultation should aim towards positive behavioral changes in the patients.

2.2. Comprehensive nutritional management based on regular clinical dialysis teams

The formation of a multidisciplinary team, including physicians, nurses, nutritionists, clinical engineers,

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physical therapists, psychologists, and social workers, can be useful for evaluating nutrition and implementing consultations.

Nutritional management in pediatric patients
Key points

1. Malnutrition has a serious impact on growth and psychomotor development in pediatric PD patients.
2. Patients under the age of 2 with reduced oral intake should be actively considered for enteral nutrition either with nasogastric tube feeding or gastrostomy.
3. Dietary content and physical measurement values, including height and growth rate, should be evaluated regularly. Focused nutrition interventions by a nutritionist are ideal.
4. The recommended energy intake amount is equivalent to that in healthy children and is based on the "Japanese dietary reference intake."
5. Protein intake should be sufficient to cover protein lost through PD, whereas excessive phosphorus intake should be avoided.
6. Dietary salt replenishment is necessary in cases where Na is lost through urine due to congenital anomalies of the kidney and urinary tract or when a relatively large amount of ultrafiltration is necessary for an infant for their physical size and Na is lost through drainage.

Explanation

1. Fundamentals of nutritional management in pediatric PD patients

The evaluation of nutritional status is critical in pediatric PD patients, with malnutrition having a severe impact on growth and psychomotor development [228, 229]. Reports have indicated that growth disorders not only preclude reaching a standard final height but also act as an independent risk factor for mortality [230, 231]. Significant growth disorders during infancy, the period with the highest growth rates, can render subsequent catching up of growth and development extremely difficult. Furthermore, growth during infancy has minimal dependence on growth hormones compared to other periods, so suitable nutritional management is essential from an early stage [232].

Decreased appetite and vomiting are observed in pediatric PD patients, making consistently sufficient nutritional intake quite challenging. This can result in decreased gastrointestinal motility, gastroesophageal reflux, cytokine generation accompanying end-stage kidney disease, and increased intra-abdominal pressure due to dialysis fluid retention [233, 234]. As such, patients with eating disorders, particularly those under the age of 2, need to consider forced nutrition or, in other words, enteral nutrition through nasogastric tubes or gastrostomas. Network registry reports of international PD, which compared nutritional management through oral intake, nasogastric tubes, and gastrostomy, showed that the duration of management with gastrostomy was significantly correlated to growth acquisition [235]. Peritonitis or surgical complication risks were present following the establishment of gastrostomy after the initiation of PD, and thus its establishment prior to or at the same time as PD initiation is considered ideal [236–238]. However, there are reports that gastrostomy placement after the initiation of PD does not increase complications [239].

2. Nutritional evaluation of pediatric PD patients

A suitable nutritional status in children is defined as the state in which a suitable variety and quantity of food is taken into the body and normal growth is maintained [232, 240]. The KDOQI guidelines recommend periodically evaluating the dietary content and SD score of height, growth rate, BMI, and head circumference (under the age of 3) in all CKD patients, including those on dialysis (Table 1). Nutritional management should be provided under the guidance of a nutritionist who is trained in pediatric kidney disease-related nutrition and with the support of the patient, their guardians (e.g., parents), and a multidisciplinary team well-versed in pediatric kidney disease treatment (physicians, nurses, and social workers) [229].

3. Nutritional management in pediatric PD patients
   3.1. Total energy intake

PD patients need to have a sufficient energy intake that is similar to patients at other stages of CKD and other healthy children [229, 241]. The intake amount is based on the "Japanese dietary reference intake," which is revised by the Japanese Ministry of Health, Labour

Table 1 Recommended nutritional evaluation criteria and evaluation intervals in pediatric peritoneal dialysis patients (modified from reference [229])

Evaluation criteria	Evaluation interval (months)		
	0 years	1–3 years	> 3 years
Nutritional intake amount	0.5–2	1–3	3–4
Height	0.5–1	1	1–3
Growth rate	0.5–1	1–2	6
Dry weight	0.25–1	0.5–1	1–3
BMI	0.5–1	1	1–3
Head circumference	0.5–1	1–2	Not recommended

BMI body mass index

and Welfare every 5 years (Table 2) [241, 242]. In actual practice, the patient starts with a set energy intake amount that corresponds to their physique and age, which is gradually increased if sufficient growth is not obtained [241]. Additional energy derived from dialysate glucose is estimated at 8–12 kcal/kg/day [232]. This is influenced by peritoneal permeability in actual practice, so regular glucose absorption amounts should also be evaluated.

3.2. Protein

The dietary reference intake amount for protein also needs to be considered. This needs to supplement the amount lost from PD, and the Japanese Society of Pediatric Dialysis indicates the recommended protein intake amount in PD children (Table 3) [243]. Care must also be taken to ensure that excess phosphorus loading is not applied to children, and a low-potassium or phosphorus formula (Meiji 8806H®) is efficacious for enteral nutrition in children with renal failure [241].

3.3. Salt

Pediatric PD patients, particularly those with congenital anomalies of the kidney and urinary tract, tend to maintain urine control and lose Na through their urine, making dietary salt replenishment necessary. Furthermore, as Na is lost through ultrafiltration, hyponatremia can easily occur if a large amount of ultrafiltration is needed compared to the physical weight of the patient even if they have anuria (e.g., infants), making dietary salt replenishment also essential in this case [244]. However, the Na removal amount can vary according to dwell time, so care must be taken [245]. Breast milk and normal milk have low Na concentrations (6–8 mEq/L). Meiji 8806H milk (27 mEq Na/L with a standard 15%

Table 2 Estimated required energy amount (kcal/day) (modified from reference [242])

Age	Male	Female
0–5 months	550	500
6–8 months	650	600
9–11 months	700	650
1–2 years	950	900
3–5 years	1300	1250
6–7 years	1550	1450
8–9 years	1850	1700
10–11 years	2250	2100
12–14 years	2600	2400
15–17 years	2850	2300

Note: Recorded as physical activity level II (normal)

Table 3 Recommended protein intake amount in pediatric peritoneal dialysis patients (modified from reference [243])

Age	Recommended protein intake amount (g/kg/day)
0–1 year	3
2–5 years	2.5
6–10 years	2
11–15 years	1.5

concentration) is efficacious. Meanwhile, patients with overhydration or hypertension need to exercise Na control [241].

Chapter 4 Peritoneal function
Key points

1. There are several well-established methods for evaluating the peritoneal function, and each has its own unique characteristics. Among them, the PET is the most widely performed method.
2. Regularly evaluating peritoneal function with standard PET or simplified methods (fast PET) is desirable.
3. Extensive researches of biomarkers in the effluent to determine peritoneal conditions have become available. We expect that these are becoming, along with PET, the new methods for evaluating peritoneal function in the future.

Explanation

1. PET

PD is a treatment method that utilizes the physiologic and anatomical properties of the peritoneum to perform blood purification. The peritoneal function in PD refers to the peritoneum conditions in each patient when performing dialysis therapy. When dialysate with a specific composition is retained in the abdominal cavity for a fixed period of time and then drained, the drainage volume and drainage solute composition vary according to the individual. These are due to the differing peritoneal solute permeability or water permeability in each individual. In this chapter, the peritoneal function is defined as the collective solute and water permeability of the peritoneum. The evaluation and comprehension of peritoneal function in each patient are critical for a proper PD prescription (e.g., determination of dwelling time, bag exchange frequency, PD fluid concentration/amount). The peritoneal function also changes over time with continued dialysis [246, 247].

There are three well-established methods for evaluating peritoneal function: (a) PET [248], (b) overall mass transfer area coefficient (MTAC) [249, 250], (c) and the

software for peritoneal function analysis [251]. Although each method is unique and useful, no clinical trials have distinguished which of these methods is the best at managing patients on PD. Therefore, peritoneal evaluation methods should be selected according to the conditions of each facility and should be continuously analyzed. The most widely used evaluation method of peritoneal function is PET, the use of which is supported by previous research reports and clinical studies.

The original techniques of PET were proposed by Twardowski et al. [248] and are used throughout the world. It is unique in that no specialized devices or software are required and comparisons between previous data or between patients can be conducted. In this method, 2.0 L of 2.5% glucose concentration dialysis fluid (or an equivalent osmotic dialysate) is used. After 2 and 4 h of dialysate infusion, the ratio of creatinine concentration in dialysis fluid (D) to plasma (P) (D/P Cr) and the ratio of glucose concentration in the dialysis fluid (D) to its initial concentration (D0) (D/D$_0$ Glu) are calculated. The data of D/P Cr and D/D$_0$ Glu are used to evaluate the removal efficiency of smaller solutes and ultrafiltration efficiency, respectively. The results of PET are plotted on a standard curve to classify patients into the following four categories: "High," "High Average," "Low Average," and "Low," in the order of transparency. PD prescriptions can be considered based on these results. In Europe, "high" can be mistaken for high solute removal, so this is referred to as "fast transporter," and "low" is referred to as "slow transporter" [252]. By measuring the D/P ratio of other measurable substances, the permeability of a substance with its molecular mass can also be evaluated. There are various modifications to the PET. The method that only evaluates data at the 4th hour of standard PET is referred to as the frequency and short-time PET (fast PET) [253]. The low rate of sample collection enables faster evaluation, but the results can be different from those of the original method, so care must be taken [254]. PET using 4.25% glucose dialysate instead of 2.5% is useful for diagnosing ultrafiltration failure and evaluating Na sieving [255, 256]. Refer to the appendix for the actual methods of PET and MTAC. PET should be conducted regularly or at least once a year to monitor the peritoneal function.

According to 2016 reports by the Japanese Society for Dialysis Therapy [257], the percentage of PD patients (excluding combined therapy) who underwent PET, including fast PET, in Japan was approximately 64%. There were no differences between sex for the average D/P Cr ratio, with values of 0.67 and 0.65 for males and females, respectively. The D/P Cr ratio tended to increase with age. Analysis of the D/P Cr ratio by primary disease showed that diabetic nephropathy and renal sclerosis tended to be high compared to other diseases.

2. Research based on PET

There are many reports of factors that influence PET results. It is thought that cytokine production, peritoneal vascular distribution, and blood flow conditions in the abdominal cavity change immediately following catheter placement, causing unstable peritoneal permeability. Actual PET data are variable for up to 1 month following initiation [258]. For these reasons, the guidelines in the USA and Canada recommend that the first PET should be performed at least 1 month after the initiation of PD [259, 260]. PD-related peritonitis significantly affects peritoneal permeability. As a result, permeability increases and the ultrafiltration rate decreases [261]. However, these changes are thought to be transient and recover by 1 month after healing of peritonitis [262, 263]. Meanwhile, long-term peritoneal inflammation may lead to the progression of angiogenesis and fibrosis, which may affect peritoneal permeability [264]. Long-term PD periods also gradually enhance peritoneal permeability (D/P Cr) and decrease ultrafiltration performance. These changes are accelerated by exposure to high glucose concentration dialysate from an early stage [265]. The results of peritoneal biopsy in Japan showed that peritoneal thickness and angiopathy progressed with long-term PD and that groups with decreased ultrafiltration performance had increased peritoneal thickness [266], suggesting that there is a close relationship between decreased peritoneal function and structural changes in the peritoneum.

Reports on the effect of icodextrin on peritoneal function have indicated that there is no statistically significant difference between it and groups who only use glucose solution [267, 268]. However, some reports indicated potentially worsened peritoneal function [269]. Therefore, further research is required. Many research reports that analyzed the differences in PET results using neutralized versus acidic dialysate indicated no differences in small molecule permeability and ultrafiltration capacity [270, 271]. Neutral dialysate has also been shown to have minimal effects on peritoneal permeability and morphology for over 3 years [272]. However, there have been reports that have indicated that neutral fluids decrease ultrafiltration performance [273, 274], and their effects are not constant. It is suggested that the biocompatibility of the dialysis solution has some impact on peritoneal function. Combined PD + HD therapy is commonly practiced in Japan, but some reports have indicated that peritoneal function changes with combined therapy [147, 275] and that D/P Cr has a decreasing tendency following the commencement of combined therapy.

Numerous research reports have analyzed the relationship between peritoneal function and prognosis. Patient

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groups with increased peritoneal permeability and decreased ultrafiltration performance, or in other words, patient groups who fit in the "High" category for PET, tended to have poor prognoses [276–279]. Peritoneal permeability is generally dependent on the dialysis period, but some patients already have increased peritoneal permeability from the initial stages of dialysis initiation. Analyses on biopsies of the peritoneum at the time of initiation indicated a statistically significant correlation between macrophage invasion extent and peritoneal permeability [280]. A wide range of factors, including local inflammation in the peritoneum, race, age, sex, residual renal function, diabetes, and hypoalbuminemia, might contribute to baseline peritoneal permeability [265, 281, 282]. Recent studies have reported a relationship between peritoneal function and genetic polymorphisms (e.g., vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), endothelial NO synthase, and receptors for advanced glycation end-products, RAS genes) [281, 283]. Therefore, furthering our understanding of indications of PD and patient prognosis may be possible at the genetic level.

3. Research on biomarkers in effluent

Research on biomarkers in effluent has been conducted, which has been useful for analyzing peritoneal function alongside PET. Measurements of the cancer antigen 125 (CA125) and IL-6 are particularly straightforward, so they have been conventionally used to evaluate peritoneal condition. CA125 is a 220-kDa glycoprotein produced in a peritoneal mesothelial cell, and its concentration in effluent is thought to reflect the amount of peritoneal mesothelial cells [284]. The level of CA125 is measured when conducting PET, which enables the evaluation of the mesothelial cell amount [285]. Reports have indicated that the concentration of CA125 in the effluent often tends to decrease with dialysis duration; this result corresponds with actual morphological findings [285]. Some facilities routinely conduct CA125 drainage measurements. Further evaluation is required to determine whether these serve as predictive or prognostic factors for EPS.

IL-6 is a versatile cytokine produced from a variety of cell types, including T cells, activated macrophages or monocytes, and vascular endothelial cells. IL-6 concentration in the effluent is thought to reflect inflammation or pre-inflammation conditions, and many reports have indicated its effect on peritoneal permeability [286] or its changes over time [287, 288]. However, further research is necessary regarding its clinical application.

Several types of research have also been conducted on the markers of peritoneal neoangiogenesis (VEGF, transforming growth factor β, tumor necrosis factor α), markers of endothelial dysfunction (E-selectin, vascular cell adhesion marker-1), markers of tissue fibrosis (IV-type collagen, plasminogen-activated control factor-1, CC chemokine ligand-18), and markers of tissue remodeling (matrix metalloprotease-2, hyaluronic acid). We anticipate their application to the increasingly accurate evaluation of peritoneal function in the future [289–291].

Supplement

A. Peritoneal equilibrium test: standard method (PET)
1. Inject 2000 mL 2.5% glucose dialysis solution (or equivalent)
2. Immediately collect a dialysate sample (=$C_D(0)$).
3. Two hours later, collect a dialysate sample (= $C_D(120)$) and a blood sample (=$\bar{C}_B$).
4. Four hours later, collect a dialysate sample (= $C_D(240)$) and drain the remaining fluid.
5. For creatinine, 3 points are plotted on a calibration curve: $C_D(0) / \bar{C}_B$, $C_D(120) / \bar{C}_B$, $C_D(240) / \bar{C}_B$.
6. For glucose, 3 points are plotted on a calibration curve: 1.0, $C_D(120) / C_D(0)$, $C_D(240) / C_D(0)$. ($C_D(0)$ may be a theoretical value of 2.27 g/dL) (Fig. 1).
7. If the creatinine and glucose results differ, prioritize the creatinine results.

B. Peritoneal equilibrium test: simple method (fast PET)
1. Inject 2000 mL 2.5% glucose dialysis solution (or equivalent)
2. Four hours later, collect a dialysate sample (= $C_D(240)$) and a blood sample (=$\bar{C}_B$), and drain the remaining fluid.
3. For creatinine, plot $C_D(240) / \bar{C}_B$ on a calibration curve.
4. For glucose, plot $C_D(240) / C_D(0)$ on a calibration curve. ($C_D(0)$ may be a theoretical value of 2.27 g/dL) (Fig. 1).
5. If the creatinine and glucose results differ, prioritize the creatinine results.

III. Calculating the total mass transfer area coefficient (MTAC)

The following procedure is applied when using the "Peritoneum equilibrium test: standard method" (2.5% glucose dialysis solution) described above. Therefore, MTAC is the result of retaining a 2.5% glucose dialysis
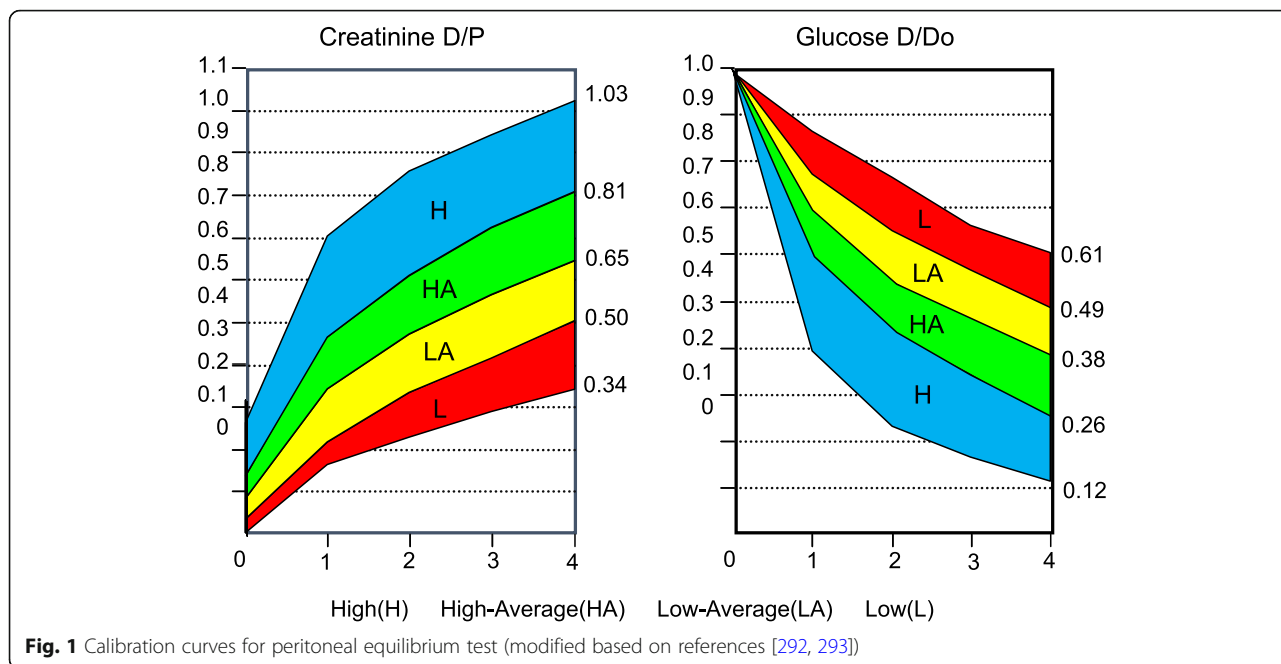
Fig. 1 Calibration curves for peritoneal equilibrium test (modified based on references [292, 293])

solution for 4 h. MTAC can be calculated the same way when another dialysis solution is used or if the solution is retained for a different amount of time.

1. Inject 2000 mL 2.5% glucose dialysis solution (or equivalent). Record the amount injected as $V_D(0)$.
2. Perform the standard peritoneal equilibrium test (see A-1 to A-4 above).
3. Record the amount of drainage as $V_D(t)$ when draining.
4. Calculate MTAC with t = 240 min and assuming the mean dialysis solution $\bar{V}_D = V_D(t)$ [249, 250].

$$MTAC = K0A$$
$$= -\frac{\bar{V}_D}{t} \ln\left[\left\{\frac{V_D(t)}{V_D(0)}\right\}^{1/2} \frac{C_D(t)-\overline{C}_B}{C_D(O)-\overline{C}_B}\right]$$

Peritoneal function in pediatric patients
Key points

1. PET for children in Japan is standardized, and evaluation standards have been established for children.
2. PET methods are the same for both children and adults, but the recommended injection amount is 1100 mL/m² for the former.
3. PET-based evaluations of peritoneal function should be conducted regularly.

Explanation

1. Standardization of PET in children and implementation methods

PET is also widely used for the evaluation of peritoneal function in pediatric patients. PET implementation methods were standardized in children by Warady et al. in 1996 [294]. Adults receive 2 L injections (from Twardowski et al. [295]), so, considering their body surface area, a corresponding injection volume of 1100 mL/m² was designated for children. As a result, there are virtually no differences in creatinine and glucose permeability according to age, and a classification that uses the same categories as that in adults was established [294]. PET in Japan was standardized by Kaku et al. using data from 175 patients, which produced a classification that uses virtually identical categories as those reported in Twardowski et al. and Warady et al. [296]. The PET evaluation standards in Japanese children (value at 240 min of retention) are shown in Tables 4 and 5 [296, 297]. PET methods follow those used in adults. However, please

Table 4 PET evaluation standards in children (D/D₀ Glu ratio) [297]

D/D₀ Glu ratio	PET category
0.51–0.76	Low
0.42–0.51	Low average
0.32–0.42	High average
0.13–0.32	High

PET peritoneal equilibration test

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Table 5 PET evaluation standards in children (D/P Cr ratio) [297]

D/P Cr ratio	PET category
0.77–1.00	High
0.64–0.77	High average
0.51–0.64	Low average
0.25–0.52	Low

PET peritoneal equilibration test

refer to the section on PET in the "Pediatric PD Treatment Manual" for more detail on standardized PET methods in Japanese children [297]. PET requires a 4-h period, so a short PET method wherein the dialysis fluid concentration (2.5%) and the injection amount are kept the same and the retention period is set at 2 h is recommended. These reports classify the 2-h and 4-h retention periods into the same categories, and its utility has been indicated [298, 299].

2. Research on PET-based peritoneal function
    2.1. Relationship between peritoneal function and age, dialysis duration, and peritonitis

Studies that implemented PET over time showed no changes in the PET categories from PD commencement to up to 2 years [300, 301]. However, reports have indicated that the D/P Cr ratio increased and the D/D_0 Glu decreased from the second year onwards [302]. Analyses of 93 PETs in 20 patients by Iwata et al. showed that PD duration had a positive and negative relationship with the D/P Cr ratio and D/D_0 Glu, respectively; each regression line showed that PET fell into the "High" category after about 6 years [303]. Concerning age, infants tended to have high peritoneal permeability [294, 304]. Reports have indicated that if there is a medical history of peritonitis, peritoneal permeability is high and the PET categories become higher [301, 305]. Enhanced peritoneal permeability is correlated to ultrafiltration failure, which is a key symptom that commonly occurs in EPS [306, 307]. Therefore, PET-based evaluations of the peritoneal function should be regularly conducted.

2.2. Influence of neutral dialysis fluid on peritoneal function

Section "Relationship between peritoneal function and age, dialysis duration, and peritonitis" focuses on evaluations with acidic dialysis fluid, but there are no reports that clearly show how neutral dialysis fluid affects PET among children. However, analyses that compared neutral dialysis fluids, which used bicarbonate and acidic dialysis fluids containing lactic acid, showed that there were no differences in the PET results. However, patients treated with neutral dialysis fluids had statistically significantly higher serum bicarbonate concentrations and dialysate CA125 concentrations, reflecting the amount of peritoneal mesothelial cells, which were two times greater than those treated with acidic dialysis fluids [308]. Reports have also indicated that neutral dialysis fluid has higher free water transport [309]. Additionally, it has been reported that neutral dialysis fluids that contain bicarbonate and not lactic acid have a higher ultrafiltration volume [310]. Further accumulation of data is needed in the future.

Chapter 5 Discontinuation of peritoneal dialysis to avoid encapsulating peritoneal sclerosis
Key points

1. PD should be discontinued in patients undergoing long-term PD or where peritoneal deterioration is suspected following intractable peritonitis to mitigate the risk of EPS development.
2. To perform PET regularly is recommended to evaluate peritoneal deterioration.

The Japanese Society for Dialysis Therapy in their 2009 Peritoneal Dialysis Guidelines (GL) presented the above two points as conditions for discontinuation in order to avoid EPS [66]. These same points are also used in the revised GL.

Peritoneal deterioration is a comprehensive concept that considers decreased peritoneal function and morphological changes of the peritoneum. Ultrafiltration failure and enhanced peritoneal permeability are characteristics of decreased peritoneal function. Morphological changes of the peritoneum refer to phenomena that can be identified with a peritoneal laparoscope, pathological peritoneal findings, and cytology of mesothelial cells in drainage fluid.

A GL public awareness survey conducted in 2011 following the publication of the Peritoneal Dialysis Guidelines in 2009 [66] revealed that the GL relating to EPS were widely recognized, with over 90% of facilities conducting PET and over 80% of facilities referring to the PD discontinuation of the GL [311]. For these reasons, this chapter takes over the 2009 PD-GL as a basis and provides explanations using subsequent evidence gathered since that time.

(1) Peritoneal deterioration and EPS

Explanation

1. Epidemiology of acidic dialysis fluid

The incidence of EPS in Japanese PD patients has been reported to be between 0.9 and 2.4% [312–315]. EPS

development is primarily associated with peritoneal deterioration, which is attributed to underlying factors such as diabetes, age, uremic toxins, drugs, peritonitis, and various biological stimulants endogenously present in PD treatment systems. Additionally, it is thought that its severity generally increases over time on PD. In this context, the effects of the bio-incompatibility of PD fluid have been a crucial issue. Causes of peritoneal deterioration include acidity, lactic acid, high osmolality, high glucose, and glucose degradation products [316, 317].

The long-term chronic diseases comprehensive research project chronic renal failure research team of the Japanese Ministry of Health, Labour and Welfare, a research team studying the evaluation and application of CAPD treatment, in their 1997 paper, "Sclerosing Encapsulating Peritonitis (SEP) Diagnosis /Treatment Guidelines (Proposed)," outlined the "CAPD discontinuation standard guidelines for avoiding SEP (EPS)." [318] Decreased peritoneal function (ultrafiltration failure), peritonitis, and PD duration (over 8 years) were defined as risk factors of SEP (EPS). The ISPD presented an international definition of this disease entity and changed the term from SEP to EPS to avoid the misunderstanding that peritonitis is a prerequisite for EPS development [316]. Subsequent Japanese prospective observational studies that examined patients on acidic fluids revealed that the incidence of EPS was 2.5% and 3.18/1000 patients/year, with the incidence increasing by PD duration, being 0%, 0.7%, 2.1%, 5.9%, 5.8%, and 17.2% in patients having undergone PD for 3, 5, 8, 10, 15, and > 15 years, respectively [314]. The Scottish Renal Registry also showed that the median 5-year incidence of EPS was 2.8% and 13.6/1000 patients, indicating that EPS onsets at earlier stages than those in Japan [319, 320]. In conclusion, PD duration is related to EPS risk, but it is thought that EPS development cannot be avoided completely even if PD duration is limited.

2. Influence of neutral dialysis fluid and current issues

Dialysis fluid in Japan today has improved, and neutral dialysis fluid with reduced glucose degradation products have been the standard solution in Japan. In the observational study (NEXT-PD), the incidence of EPS was reportedly reduced [315]. The NEXT-PD study employed virtually the same protocol as the prospective observational study conducted with acidic solutions [314], where the incidence of EPS was 1.0% and 2.3/1000 patients/year in patients on neutral solution, with majority displaying mild clinical symptoms. Furthermore, histological examinations of the parietal peritoneum revealed that patients on neutral dialysis fluid have minimal peritoneal blood vessel degeneration [321–323]. These results suggest that EPS risk decreases with neutral dialysis

fluid use. At present, it is not uncommon to limit PD duration in order to avoid EPS development in Japan. However, this limit was empirically established based only on clinical experiences during the periods of acidic fluid. For this reason, there is no medical rationale for setting a time limit on PD in patients on neutral solution in the clinical setting. Meanwhile, the relationship between EPS development and peritonitis is thought to be important [312], but its influence is not the same between short-term and long-term PD. There is a possibility that even a singular episode of peritonitis during long-term cases can serve as the trigger for EPS development [324, 325]. Additionally, decreased peritoneal function, PD duration, and the number of peritonitis incidents mutually correlate, but the independence of each factor to EPS risk has not been sufficiently elucidated [326]. Regarding the influence of kidney transplantation, it has been reported that there are cases in which EPS developed after kidney transplantation [327, 328], while it has been reported that there are cases showing EPS remission with immunosuppressant use [329]. No definitive remarks can be made regarding kidney transplantation and EPS risk at present. In conclusion, it is essential to consider the risks of EPS in each patient and monitor them over time to avoid EPS.

(2) Decision methods of peritoneal deterioration and issues

Explanation

1. Peritoneal deterioration

Peritoneal deterioration comprehensively refers to changes in peritoneal function and morphology due to PD treatment [330]. The characteristics of decreased peritoneal function are ultrafiltration failure and increased peritoneal permeability. Ultrafiltration volume using 4.25% glucose PD solution and Na sieving confirmation is recommended for determining ultrafiltration failure. In Japan, the clinical indicator is an ultrafiltration volume less than 500 mL, while using 2.5% of glucose PD solution (2 L) 4 times a day [318]. Peritoneal permeability is confirmed with an increased D/P creatinine ratio (D/P Cr), which is calculated using PET. Laparoscopy [331–333], (parietal) peritoneum biopsy [323, 334], and mesothelial cell cytology in drainage fluid [335] are conducted for evaluating peritoneal morphology. Clinical efficiency of surrogate markers in drainage fluid has been reported as markers for peritoneal deterioration (e.g., CA125, hyaluronic acid, matrix metalloprotease-2 [MMP-2], IL-6, VEGF, coagulation/fibrinolytic factors, and Na sieving) [336–341]. There are reports indicating that increased blood β_2 microglobulin [342] and genetic

polymorphisms of receptors for advanced glycation end-products [343] contribute to EPS risk. However, these surrogates are not independent, and there are correlations between histological changes, mesothelial cell cytology, D/P Cr, and circulating factors [344–348].

2. EPS and peritoneal deterioration

Correlations have been reported between EPS development and increased D/P Cr [349–352], mesothelial cell surface area [352], MMP-2 drainage [338, 353], and IL-6 drainage [354].

PET-based peritoneal function determination is not only non-invasive but also objective, simple, and cost-efficient. The ISPD Position Paper [355] underlined peritoneal permeability with a focus on PET results. Reportedly, many EPS cases presented increased peritoneal permeability, but long-term PD patients had increased permeability as well, and thus it is not thought to be a distinct prognosis factor for EPS. Clearly, D/P Cr is insufficient for predicting EPS onset with a single examination, but it provides data about change of peritoneal function over time [350, 351]. Patients whose D/R Cr increases over time and are categorized as "High" for over 12 months should signify advanced peritoneal deterioration, and the discontinuation of PD therapy must be considered. In this regard, ideally, PET should be conducted at least once a year, and changes in D/P Cr should be monitored.

Meanwhile, mesothelial cell cytology is reportedly correlated to EPS risk, and its clinical utility has been demonstrated [352] in predicting EPS development, but there are issues in its sensitivity and specificity as a predictive factor. The same issue has remained unsolved in the clinical application of surrogate markers in PD drainage fluid. For this reason, a diagnosis of peritoneal degeneration should be based on the comprehensive and multiple findings of the clinical markers that are currently available.

A total of 70% of EPS cases developed this disease after PD withdrawal in Japan when acidic solutions were used as standard solution [314]. Therefore, changes within the abdominal cavity after PD withdrawal are thought to be clinically important. There may be some clinical value in retaining the PD catheter for a fixed period of time even after PD withdrawal to observe the characteristics of the drainage fluid and changes in peritoneal function in cases of long-term PD therapy or in cases of suspected peritoneal deterioration. Direct laparoscopic examination is useful in confirming peritoneal deterioration and EPS. However, this procedure carries a risk of infectious peritonitis as well. Additionally, there is no as to the issue whether the so-called peritoneal lavage benefits patients by preventing EPS development after PD discontinuation [352, 356, 357]. Looking at the current information, peritoneal lavage should only be conducted in cases with a high clinical risk of EPS.

(3) Recognition and current status of EPS

Explanation

1. Onset pattern

The detachment and loss of peritoneal mesothelial cells due to long-term exposure to PD fluid trigger peritoneal fibrosis with an exaggerated peritoneal thickness (deterioration). Moreover, capillary vessels in the peritoneum present hyaline degeneration and lumen narrowing, which increases peritoneal permeability (first hit). In cases of a complicating inflammatory condition (i.e., bacterial peritonitis, or some other unknown factor), there is neoangiogenesis of capillary vessels in the peritoneal membrane. This furthermore increases peritoneal permeability even for macromolecules such as albumin and fibrin, causing fibrin-rich membrane formation over the original thickened peritoneal membrane (two-hit theory) [358, 359]. These findings have also been observed in histological analyses of peritoneal tissue [323, 360].

Clinical symptoms appear when the hard fibrin membrane extends to cover the entire intestine, restricting intestinal motility. The fibrin membrane is continuously formed from the parietal to the visceral peritoneum side, often accompanying ascites inside. Its condition can be easily confirmed with abdominal computed tomography (CT). However, the severity of peritoneal deterioration does not always correlate with the formation of an encapsulating membrane, as this can be formed with even mild inflammation in cases of advanced peritoneal deterioration. On the other hand, EPS can occur with sustained inflammation even in cases with absent or mild peritoneal deterioration. The balance between deterioration and inflammation of the peritoneal membrane is important; this is why EPS can occur in patients even with a relatively short PD duration. Furthermore, patients with severe peritoneal fibrosis or secondary hyperparathyroidism can experience diffuse calcium deposition between the encapsulating membrane and degenerated peritoneum, potentially resulting in intestinal obstruction.

For the diagnosis, EPS was defined in 1997 as a "syndrome that represents continuous, intermittent, or repeated ileus symptoms due to wide-ranging adhesion of the diffusely-thickened peritoneum" [318]. Intestinal obstruction symptoms occur due to the formation of an encapsulating membrane that restricts intestinal motility. Symptoms can improve with conservative support, such

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as temporary fasting, but these often relapse after a few months. Clinically, EPS can be diagnosed if the periods between relapses become shorter. Abdominal CT is recommended as a supplemental tool for diagnosis [361, 362]. Lastly, it is not recommended use the term "pre-EPS" for the stage prior to EPS onset.

2. Treatment

Pharmacological agents (corticosteroids, tamoxifen) and surgical therapy are currently used in the management of EPS.

Regarding drug therapy for EPS, corticoids are considered the first choice for treatment in Japan [363]. This drug prevents ascites accumulation and fibrin precipitation through the mechanism of suppressing inflammation. For this reason, corticosteroids should be given immediately at the onset of EPS, and timely tapering of the agents according to inflammatory status is crucial. However, there are limited reports on the use of corticosteroids for EPS in countries outside Japan, and there is also no international consensus on the choice of corticosteroids as the first-line treatment for EPS [355]. On the other hand, there are no reports regarding the usage of the estrogen receptor modulator, tamoxifen, in Japan, with this drug primarily being used in Europe. It is thought to prevent peritoneal fibrosis by regulating the expression of the gene for fibrosis, suppressing mesothelial-mesenchymal transformation of mesothelial cells, and enhancing the removal of degenerated collagen [364, 365]. The Dutch EPS Registry research found that groups using tamoxifen have significantly improved survival rates [366]. A Dutch EPS GL has also released a treatment algorithm based on these results, which includes a step of drug therapy (steroids, Tamoxifen) and timing of surgical therapy [367]. However, the literature on drug therapy mostly consists of case series or small-scale patient research, and no definitive conclusions can be made regarding its clinical efficacy. The British National Institute for Health and Care Excellence (NICE)-GL [368] indicated that there is no clear evidence regarding the efficacy of drug therapy, leaving its use to the discretion of the physician.

Surgical therapy was initially contraindicated [369], but reports in Japan have indicated favorable results with enterolysis [358, 370, 371]. NICE-GL indicated that surgical treatment should be implemented at an early stage by experienced teams for established EPS cases. Statistical surveys by the Japanese Society for Dialysis Therapy (JRDS) also reported that 79.5% of patients with a medical history of EPS had undergone some form of surgical therapy [363]. Reports from Japan [371], the UK [372], Germany [373], and the Netherlands [374] have reported a mortality rate of between 32 and 35%, with a more

favorable performance than conservative therapy [366, 375, 376]. It is thought that treatment performed by surgical teams that are experienced with EPS is clinically valid.

3. Future of EPS

EPS onset rates have decreased with the initiation of neutral dialysis fluid in Japan. However, some patients develop EPS after a relatively short period of time on PD, and peritonitis is thought to contribute to many of these cases. It is essential to establish a treatment flow process that prevents peritonitis and minimizes inflammation and to establish a preventative treatment method to further control EPS in the future.

Discontinuation of PD to avoid EPS in pediatric patients
Key points

1. Long-term PD therapy has a higher risk of developing EPS, so the risks and benefits of continuing treatment need to be considered. Unnecessary long-term treatment should be avoided.
2. PET should be regularly conducted to evaluate peritoneal function.
3. EPS can occur even after changing treatment from PD to HD or transplantation. Follow-up is necessary, and the abdominal symptoms of EPS should be kept in mind.

Explanation
PD is the main treatment of renal replacement therapy in children, and sufficient care must be taken to consider the risks of EPS.

1. PD duration

Reports in three pediatric registries have indicated that EPS onset is more likely with longer PD duration. The earliest reported registry data in Japan (1981–1999, 843 patients) indicated 17 EPS cases (prevalence of 2.0%), and this was equivalent to the incidence in adults at the time [377, 378]. An analysis of PD treatment duration found that a longer duration resulted in a higher incidence of EPS, with durations longer than 5, 8, and 10 years at incidence rates of 6.6%, 12.0%, and 22%, respectively [377, 378]. Registries of 14 European pediatric dialysis facilities (EPDWG) [379] reported EPS onset in 22 out of 1472 patients from 2001 to 2010 (prevalence of 1.5%, 8.7/1000 people/year). Statistically significant differences in PD treatment duration were observed between EPS and non-EPS patients ($p < 0.00001$), with

average durations of 5.9 (1.6–10.2) and 1.7 (0.7–7.7) years, respectively [379]. Italian registries from 1986 to 2011 [380] reported EPS onset in 14 out of 712 patients (prevalence of 1.9%), of which 11 underwent PD treatment for over 5 years. These three registries suggest that prevalence is between 1.5 and 2.0% and that EPS risk increases with a longer PD treatment duration.

2. Dialysis fluid types

The NEXT-PD study data on Japanese adults reported that EPS onset decreased with neutral dialysate [315]. All patients in pediatric registries in Japan were in periods when acidic dialysate was used and thus cannot be compared. In the EPDWG, 5 out of 22 patients used neutral dialysate through the entire PD treatment period, and the EPS onset frequency was analyzed in relation to differences in the dialysate (i.e., acidic vs. neutral dialysate). However, the results indicated no statistical differences (p = 0.8) [379], and the decreased frequency due to neutral dialysate has, at the very least, not been confirmed in children.

3. Ultrafiltration failure, peritoneal equilibration test (PET) categories

Patients with EPS had a high frequency of ultrafiltration failure at the time of EPS onset (Japan 76% [377], Europe 88% [379]), and all cases were categorized as "high" by PET [379]. Evaluations of peritoneal function, such as the presence of ultrafiltration failure, should be regularly tested with PET. Meanwhile, the number of patients who were categorized as "high" by PET multiple times prior to EPS onset were as follows: 3 out of 6 patients in the Japanese registry [377], 0 out of 3 patients in the European registry [379], and 4 out of 4 patients in the Italian registry [380]. Care must be taken as EPS onset can occur even if PET does not classify the patient into the "high transporter" category.

4. Peritonitis

The EPDWG reported that peritonitis in EPS patients is significantly higher than in non-EPS patients (p = 0.02), with average frequencies of 1.9 (0.9–3.1) and 0.72 (0.3–1.2) times per year for EPS and non-EPS patients, respectively [315]. However, no significant differences were observed in the registries of either Japan (EPS 0.44 times/year; non-EPS 0.42 times/year) [377] or Italy (EPS 0.45 times/year; non-EPS 0.42 times/year) [380]. However, EPS onset was observed immediately after peritonitis in 9 out of 17 patients with EPS in Japan [378]. The EPDWG also reported that the frequency of peritonitis in patients with EPS is four times higher than that in

patients reported in other registries. Thus, EPS onset needs to be considered in patients who frequently suffer from peritonitis or when peritonitis develops with deteriorated peritoneum due to long-term PD.

5. Time of onset

EPS onset often occurs during PD treatment (64–77%) [377, 379, 380], but it can also occur after transitioning to HD (14–29%) [378–380] or after transplantation (9–21%) [379, 380]. EPS onset is common in the first year after transitioning to HD [380], but there are also reports of pediatric cases where EPS onset occurred 8 years after transplantation [381], so care must be taken in clinical symptoms which suggest EPS even after PD therapy.

6. Predictive factors

EPS is challenging to diagnose prior to the onset of clinical symptoms. The value of PET data has been discussed in the above sections. There are data regarding the use of CT scans in adults, but EPS can occur even if the CT performed within a year shows no abnormalities [362]. Therefore, CT is not suitable as a screening tool [382]. Reports of peritoneum biopsies in patients who had undergone PD for over 5 years or were clinically suspected of having EPS indicated that patients with no EPS symptoms could continue PD treatment if mesothelial detachment in the peritoneum and stenoses in the lumen of the arteriole were not present [383] However, conducting routine peritoneal biopsy may be challenging in the decision of whether to continue PD treatment [382].

7. Prognosis

Mortality was 17% in Japan [378], 13% (average of 4.8 years in duration after diagnosis) in EPDWG [379], and 43% in Italy [380]. It is surmised that reports in Japan were lower than those in Italy because Japan does not include transplant patients, which are likely to have more severe prognoses [380]. However, the difference in prognoses between the Italian registry and other registries is unknown. Both the Japan and EPDWG data displayed a more favorable prognosis in pediatric EPS cases than in adult cases [379].

Chapter 6 Peritonitis management

(1) Epidemiology and incidence of PD-related peritonitis

(A) Causes of infection and definition of peritonitis

Key points

1. PD-related peritonitis results in decreased peritoneal function, catheter removal, transfer to HD, progression to EPS, and death. Therefore, its prevention and/or early-stage treatment is vital.
2. Peritonitis is classified according to the cause (infection pathway) into exogenous and endogenous infections.
3. Patients that have had peritonitis and experience recurrence after it was healed are classified as recurrent if the recurrence occurred within 4 weeks. Peritonitis can also be classified as recurrent, relapsing, repeat, refractory, or as catheter-related peritonitis.

Explanation

PD-related peritonitis in PD patients causes decreased ultrafiltration capacity or peritoneal dysfunction. It is a major problem as it can lead to catheter removal, transfer to HD, progression to EPS, and death; this further highlights the importance of prevention and/or early-stage treatment [384–388]. There are various infection pathways, which can be classified as follows:

A. Exogenous infection
   (a) Transcatheter infection due to operational error of bag exchange
   (b) Paracatheter infection due to subcutaneous tunnel infection spread from exit-site infection
   (c) Infection by the catheter at the time of its insertion
B. Endogenous infection
   (a) Transintestinal infection via bacterial migration due to diverticulitis
   (b) Hematogenous infection
   (c) Infection through the vagina
   (d) Miscellaneous infection such as intraperitoneal abscesses

The infection typically occurs due to touch contamination or spread of exit-site/tunnel infection. Other endogenous infections include spread of intestinal infection (cholecystitis, appendicitis, ruptured diverticulum, severe diarrhea, intestinal perforation, ileus, incarcerated hernias) and hematogenous infections [389–394].

Peritonitis includes recurrent peritonitis, relapsing peritonitis, repeat peritonitis, refractory peritonitis, and catheter-related peritonitis, which are defined as follows [395]:

– Recurrent: An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism
– Relapsing: An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile episode
– Repeat: An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism
– Refractory: Failure of the effluent to clear after 5 days of appropriate antibiotics
– Catheter-related peritonitis: Peritonitis in conjunction with an exit-site or tunnel infection with the same organism or one site sterile

(B) Incidence

Key points

The incidence of peritonitis should be expressed as the number of patients in a given year. The incidence of peritonitis in Japan is low, at 0.21–0.24 patients/year.

Explanation

The incidence of peritonitis has been reported as one episode per number of patient-month of treatment. However, the ISPD Committee has recommended to report the incidence as number of episodes per patient-year [395]. Points of caution include counting from the first date of starting PD training (at the time of PD start), counting relapsing peritonitis (peritonitis that occurs due to the same microbe within 4 weeks after the end of peritonitis treatment) as one time, and counting peritonitis that occurred when medical staff exchanged bags during hospitalization as one time.

In addition to the calculations of the overall incidence of peritonitis, statistics according to the causative organism and its antibiotic sensitivity also need to be considered [391]. The tendency of the causative organism may vary according to the facility, and countermeasures need to be prepared for high-incidence facilities. Therefore, it is important to know the infection tendencies at each facility [395]. ISPD guidelines have advised a target incidence of peritonitis of no higher than 0.67/patient/year and an ideal incidence of less than 0.36/patient/year until 2010 [396]. However, they stated, in 2016, that it should not exceed 0.5/patient/year [395].

There have been numerous reports on the incidence of peritonitis in recent years, and reports often indicate an incidence of around 0.18–0.5/patient/year [397–412].

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There appear to be no differences according to the primary disease, even with lupus nephritis or polycystic kidney disease [413, 414]. A retrospective study on the incidence of peritonitis in Japan in 1996 reported a value of 0.23/patient/year [415]. The Japanese Society for Dialysis Therapy indicated an incidence of 0.21–0.24/patient/year with no large variations observed from 2012 to 2015, suggesting that the management of peritonitis is favorable in Japan. A report in 2015 indicated that the incidence of peritonitis was rather high among males and tended to increase with age. No correlations were observed between the incidence of peritonitis and history of dialysis. The incidence of peritonitis according to the primary disease was reported to increase in cases of nephrosclerosis or diabetic nephropathy.

As just described, the incidence of peritonitis in Japan is low and well-managed. However, peritonitis remains the primary cause of PD withdrawal, and the development of continuous preventative measures is anticipated in the future [385].

(III)Risk factors

Key points
Diabetes and obesity are considered risk factors for peritonitis, but the dialysis method-based effects are unclear.

Explanation
Risk factors for PD-related peritonitis include diabetes, obesity, ethnicity, climate, and depression [416]. Reports have also indicated that PD catheter morphology and Y-bags can control the incidence of peritonitis after PD [417, 418]. No differences in the incidence have been observed between APD and CAPD [419].

(IV)Causative organisms

Key points

1. Causative organisms in Japan often include gram-positive cocci (commonly coagulase-negative staphylococci).
2. Peritonitis due to mycobacteria, fungi, or anaerobic bacteria is refractory, and catheter removal rates are high.

Explanation
The most common causative organism is coagulase-negative staphylococci [412]. Reports from Japan indicated that 42.7% were gram-positive cocci, of which the most common was *Staphylococcus* at 21.5% [387]. Research on 6639 patients from 2003 to 2008 in Australia indicated that gram-positive and negative cocci accounted for 53.4% and 23.6%, respectively. The report

indicated that mycobacterial and fungal infections were rare, but catheter removal rates were high in conjunction with anaerobic bacteria [420]. There were various causative organisms in each facility, and it is, therefore, important to know their frequencies at each facility [395].

(2) PD-related peritonitis symptoms and diagnosis

(A) Peritonitis symptoms

Key points
The primary symptoms of peritonitis include abdominal pain and/or cloudy dialysis effluent. Cloudy effluent can appear even without abdominal pain, so daily observations of dialysis effluent are important.

Explanation
Many patients with peritonitis report symptoms of abdominal pain and cloudy dialysis effluent. Reports indicate a prevalence of abdominal pain in 80% of patients, fever over 37.5 °C in 30%, nausea and/or vomiting in 50%, cloudy effluent in 80%, and hypotension in 20% [392]. Patients with peritonitis usually have abdominal pain and rebound tenderness without having a board-like abdomen. Abdominal pain and cloudy effluent do not necessarily have to occur simultaneously, and cloudy effluent may occur after a delay. Cloudy effluent is a symptom that can often be tied to diseases other than peritonitis, but it is often associated with PD-related peritonitis [421]. Diagnosis can be considerably delayed if the patient has no abdominal pain and cloudy effluent is not recognized, so daily observations of dialysis effluent are important.

(B) Diagnosis of peritonitis

Key points
Peritonitis is diagnosed when at least two of the following are observed: (a) abdominal pain and/or cloudy dialysis effluent, (b) white blood cell count in dialysate effluent of above 100/μL or above 0.1×10 [9]/L (after a dwell time of at least 2 h) with a polynuclear leukocyte count of over 50%, and (c) positive dialysis effluent culture.

Peritonitis is diagnosed in APD patients if the neutrophil percentage is over 50%, even with a leukocyte count below 100/μL.

Explanation
If peritonitis is suspected, it is recommended that the dialysate be drained, the external appearance of the effluent be carefully observed, and the effluent be submitted

for cell count (including differentiation), Gram staining, and culture tests [422]. The ISPD guidelines indicate that PD patients with cloudy dialysis effluent should be assumed to have peritonitis and recommend to continue treatment for peritonitis until the diagnosis is confirmed or excluded [395].

Following proposals by the ISPD in 2016 [395], the criteria for diagnosis of peritonitis currently used throughout the world are as noted below [423, 424]. A diagnosis of peritonitis is recommended if at least two of the following clinical criteria are met [395]:

(a) Clinical signs of peritonitis: abdominal pain and/or cloudy dialysis effluent
(b) White blood cell count in dialysate effluent of above 100/μL or 0.1 × 10 [9]/L (after a dwell time of at least 2 h), and a polynuclear leukocyte percentage of at least 50% [425].
(c) Positive dialysis effluent culture

Physicians should consider the patient's symptoms, presence of contamination during recent PD fluid exchange, opportunities for bacterial contamination such as unexpected PD connection problems or tube cutting, upper/lower endoscopy or gynecologic procedure, diarrhea or constipation, history of peritonitis, and past or current exit-site infections. The tunnel or exit sites of catheters should be carefully observed and actively checked for any pus discharge. Cultures of any discharge should be taken.

Typical physical findings include abdominal pain, which spreads throughout the abdominal area and, at times, is accompanied by a muscular defense. Patients with endogenous peritonitis often have systematic illnesses such as sepsis. Therefore, those with localized pain/tenderness or pus discharge within their dialysis effluent need to be carefully examined for surgical etiologies such as intraabdominal abscesses. Abdominal X-rays and blood cultures are not essential in cases of standard PD-related peritonitis, but these should be conducted if sepsis due to endogenous infection is suspected from clinical symptoms such as those outlined above.

Meanwhile, APD patients often do not recognize cloudy effluent as white blood cell count in dialysate effluent is influenced in part by the dwell time. For these reasons, percentages of polymorphonuclear cells in the dialysate effluent, in along with confirmation of cloudy dialysis effluent, are used for diagnosing peritonitis rather than absolute white blood cell count in patients on APD with rapid cycle treatment. If the percentage of polymorphonuclear cells is over 50%, the patient is diagnosed with peritonitis even if the white blood cell count is below 100/μL [425]. In patients on APD without any dialysate dwell during the daytime, 1 L of dialysis solution should be infused, dwelled for 1–2 h, and then drained for further examination.

Following a diagnosis of peritonitis, the current episode must be classified as either recurrent, relapsing, or repeat peritonitis. This is because the incidences of recurrent and relapsing peritonitis are 14% and 5%, respectively, and both are considered risk factors for catheter removal or permanent HD transfer [426]. Repeat peritonitis occurs at an incidence of around 10%, and the most common form of onset is that which occurs within 2 months after resolution of the last peritonitis by antibacterial drug therapy [427, 428].

(III) Methods for analyzing causative organisms

Key points

1. The identification of causative organisms is essential for determining the causes of infection, selecting antibacterial drugs, and preparing subsequent preventative measures.
2. Blood culture bottles should be used for the bacterial cultures of PD effluent.
3. Culturing the effluent after centrifugal separation not only increases the bacteria detection rate but also reduces the time to culture positivity.

Explanation

The ISPD guidelines [395] recommend the following with regard to the identification of causative organisms:

– Use of blood culture bottles for the bacterial cultures of PD effluent.
– The sample collection and culture methods should be reviewed and revised in the facilities where the culture-negative rate is above 15%.

Cultures of PD effluent allow for the selection of appropriate antibacterial drugs by identifying the pathogen and testing antibacterial drug sensitivity. Depending on the pathogen identified, it can also indicate specific infection sources. Gram staining of PD effluent often yields a negative result, but it should still be conducted considering its contribution to early-stage antibacterial drug selection and administration if it turns out positive [429]. Gram staining positivity increases by a factor of 5 to 10 by conducting centrifugal separation for 15 min with 50 mL of dialysis effluent at 3000g, suspending with 3–5 mL of physiological saline solution, and planting them in a solid medium or standard blood medium afterwards [430].

Favorable sensitivity is obtained by injecting 5–10 mL of PD effluent into a blood culture bottle (aerobic/anaerobic), and the culture negativity rate is typically around

10–20% when these methods are used [431, 432]. The detectable strains can vary according to whether the method is based on dissolution in water, or the addition of surfactants such as Tween-80 and Triton-X and culture in blood agar. Reports have indicated that the combination of these two methods increased positivity [433]. Samples should ideally be delivered to laboratories within 6 h, but if this is difficult, the blood culture bottles with the PD effluent injected should be cultured at 37 °C. Culturing of the solid medium should be done in aerobic, microaerophilic, and anaerobic environments.

The time taken until pathogens are identified is crucial. The previously mentioned centrifugal sedimentation treatment not only increases the bacteria detection rate but also reduces the time until culture positivity. Microbiological diagnoses can be confirmed within 3 days for over 75% of patients. If the culture is negative even 3–5 days after commencement, the cell count and differentiation of the PD effluent should be re-measured and a fungal/mycobacterial culture should be conducted alongside the confirmation of treatment reactivity. Furthermore, conducting subcultures for 3–4 days under aerobic, microaerophilic, and anaerobic culture conditions can detect slow-developing bacteria or yeast, which would not be detected using automatic culture systems.

(IV) New detection methods

Key points
Various early diagnosis techniques have been reported, but none have been established as superior to conventional methods.

Explanation
There are various early diagnosis techniques currently being proposed. Leukocyte esterase reagent strips [434], biomarker assays [435], and the polymerase chain reaction (PCR) analysis of bacterially derived DNA fragments [436, 437] were proposed in the 2000s. Reports in the 2010s used bacterial 16S rRNA gene sequence analysis [438], matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (MALDI-TOF) [439], and pathogen-specific local immune fingerprints [440, 441]. However, there is no evidence that any of these techniques are superior to conventional methods.

(3) PD-related peritonitis treatment

Key points

1. Empiric treatment should be promptly started with antibacterial drugs once samples have been collected for identification.

2. Empiric treatment should include 1st-generation cephalosporin administration for Gram-positive bacteria and 3rd-generation cephalosporins or aminoglycosides for Gram-negative bacteria. Vancomycin should be administered for methicillin-resistant *Staphylococcus aureus* (MRSA).

3. Treatment should be switched to a suitable antibacterial drug, and an appropriate treatment duration should be implemented once culture results and sensitivity are determined.

Explanation
Impacts on disease severity and peritoneal function can be reduced by beginning antibacterial drug treatment for peritonitis as soon after sample collection as possible. An antibacterial drug that can cover Gram-positive or negative bacteria needs to be selected as an empiric treatment prior to determining the causative organism. The effectiveness of treatment with 1st-generation cephalosporin or quinolone alone is less than 70% [442].

Antibacterial drugs used for Gram-positive bacteria include 1st-generation cephalosporin or glycopeptides (vancomycin or teicoplanin). Comparisons between 1st-generation cephalosporin and vancomycin have suggested that the latter has superior performance with regard to peritonitis resolution rate, hospitalization rate, and superinfection [443]. However, some reports have also indicated that there were no significant differences in the resolution rate [444]. A meta-analysis showed that glycopeptides are superior to 1st-generation cephalosporins, but reports of the former, which used glycopeptides [443], indicated that this might largely be due to the insufficient dose of cefazolin used [416]. ISPD guidelines recommend that facilities with high methicillin-resistant bacteria detection rates use vancomycin [395, 445], but its usage is covered by health insurance only for MRSA infections, so facilities use it for these purposes instead.

Antibacterial drugs for Gram-negative bacteria include 3rd-generation cephalosporins and aminoglycosides. Other effective drugs include cefepime and carbapenem. Quinolone is efficacious in regions where resistance against it is not advanced.

There have been reports on various combinations of these drugs. Studies that compared combined ceftazidime + cefazolin treatment and combined aminoglycoside (netilmicin) + cefazolin showed no significant differences [446]. There were no significant differences between combined cefazolin + aminoglycoside (netilmicin) treatment and combined vancomycin + ceftazidime treatment either [447]. There were also no significant differences in the reactivity or resolution rate between cefepime treatment and combined vancomycin + aminoglycoside (netilmicin) treatment [448].

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There were no significant differences in the reactivity between combined carbapenem (meropenem) + aminoglycoside (tobramycin) treatment and combined carbapenem (meropenem) + vancomycin treatment [449]. There were no significant differences in effectiveness between combined ceftazidime + cefazolin treatment and carbapenem (imipenem/cilastatin) treatment either [450]. Reports have also examined the effectiveness of quinolone. There were no significant differences in the effectiveness of quinolone (ofloxacin) treatment and combined cephalothin + aminoglycoside (tobramycin) treatment [451]. However, reports have indicated that *S. aureus* elimination was slow with quinolone (ciprofloxacin) [452]. There were no significant differences in effectiveness between combined quinolone (pefloxacin) + vancomycin treatment and aminoglycoside (gentamicin) + vancomycin treatment [453]. There were no significant differences in effectiveness between combined quinolone (levofloxacin) + vancomycin treatment and combined aminoglycoside (netilmicin) + vancomycin treatment [454]. However, combined vancomycin + quinolone (ciprofloxacin) treatment [455] and combined cefazolin + quinolone (ciprofloxacin) treatment [456] were shown to be effective. Patients with allergies to cephalosporin can use aztreonam as a replacement. Combined aztreonam + cefuroxime treatment was found to be effective [457]. Reports have not indicated decreased residual renal function with short-term aminoglycoside treatment [458, 459], but long-term (i.e., over 3 weeks) or repeated use should be avoided as it can increase the risk of developing a hearing disorder [460].

Regarding antibacterial drug administration pathways, drug concentrations within the abdominal cavity are higher with intra-abdominal administration compared to intravenous administration, so ISPD guidelines recommend the former. The current systematic review results are as indicated in CQ 5 (note: intra-abdominal administration is currently not covered by health insurance). Reports have indicated that cefazolin was retained for 6 h in the abdominal cavity and that suitable blood and intra-abdominal concentrations were maintained for 24 h [461]. Recent reports have conducted detailed analyses on intravenous and intra-abdominal meropenem administration. The results indicated that the blood concentrations were equivalent but that concentrations in the dialysis fluid were lower with intravenous administration [462]. There are continuous and intermittent (once/day) administrations of antibacterial drugs in the abdominal cavity, but the latter is generally used. Intermittent administration requires at least 6 h of retention in the abdominal cavity for sufficient absorption [463]. Vancomycin, aminoglycosides, and cephalosporin can all be added into the same dialysis fluid, but aminoglycosides and penicillin cannot be added due to their incompatibility [464].

Please refer to Tables 6 and 7 for antibacterial drug doses.

Analyses have also been done on antibacterial drug stability in the dialysis fluid of antibiotics. The combination of cefazolin and ceftazidime in glucose-based PD fluid and icodextrin-based dialysis fluid was stable for 24 h and 7 days at 37 °C and 4 °C, respectively [465]. Other reports have indicated that this combination was stable for 14 days at 4 °C [466]. These results suggest that 4 C is optimal when storing for more than 1 day.

Patients undergoing APD may have insufficient intra-abdominal concentrations of the antibacterial drug due to frequent exchange because of the cycler, so temporarily switching from APD to CAPD should be considered. Reports have indicated that there were no significant differences in the recurrence rate, mortality, and catheter removal between APD and CAPD for peritonitis treatment. However, an increased leukocyte count period and longer antibacterial drug treatment period were observed with APD [467].

Many patients showed clinical improvements within 48 h of empiric treatment of generic peritonitis. Cell count and bacterial cultures in the drainage fluid need to be re-evaluated in patients who did not improve. Reports have indicated that drainage fluid leukocyte counts above 1090/mm [3] after the 3rd day of treatment was an independent predictive factor for failed treatment [468].

(4) Treatment according to causative organism

(A) Coagulase-negative Staphylococci

Key points
Intra-abdominal administrations of cephalosporin-based antibacterial drugs (vancomycin with resistant bacteria) are to be given for 2 weeks.

Explanation
Coagulase-negative staphylococci (CNS) are normal bacteria found on the skin and include *Staphylococcus epidermidis*. Touch contamination is the cause of many cases. Symptoms are usually not severe, and reactions to antibacterial drugs are favorable [469]. Vancomycin is used in patients with methicillin resistance. Reports on 232 patients with CNS-induced peritonitis indicated that the initial-stage reaction rate was 95.3% in a hospital in Hong Kong, with 49.5% being methicillin-resistant bacteria [470]. Reports on 65 patients with CNS-induced

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Table 6 Recommended intraperitoneal anti-microbial agent dose for peritonitis treatment

	Intermittent (once per day)	Continuous (for each exchange)
Aminoglycoside		
Amikacin	2 mg/kg/day	LD 25 mg/L, MD 12 mg/L
Gentamicin	0.6 mg/kg/day	
Tobramycin	0.6 mg/kg/day	
Cephalosporin		
Cefazolin	15–20 mg/kg/day	LD 500 mg/L, MD 125 mg/L
Cefepime	1000 mg/day	LD 250–500 mg/L, MD 100–125 mg/L
Cefoperazone	No data	LD 500 mg/L, MD 62.5–125 mg/L
Cefotaxime	500–1000 mg/day	No data
Ceftazidime	1000–1500 mg/day	LD 500 mg/L, MD 125 mg/L
Ceftriaxone	1000 mg/day	No data
Penicillin		
Penicillin G	No data	LD 50,000 unit/L, MD 25,000 unit/L
Amoxicillin	No data	MD 150 mg/L
Ampicillin	No data	MD 125 mg/L
Ampicillin / Sulbactam	2 g / 1 g every 12 h	LD 750–1000 mg/L, MD 100 mg/L
Piperacillin / Tazobactam	No data	LD 4 g / 0.5 g, MD 1 g / 0.125 g
Other		
Aztreonam	2 g/day	LD 1000 mg/L, MD 250 mg/L
Ciprofloxacin	No data	MD 50 mg/L
Clindamycin	No data	MD 600 mg/bag
Daptomycin	No data	LD 100 mg/L, MD 20 mg/L
Imipenem / Cilastin		LD 250 mg/L, MD 50 mg/L
Ofloxacin	No data	LD 200 mg/L, MD 25 mg/L
Polymyxin B	No data	MD 300,000 units (30 mg)/bag
Quinupristin / Dalfopristin	25 mg/L per bag exchange [a]	No data
Meropenem	1 g/day	No data
Teicoplanin	15 mg/kg every 5 days	LD 400 mg/bag, MD 20 mg/bag
Vancomycin	15–30 mg/kg every 5–7 days [b]	LD 30 mg/kg/bag, MD 1.5 mg/kg/bag
Anti-fungal agents		
Fluconazole	200 mg IP every 24–48 h	No data
Voriconazole	2.5 mg/kg/day IP	No data

LD initial (load) dose; *MD* maintenance dose; *IP* intraperitoneal; *APD* automatic peritoneal dialysis
[a]Implemented in combination with a 500 mg intravenous injection twice per day
[b]Supplemental dose may be necessary for APD patients
Revised from Reference [395]

peritonitis indicated that 58.5% were cephalosporin-resistant [471]. Generally, 2 weeks of antibacterial drug treatment were sufficient for the patients in these reports. Vancomycin use was a prognosis factor for methicillin-resistant bacteria [472]. Relapsing peritonitis can occur when a biofilm is formed on a PD catheter, and catheter replacement is necessary for such cases [472].

(B) *Staphylococcus aureus*

Key points
Antibacterial drugs should be administered for 3 weeks.

Explanation
S. aureus-based peritonitis can occur with touch contamination, exit-site infection, and tunnel infection. Intra-abdominal administrations of 1st-generation cephalosporins should be done if the patient is sensitive, and vancomycin should be used if MRSA is present. Studies that compared administrations of cefazolin and

Table 7 Recommended whole body anti-microbial agent dose for peritonitis treatment

Drug	Dose
Anti-microbial agent	
Ciprofloxacin	Orally, 250 mg, twice a day [a]
Levofloxacin	Orally, 250 mg/day
Linezolid	IV or orally 600 mg, twice a day
Moxifloxacin	Orally, 400 mg/day
Rifampicin	Sub-50 kg weight: 450 mg/day; over 50 kg weight: 600 mg/day
Trimethoprim / Sulfamethoxazole	Orally, 160 mg / 800 mg, twice per day
Anti-fungal agent	
Amphotericin	Initial dose: IV test dose, 1 mg; 6 h from start: 0.1 mg/kg/day; Increasing from maintenance dose from day 4: 0.75–1.0 mg/kg/day
Caspofungin	Starting dose: IV 70 mg, other 50 mg/day
Fluconazole	Starting dose: orally 200 mg, other 50–100 mg/day
Flucytosine	Orally 1 g/day
Voriconazole	Orally 200 mg every 12 h

IV intravenous administration

[a]500 mg ciprofloxacin administered twice per day if the residual renal function is above 5 mL/min GFR

vancomycin as an initial-stage treatment in 503 patients with *S. aureus*-based peritonitis showed no significant differences in resolution rate between the two groups [473]. The presence of MRSA was an independent risk factor for HD transition [472]. Similarly, reports on 245 cases with *S. aureus* indicated no significant differences in the resolution rate [474]. These reports indicated that combined rifampicin therapy reduced relapsing and recurrent peritonitis risk but that care must be taken for bacterial resistance and drug interactions induced by long-term administration [473]. Reports have indicated that administrations of teicoplanin and daptomycin were efficacious as replacement drugs [475, 476]. A treatment period of 3 weeks is ideal [473, 474]. Peritonitis induced by *S. aureus* due to catheter infection is refractory, and many cases require catheter removal [477].

(III)Enterococcus

Key points

Intra-abdominal administrations of vancomycin should be conducted for 3 weeks. Additional administrations of aminoglycoside-based antibacterial drugs should be considered for severe cases.

Explanation

Enterococcus-based peritonitis is often accompanied by intense stomach pain and can often become severe. *Enterococcus* is a normal bacterial flora in the intestinal canal, and the causes of peritonitis may not only be due to touch contamination or catheter-related infection but can also be related to the abdominal cavity. Reports on 116 cases of *Enterococcus*-based peritonitis indicated increased catheter removal, HD transition, and mortality rates with polymicrobial detection [478]. Furthermore, reports have indicated that HD transitions can be reduced by conducting catheter removal within 1 week. *Enterococcus* is typically cephalosporin-resistant, but pediatric research reported that cephalosporin was efficacious as an initial-stage treatment [479]. Intra-abdominal administration of vancomycin is recommended if the patient is sensitive to vancomycin. Severe cases should consider additional administration of aminoglycoside-based antibacterial drugs. For vancomycin-resistant *Enterococcus* (VRE), intra-abdominal administrations of ampicillin should be conducted if the patient is sensitive to ampicillin. Reports have indicated that linezolid [480], quinupristin/dalfopristin [481], and daptomycin [482] were efficacious if the bacterial infection is resistant to ampicillin.

(IV)Streptococcus

Key points

Antibacterial drugs should be continuously administered for 2 weeks.

Explanation

Streptococcus is often orally derived and usually reacts favorably to antibacterial drugs. Reports on 256 patients with *Streptococcus*-induced peritonitis indicated that the intra-abdominal administration of 1st-generation cephalosporin or vancomycin had a lower recurrence, catheter removal, and mortality related to other strains [483]. Reports have indicated that *Streptococcus viridans*, a normal bacterial flora of the oral cavity, has weak reactions to antibacterial drugs, and are highly recurrent [484, 485].

(E) Corynebacterium

Key points

Treatment is conducted for 3 weeks with antibacterial drugs.

Explanation

Corynebacterium are normal bacterial flora on the skin, but peritonitis due to these bacteria is rare. Analyses of 27 patients with corynebacterial peritonitis indicated

that 13 patients were recurrent, of which 8 were healed after 3 weeks of vancomycin administration [486]. Analyses of 82 patients with corynebacterial peritonitis indicated that the outcome of 2 weeks of vancomycin treatment was as follows: relapse in 18%, recurrence in 15%, catheter removal in 21%, HD transition in 15%, and death in 2% [487].

(F) *Pseudomonas aeruginosa*

Key points

Two types of antibacterial drugs with different mechanisms should be administered for 3 weeks. Many patients with catheter infections will need to have their catheters removed.

Explanation

Pseudomonas aeruginosa-induced peritonitis is severe, and many patients with catheter infections will need to have them removed [488]. Analyses of 104 patients with *Pseudomonas aeruginosa*-induced peritonitis showed that 45.2% had exit-site infections and that the initial-stage reaction rate was 60.6%, while the complete resolution rate was 22.1%. Furthermore, groups that used 3rd-generation cephalosporin had significantly more favorable reactivity than those who used aminoglycosides [489]. Analyses of 191 patients with *Pseudomonas aeruginosa*-induced peritonitis showed that catheter removal and HD transitions were significantly higher than in those of other bacterial strains [490]. Empiric treatment results showed no differences, but subsequent use of two antibacterial drug types for *Pseudomonas aeruginosa* could reduce HD transitions, and the mortality rate was lower with catheter removal than with singular antibacterial drug therapy [488]. Antibacterial drugs with two different treatment mechanisms need to be selected. A combination of either intra-abdominal administration of gentamicin or oral administration of ciprofloxacin and intra-abdominal administration of either ceftazidime or cefepime should be conducted. Carbapenem-based drugs should be administered for *Pseudomonas aeruginosa*, which is resistant to cephalosporin or penicillin [395].

(G) Other Gram-negative bacteria

Key points

Antibacterial drugs should be administered for 3 weeks.

Explanation

The causes of peritonitis due to gram-negative bacteria other than *Pseudomonas aeruginosa* are said to be due to touch contamination, exit-site infections, constipation, and colitis. Antibacterial drugs should be selected based on infectivity, safety, and simplicity in cases where

these were singularly detected. Analyses in Australia indicated that 23.3% of all peritonitis patients were from causes other than *Pseudomonas aeruginosa*, a Gram-negative bacterium, with the most common being *Escherichia coli*, but this also included *Klebsiella, Enterobacter, Serratia, Acinetobacter, Proteus,* and *Citrobacter*. Additionally, a quarter of the cases had multiple bacteria types present [491]. Analyses of 210 patients with enterobacterial peritonitis indicated that 111 were due to *E. coli*, with an initial reaction rate of 84.8% and a resolution rate of 58.1%. Of these, 39% did not respond to singular antibacterial drug treatment, where in vitro sensitivity was confirmed, and a second antibacterial drug was added. Patients who were administered a second antibacterial drug had only a slightly lower risk of relapse and recurrence than those who were administered only one antibacterial [492]. Antibacterials at times showed no effect on patients who exhibited biofilm formation, even if they were sensitive [493].

Extended-spectrum beta-lactamases (ESBLs) have increased in recent years [494]. ESBLs are resistant to all cephalosporin-based antibacterial drugs, but they are typically sensitive to carbapenem-based antibacterial drugs [50, 494]. Carbapenem-resistant enterobacteria have also increased. They usually are resistant to all beta-lactam derivative antibacterial drugs and fluoroquinolone, but they variably respond to aminoglycosides, with sensitivity observed for polymyxin and colistin [495, 496].

Although rare, *Stenotrophomonas* respond to only a few antibacterial drugs [497]. Reports have indicated that even if improvements are seen with *Stenotrophomonas*-based peritonitis, two types of efficacious antibacterial drugs should be administered for 3–4 weeks. Other efficacious treatments include oral administrations of trimethoprim/sulfamethoxazole (ST compound), tigecycline, polymyxin B, and colistin.

(H) Polymicrobial peritonitis

Key points

1. The necessity for surgical intervention should be quickly evaluated when polymicrobial enterobacterial infection is detected.
2. Antibacterial drug therapy should be continued for 3 weeks where polymicrobial Gram-positive bacterial infection is detected.

Explanation

Reports have indicated that bacterial strains in polymicrobial peritonitis were combinations of *S. epidermidis* and either coagulase-negative *Staphylococci, Klebsiella*, and *Enterococci* or *Escherichia coli* and *Klebsiella*.

Patients with chronic respiratory disease more commonly have polymicrobial infections than infections from a single bacterial infection, and the former is associated with a higher risk of hospitalization, catheter removal, HD transition, and death [478, 498–500]. Analyses of 140 patients with peritonitis in Japan indicated that 19 (13.5%) had polymicrobial infections [398].

Antibacterial drug therapy for polymicrobial peritonitis (including those due to *Enterococci*) often include cefazolin, vancomycin, gentamicin, and ceftazidime as a primary regimen, with the addition of vancomycin, gentamicin, 3rd-generation cephem antibiotics, carbapenem, or anti-fungal agents as a secondary regimen [478], Analyses of protocol utility on bacteria from the intestinal canal for peritonitis indicated that 20–24.9% were polymicrobial. Observational studies also indicated that conducting three steps of (1) suspending PD for 1 week without removing the catheter, (2) injecting intravenous meropenem (0.5 g/day), and (3) retaining meropenem in the catheter (dilute 0.125 g in 25 mL of physiological saline solution and retain) was significantly more efficacious for polymicrobial infections than the intra-abdominal administration of gentamicin (20 mg/L, once per day) and rifampicin (50 mg/L, every session) [394, 501]. However, intra-abdominal rifampicin administration is not common in Japan. The primary antibacterial drug regimen for peritonitis in Japan is often cefazolin and ceftazidime, and 75% of peritonitis patients undergo a therapy with two types of antibacterial drugs [502].

In conclusion, treatment should begin with the primary regimen set up in each facility, with vancomycin, aminoglycosides, new quinolones, and anti-fungal agents added based on the bacteria identification or sensitivity results. Antibacterial drug therapy should be conducted for 3 weeks.

The abdominal cavity should be considered as the cause of illness if multiple enterobacteria were cultured from the PD drainage fluid. Patients with hypotension, septicemia, lactic acid acidosis, or drainage fluid amylase concentration increases have an increased possibility of serious issues in the abdominal cavity [503, 504]. Enhanced CT-based imaging should be promptly conducted, and the necessity of surgical treatment, including ventrotomy, should be discussed. When necessary, surgical procedures should be performed immediately. An antibacterial drug with anaerobic coverage should be given. Meanwhile, favorable progress is observed when the cause of peritonitis is due to multiple Gram-positive bacteria [498, 505].

(I) Culture-negative peritonitis

Key points

1. The 2016 ISPD guidelines recommend that the incidence of culture-negative peritonitis should be kept below 15%.

2. Catheter removal should actively be considered if the infection is not sufficiently resolved after 5 days of antibacterial drug therapy.

Explanation

The 2016 ISPD guidelines recommend to keep the incidence of culture-negative peritonitis below 15% [395]. Culture-negative peritonitis is common among female patients with diabetes or those within 3 months of starting PD. Reports have indicated that many patients use antibacterial drugs prior to onset compared to those with culture-positive peritonitis [506, 507]. Culture-negative peritonitis can be healed with antibacterial drug therapy alone and has low rates of hospitalization, catheter removal, HD transition, and death [506]. However, recurrent culture-negative peritonitis often involves catheter removal [506]. Reports of culture-negative rates range from 10 to 32% [384, 391, 398, 508–510]. Catheter removal was conducted in 103 out of 808 patients with culture-negative peritonitis [420]. Culture-negative peritonitis rates with biocompatible neutral PD fluid were comparable with those using conventional dialysis fluid [511]. Analyses of PD-related peritonitis in Japan in a 1-year period in 2013 indicated a culture-negative rate of 23.4% [502]. Out of 120 patients with culture-negative peritonitis, 15 had suspended PD [502]. Concentrated culture methods had lower culture-negative rates than other methods [512]. Reports have indicated cases with *Paracoccus yeei* and *Mycobacterium abscessus* even if the PD peritonitis was culture-negative at first, and multiple cultures were required due to the possibility of non-conventional microbes [513, 514].

Many reports have indicated treatment using vancomycin or cefazolin in addition to gentamicin for culture-negative peritonitis [515, 516]. Antibacterial drugs are used for 14 days as an initial-stage treatment for culture-negative peritonitis [517, 518]. Antibacterial drugs such as cefazolin and ceftazidime are often used as a primary regimen in Japan, and 75% of treatments consist of two types of antibacterial drugs [502]. Catheter removal should actively be considered if the infection is not sufficiently resolved after 5 days of empiric antibacterial drug therapy.

(J) Fungal peritonitis

Key points

1. The catheter should be promptly removed in patients with fungal peritonitis.
2. Anti-fungal agents should be administered continuously for 2 weeks after catheter removal.

Explanation

Fungal peritonitis is a serious complication that has a high risk of catheter removal, HD transition, and mortality [420, 519]. Fungal peritonitis is rare among PD-related peritonitis cases, and its incidence is reported to be 2.6–3.1% [420, 500]. Reports have indicated that fungal peritonitis is common in tropical regions or in the summer and autumn months [423, 520, 521].

Initial-stage treatment generally involves a combination of amphotericin B and flucytosine. However, the intra-abdominal administration of amphotericin B can cause chemical peritonitis and pain due to chemical stimulation. Meanwhile, intravenous administration does not allow for favorable migration properties to the peritoneum. Frequent monitoring of flucytosine concentration in the blood is essential when using this drug to avoid myelosuppression. Serum flucytosine concentration peaks are to be measured 1–2 h after oral administration and controlled to 25–50 μg/mL [522]. Out of 10 patients with non-*Candida* fungal peritonitis, 9 had their catheters removed and received either fluconazole or itraconazole [523]. Preventative administration of two types of anti-fungal agents has been shown to be effective [524–526]. Other selections for anti-fungal agents include fluconazole, echinocandin-based anti-fungal agents, posaconazole, and voriconazole. Fluconazole is widely used, but azole-type anti-fungal agent-resistant cases have been increasing [527]. Fluconazole is effective for only *Candida* and *Cryptococcus*. Echinocandin-based anti-fungal agents are effective for *Aspergillus* and *Candida* (except for *Candida albicans*). Additionally, fluconazole should be administered to patients who do not respond to other forms of anti-fungal agent therapy [528–530]. Caspofungin is effective as a singular therapy or in combination with amphotericin [528, 529]. Posaconazole and voriconazole are effective in treating peritonitis induced by filamentous fungi [531–533]. Voriconazole has been shown to be effective for *Cryptococcus* [534]. Combined micafungin, voriconazole, amphotericin B, and flucytosine therapy has been shown to be effective for peritonitis induced by *Candida albicans* [535].

Observational studies have shown that the rapid removal of the catheter regardless of the selected anti-fungal agent was likely to improve outcomes and reduce mortality [530, 532, 533, 536–538]. Anti-fungal agents should be continued for a minimum of 2 weeks after catheter removal. Recent research results have reported that a third of patients were able to return to PD [539].

(K) Tuberculous peritonitis

Key points

Basic treatment comprises a combination of isoniazid, rifampicin, ethambutol, and pyrazinamide.

Explanation

Tuberculous peritonitis should be suspected in all patients who have culture-negative refractory or relapsing peritonitis. This is similar to bacterial peritonitis, and initial-stage findings of almost all tuberculous peritonitis cases exhibit polynuclear leukocytes in the PD drainage fluid. However, increased lymphocytes in the dialysis drainage fluid typically become evident in later stages. Ziehl-Neelsen staining of the PD drainage fluid is frequently negative, and there are not enough positive rates because typical culturing methods are too slow. A liquid medium can significantly reduce the time until positive culture results are obtained. This applies to all diagnoses, but placing the precipitates, which can be obtained by centrifugally separating a large volume of drainage fluid (50–100 mL), into a solid medium and liquid medium and culturing them, increases the positivity rate. A separate method involves conducting mycobacterial DNA PCR tests with drainage fluid, but false-positives are not uncommon [540]. If this is suspected, peritoneum or omentum biopsies with a laparoscope should be conducted for a rapid diagnosis [541].

Standard treatment for patients with tuberculous peritonitis comprises combined isoniazid, rifampicin, ethambutol, and pyrazinamide therapy. In cases where pyrazinamide cannot be used, the three other drugs will instead be combined for treatment [542, 543]. Protocols where ofloxacin is added are also standard. Previous reports have indicated that rifampicin concentrations in PD drainage fluid were often low [544]. For these reasons, some countries recommend intra-abdominal administration of rifampicin, as in the ISPD guidelines, but this is not standard practice in Japan. Generally, pyrazinamide, ethambutol, and ofloxacin can be suspended after 2 months, whereas rifampicin and isoniazid administration should be continued for 12–18 months [542, 544–550]. Pyridoxine (50–100 mg/day) should be administered to avoid neurotoxicity due to isoniazid. Meanwhile, the long-term administration of pyridoxine at high doses (e.g., at 200 mg/day) can also induce neurotoxicity and should be avoided. Even if streptomycin is used at a lower dose, its long-term use can result in auditory nerve toxicity. Ethambutol has high risks for dialysis patients and can result in optic nerve inflammation. For these reasons, this must be used at the lowest dose possible. Prior reports have indicated that administering 15 mg/kg every 48 h or three times a week for 2 months is ideal [451].

There are some cases where treatment is conducted without removing the catheter, but over half of cases had it removed [420, 544–547].

(XII) Nontuberculous mycobacterial peritonitis

Key points
Nontuberculous mycobacterial peritonitis is treated with multiple antibacterial drugs, including amikacin and clarithromycin.

Explanation
Mycobacterial peritonitis comprises 0.3–1.3% of all peritonitis cases [420, 500]. Treatment often involves clarithromycin and amikacin [551]. Many include *Mycobacterium fortuitum*, *M. chelonae*, and *M. abscessus* [552, 553]. *M. abscessus* is common in Asia, and reports have indicated treatment with amikacin, clarithromycin, meropenem, and cefmetazole [514, 554, 555]. Reports for *M. iranicum* treatment include levofloxacin, clarithromycin, imipenem, and minocycline [556]. The local application of gentamicin ointment to exit-site infections may render the exit site more susceptible to nontuberculous mycobacterial infection [557]. Treatment regimens for nontuberculous mycobacteria have not been sufficiently established, so individual protocols based on sensitivity trial results are needed. Furthermore, treatment periods are not fixed, but these have been found to range between 6 and 52 weeks [555, 557]. Catheter removal is typically needed, and there are limited reports of treatment without removal [552, 554].

(XIII) Catheter removal and re-insertion

Key points

1. The PD catheter should be removed for refractory, relapsing, and fungal peritonitis if there are no clinical contraindications. The fundamental principle is not to preserve the catheter but "how best to protect the peritoneum."
2. If re-insertion of a new catheter is being considered after removing the previous PD catheter in patients with refractory, relapsing, or fungal peritonitis, there should be at least a 2-week interval from the time that the catheter was removed in order to allow for the full recovery from the peritonitis symptoms.

Explanation
The applications for catheter removal are summarized in Table 8. The re-insertion of a new PD catheter shortly after catheter removal is not ideal for patients with refractory or fungal peritonitis. Patients should temporarily

Table 8 Catheter removal applications

-Refractory peritonitis
-Relapsing peritonitis
-Refractory exit-site infection, and refractory tunnel infection
-Fungal peritonitis
-Catheter removal should be considered for the following pathologies as well:
- Repeated peritonitis
- Mycobacterial peritonitis
- Enterobacterial peritonitis

manage their symptoms with HD. Observational studies have indicated that antibacterial drugs should be continued for a minimum of 2 weeks after catheter removal for refractory peritonitis [558, 559]. Approximately 50% of patients were able to return to PD even after serious peritonitis onset [558–560]. There are virtually no data on the optimal time period between catheter removal and new catheter re-insertion, but observational studies have indicated that this should be at least 2–3 weeks [558, 559, 561, 562]. Patients with fungal peritonitis should have a more extended time until re-insertion [530, 536].

(5) Peritonitis prevention

(A) Catheter implantation

Key points
Antibacterial drugs should be administered to prevent peritonitis immediately before catheter implantation.

Explanation
Antibacterial drugs are administered to prevent peritonitis immediately before catheter implantation [563, 564]. Four RCTs have compared a group that had pre-surgery intravenous administrations of cefuroxime [565], gentamicin [566, 567], vancomycin [389], and cefazolin [389, 567] and a group that had no treatment. Three out of these four RCTs found that the pre-surgical administration of antibacterial drugs reduced incidence of early-stage peritonitis [389, 566, 567]. Meanwhile, a report indicated that cefazolin and gentamicin usage had no efficacy whatsoever [567]. There is a single research study that compared vancomycin and cefazolin on a one-on-one basis [389]. This indicated that vancomycin was more efficacious than cefazolin. There is a systematic review of four trials that evaluated the efficacy of preventative intravenous injections of antibacterial drugs in the perioperative period [526]. This review indicated that 1st-generation cephalosporins had slightly inferior

efficacy than vancomycin but that cephalosporins are still generally used to avoid vancomycin resistivity. Reviews of antibacterial drug-resistant strains in each facility indicated that preventative antibacterial drugs should be used for each PD program. Some data suggests that designated inspections on the presence of intranasal *Staphylococcus aureus* prior to catheter insertion and sterilization (e.g., intranasal administration of mupirocin) are effective in preventing exit-site and tunnel infections. However, no data indicates that this is efficacious in preventing peritonitis [526].

There are a variety of methods regarding catheter implantation besides preventative antibacterial drug administration. There are four RCTs that compared implantation based on laparoscope use and conventional implantation based on ventrotomy [568–571]. The first trial indicated that the incidence of early-stage peritonitis was significantly lower when laparoscopes were used for implantation [568]. However, these results were not observed in the other three RCTs [569–571]. Systematic reviews indicated that the above implantation methods had no significant effect on the incidence of peritonitis [572]. There are two reports on insertions from median and lateral incisions [573, 574]. However, neither reported significant differences in the incidence of peritonitis. Several research studies have been conducted on methods to embed a catheter subcutaneously for 4–6 weeks [16, 575, 576]. The first prospective trial reported reduced incidence of peritonitis compared to conventional methods [16]. Of the next two RCTs conducted, one indicated that the embedded method led to a lower incidence of peritonitis [575]. However, the other trial indicated no significant differences [576]. A retrospective trial on a swan-neck catheter embedded between the presternal area and abdominal wall indicated no significant differences in the incidence [577]. In conclusion, there is no clear data that suggests that prior embedding reduces the incidence of peritonitis.

(B) Catheter design

Key points
There are no specific recommendations for catheter design regarding its effect on peritonitis prevention.

Explanation
There are no reports on how catheter design and shape influences peritonitis onset risk. Two systematic reviews also concluded that there were no significant differences in the incidence of peritonitis between linear and coil PD catheters [417, 572]. When comparing single-cuff and two-cuff catheters, numerous retrospective analyses indicated decreased incidence of peritonitis with the two-cuff catheters [578–581]. However, the single RCT

that compared these two catheters indicated no significant differences in the risk of peritonitis onset [582]. Theoretically, creating a subcutaneous tunnel exit site in the downward direction should have preventative effects for catheter-related peritonitis, but there is little evidence to prove this.

(III)Education program

Key points

1. The most recent ISPD recommendations regarding PD patient and staff education should be followed.
2. PD education should be conducted by experienced nurses.

Explanation
Education has a significant impact on the onset of PD-related infection. Here, we use the ISPD education programs as a reference [583]. Significant amounts of research have been conducted on how to best educate patients on PD techniques to reduce PD-related infections. However, there is not enough high-level evidence that guides the "who," "where," "when," and "how" of PD education [584]. All nurses who oversee PD education need to receive specific education for teaching, be updated on the latest knowledge, and further their study on educational techniques. Individual education programs should strive to base themselves on experience that teaches PD theory and techniques. Conducting evaluations of the techniques taught at the end of the patient education session is an essential component.

Once PD education has ended and the patient begins PD education at home, the PD nurse should conduct a home visit and check whether there are any issues with bag exchange, that the patient is observing the predetermined treatment plan, and whether there are any issues in the patient's home environment or daily life that may increase the risk of peritonitis onset [585, 586].

According to education specialists, it is important to conduct re-education in addition to the initial-stage education to reduce error [587]. Reports in multiple trials have indicated that observation of the bag exchange technique significantly correlates with the rate of peritonitis onset [587, 588]. Other reports have indicated that after 6 months of starting PD, almost all patients have simplified the necessary tasks, changed the standard exchange methods, and were not observing aseptic procedure [589]. From these perspectives, re-education may be able to reduce the risk of peritonitis onset, but this is only based on the data of a small number of patients from two studies [587, 590]. As such, there are no clear definitions on the applications of re-education, suitable implementation periods, and its content. Home

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visits by PD nurses are useful for determining which patients require re-education [587]. Other situations wherein re-education may be warranted are shown in Table 9 [583, 591].

(IV) Dialysis fluid

Key points
No specific recommendations are made for dialysis fluid selection from the perspective of peritonitis onset prevention.

Explanation
A meta-analysis conducted on six RCTs had low trial quality, and there was high variability between each trial, so the effects of neutral and low-GDP PD fluid on peritonitis onset rate were unclear [592]. Because of these inconclusive data, dialysis fluid should not be selected from the perspective of peritonitis risk.

(E) Infection due to intestinal or gynecological causes

Key points
Preventative antibacterial drug administration should be conducted in anticipation of a colonoscopy or invasive gynecological procedures.

Explanation
PD-related peritonitis frequently occurs after an invasive procedure (e.g., colonoscopy, hysteroscopy, cholecystectomy) [593–597]. An analysis of a facility that had conducted 97 colonoscopies on 77 CAPD patients revealed that in the 79 colonoscopy sessions that were conducted without preventative antibacterial drug administration, 5 patients (6.3%) developed peritonitis. Although there were no significant differences, there was not a single patient out of the 18 who was preventatively administered antibacterial drugs that had peritonitis onset [594]. Other small-scale retrospective observational studies reported that, except for most endoscopy or upper gastrointestinal endoscopy procedures, the preventative administration of antibacterial drugs prior to the use of a colonoscope, sigmoidoscope, or cystoscope or the implantation/removal of an intrauterine device with a

Table 9 Re-education applications

-When hospitalization is over an extended period of time

-When there is either peritonitis or a catheter infection

-When there are changes to dexterous movement or vision, or when the patient is psychologically confused

-When there are changes to the company that handles the PD device or its connection system

-When PD was suspended for a given reason

PD peritoneal dialysis

hysteroscope reduced peritonitis onset [598]. A variety of antibacterial drugs were used, but peritonitis onset did not occur in any patients who were administered 1 g of ceftriaxone prior to a colonoscopy as well as those who were administered clindamycin and 1st-generation cephalosporin prior to gynecological treatment [598]. However, there are no definitive results in any clinical trials regarding the most suitable antibacterial treatment method to use.

Reports have indicated that problems related to the digestive tract such as constipation and enteritis correlated with peritonitis [599]. Numerous research reports have indicated that hypokalemia increases the risk of intestine-derived peritonitis [600–602]. However, there is no definitive proof that the treatment of hypokalemia, constipation, and gastroenteritis, which are daily problems for a PD patient, reduces the rate of peritonitis onset. Some observational studies have reported that routine usage of lactulose could reduce the peritonitis onset rate [603].

(F) Other correctable causes

Explanation
In addition to those previously mentioned, many reports have indicated factors that can be corrected in relation to PD peritonitis. There have been reports of peritonitis onset in females after conducting biopsies with a hysteroscope [604], similar to those seen with vaginal fistulas and leakage [605, 606]. Retrospective studies on 13 patients undergoing gynecological treatment indicated that preventative administration of antibacterial drugs was not significant but tended to decrease peritonitis onset [598]. Transient bacteremia is known to occur after dental treatment, but this can also lead to peritonitis [484, 607]. Preventative administration of antibacterial drugs (e.g., singular oral administrations of amoxicillin) prior to wide-ranging dental treatments is likely to be useful.

Preventative administration of antibacterial drugs is generally ideal when there is a possibility of contamination, such as when potentially contaminated dialysis fluid was injected or when a catheter is left in an open state [591].

There have been many other reports on the correctable risk factors of peritonitis [608], with hypoalbuminemia [609, 610], depression [611], and immobilized states [612] repeatedly indicated as important risk factors. However, there are no published reports which have been able to show a decreased peritonitis onset rate by addressing these factors. Similarly, interacting with a pet that resides at home is another risk factor [613, 614]. The animal needs to be removed from the area where PD procedures are undertaken [614]. Two observational studies indicated that the oral administration of vitamin

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D was significantly able to reduce the peritonitis onset rate [615, 616]. However, prospective RCTs are required to confirm these results.

(G) Secondary prevention

Fungal peritonitis cases often occurred after previous antibacterial drug therapy [617, 618]. Many observational studies and RCTs have analyzed the preventative administration of oral nystatin or fluconazole during the antibacterial drug treatment period [524, 525, 619–621]. Significant effects were observed in two RCTs [524, 525] and one systematic review [526]. Observational study data and an RCT indicated that the preventative administration of fluconazole was effective [525]. However, there are underlying issues that need to be considered with the preventative administration of fluconazole.

Peritonitis management in pediatric patients
Key points

1. PD-related peritonitis is the primary reason for PD withdrawal in pediatric patients as well.
2. The incidence rate of peritonitis in pediatric PD patients is higher than in adult patients, with greater risk in younger children.

Explanation

1. PD-related peritonitis in pediatric PD patients

PD-related related peritonitis is the primary reason for PD withdrawal (change in dialysis modality) in pediatric patients as well. The International Pediatric Peritonitis Registry (IPPR) [622] reported that 10.5% of all peritonitis cases required PD withdrawal (temporary: 2.5%, permanent: 8.0%), and the North American registry, NAPR TCS [623], reported that 30.5% of PD withdrawal cases were due to PD-related infections.

In children, due to factors such as body constitution, PD is frequently selected for the treatment modality of end-stage kidney disease (for initial renal replacement therapy selection is 50% globally [624], 27% in North America [625], and 61% in Japan [45]). PD withdrawal may force the patient to undergo long-term hospitalized management with HD, which uses vascular access catheters. Therefore, its prevention and management are vital. Guidelines for the management of pediatric peritonitis have been issued by the Japanese Society of Pediatric Dialysis in 2005 [626] and by the ISPD in 2012 [238].

The incidence of peritonitis in pediatric PD patients is higher than in adult patients due to skin fragility during infancy, diaper usage (the risk that the Tenckhoff catheter exit site is in a diaper), difficulty in ensuring a sufficient subcutaneous tunneling length due to body constitution, and less developed immune system [238]. The risk of peritonitis is known to be higher in younger children [238, 623, 627, 628]. Analyses from the USA between 2011 and 2014 [627] showed an incidence rate across all age groups at 0.46 times/patient-year, with an age-based breakdown as follows; younger than 2 years old: 0.62 times/patient-year, 2–5 years: 0.50 times/patient-year, 6–12 years: 0.38 times/patient-year, and 13–17 years: 0.37 times/patient-year. In Japan, favorable outcomes were reported in the 1999–2003 survey, with an incidence rate of 0.17 times/patient-year across all age groups, 0.24 times/patient-year in patients under the age of 6, and 0.11 times/patient-year in those over the age of 6 [628].

2. Diagnosis and treatment of PD-related peritonitis in children

The diagnostic standards for pediatric peritonitis are the same for adult peritonitis. In adults, treatment is initiated with empiric therapy, switching to responsive antibacterial drugs after identifying causative bacteria. The initiation of dialysis in patients with underlying diseases has increased, and it is important to conduct surveillance of causative bacteria and antibacterial drug sensitivity for each facility to select the drugs used in empiric therapy. The antibacterial drug dosage administered at the time of peritonitis treatment in pediatric PD patients is shown in Table 10. Points of consideration are outlined below.

– Storage time: the recommended initial loading time for continuous dosing method is 3–6 h, and the intermittent dosing method is 6 h or more.
– Aminoglycosides and penicillin should not be mixed as they can deactivate one another.
– Intermittent glycopeptide administration in patients with remaining renal function should always conduct blood concentration monitoring, with re-administration conducted when vancomycin is below 15 mg/L and teicoplanin is below 8 mg/L. Intermittent glycopeptide administration in patients with remaining renal function should be avoided in cases where blood concentration monitoring cannot be conducted.
– Dialysis fluid dose to be used: concentration should be set at 1100 mL/m^2 for continuous administration. The antibacterial dosage can be insufficient in cases where the injected dose is below 1100 mL/m^2, and the total dose of antibacterial drugs used should be the same as that of 1100 mL/m^2.

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Table 10 Antibacterial drugs and administered doses used in the treatment of pediatric PD-related peritonitis (modified from reference [238])

Antibiotic type	No residual renal function	Residual renal function	Continuous Initial (loading) dose	Intermittent Maintenance dose
Aminoglycosides (IP)				
Gentamicin	8 mg/L	4 mg/L	0.6 mg/kg	0.75 mg/kg
Netilmicin	8 mg/L	4 mg/L	0.6 mg/kg	0.75 mg/kg
Tobramycin	8 mg/L	4 mg/L	0.6 mg/kg	0.75 mg/kg
Amikacin	25 mg/L	25 mg/L	0.6 mg/kg	0.75 mg/kg
Cephalosporins (IP)				
Cefazolin	500 mg/L	125 mg/L	20 mg/kg	500 mg/L
Cefepime	500 mg/L	125 mg/L	15 mg/kg	500 mg/L
Cefotaxime	500 mg/L	250 mg/L	30 mg/kg	500 mg/L
Ceftazidime	500 mg/L	125 mg/L	20 mg/kg	500 mg/L
Glycopeptides (IP)				
Vancomycin	1000 mg/L	25 mg/L	Initial dose: 30 mg/kg Afterward, 15 mg/kg every 3–5 days	
Teicoplanin	400 mg/L	20 mg/L	15 mg/kg every 5–7 days	
Penicillin's (IP)				
Ampicillin	No data	125 mg/L	No data	
Quinolones (IP)				
Ciprofloxacin	50 mg/L	25 mg/L	No data	
Others				
Aztreonam (IP)	1000 mg/L	250 mg/L	No data	
Clindamycin (IP)	300 mg/L	150 mg/L	No data	
Imiprem / cilastin (IP)	250 mg/L	50 mg/L	No data	
Linezolid (PO)	< 5 years: 30 mg/kg/day, divided into three doses 5–11 years: 20 mg/kg/day, divided into two doses 12 years≤: 600 mg/session, twice per day			
Metronidazole (PO)	30 mg/kg/day, divided into three doses (maximum of 1200 mg/day)			
Rifampin (PO)	10–20 mg/kg/day, divided into two doses (maximum of 600 mg/day)			
Anti-fungals				
Fluconazole (IP, IV, PO)	6–12 mg/kg/session, every 24–48 h (maximum of 400 mg/day)			
Caspofungin (IV)	Initial dose: 70 mg/m^2/day (maximum 70 mg/day) Afterwards: 50 mg/m^2/day (maximum 50 mg/day)			

IP intraperitoneally, *IV* intravenously, *PO* orally

Example: A continuous dose of cefazolin at a single injection volume of 800 mL/m^2

As the recommended concentration is 125 mg/L at 1100 mL/m^2, prepare at a concentration of 125 × 1.1 / 0.8 = 170 mg/L.

Chapter 7 Catheter and exit-site management

(1) PD catheter insertion procedures

Key points

1. Favorable outcomes of peritoneal access surgery are related to subsequent PD management.
2. Pre-operative preparation, surgery, and post-operative care need to all work together to ensure a successful operation.
3. Abnormalities with catheter placement can be reduced with modifications made during insertion.
4. There are no RCTs that confirm which placement method is superior.

Explanation

As a matter common to all surgical procedures, perioperative management is very important. It is particularly essential to ensure a sterile environment while the PD catheter is inserted into the abdominal cavity. Conducting a sterile catheter insertion procedure is important to continue PD stably.

(A) Perioperative management

1. Pre-operative preparation

The categories that should be confirmed prior to surgery are shown in Table 11. A portion of this references the United States of America Centers for Disease Control and Prevention (CDC) guidelines [629]. As much interventions as possible should be provided beforehand when there is an infected wound in the operating field, or alternatively, the location of the operating wound can be changed (e.g., changing the insertion position or exit site). Disinfecting the exit site prior to operation should be considered according to the standards of each facility for patients with MRSA, keeping in mind that there may be a subsequent exit-site infection. Furthermore, strict guidelines should be provided to patients in order to stabilize the perioperative period, for example, by telling patients with diabetes to strictly control their blood glucose levels and telling smokers to abstain from smoking prior to surgery. The Japanese Society of Anesthesiologists [630] has indicated that smoking, in particular, increases a variety of perioperative complications and delays post-operative recovery. Therefore, patients should be advised not to smoke prior to a PD catheter insertion procedure or surgery.

Existing abdominal surgery procedures generally are not an exclusion factor for PD. However, regardless of

Table 11 Confirmation criteria prior to peritoneal dialysis (PD) catheter insertion procedure (partially references the United States of America, Centers for Disease Control and Prevention (CDC) guidelines)

-Treat if there is an infection in the vicinity of the surgical wound

-Confirm the normal bacterial flora (nasal cavity, navel bacterial culture tests) and sterilize as needed

-For patients with diabetes: blood glucose management

-For smokers: instruct patient to stop smoking as much as possible

-Confirm if the patient has had any prior abdominal surgeries

-Determine the exit-site creation placement

-Remove body hair as appropriate

-Conduct preoperative cleaning of the surgical wound area

-Maintain the abdominal cavity content volume (enemas, emptied bladder)

whether the past surgery history is laparoscopic surgery or laparotomy, if there is a possibility of adhesion of the abdominal cavity contents to the incision of the peritoneum and if intraoperative abdominal adhesion is assumed by the surgeon, the insertion position and method is should be carefully considered. The need for laparoscopic insertion is not high for normal risk-free cases, but if there is a possibility of adhesion, it is possible to insert a catheter into the pouch of Douglas or detach the adhesion. Furthermore, long catheters up to 65 or 80 cm can be used for the exit site in Japan so that free exit site can be conducted. For these reasons, it should be decided prior to surgery where the exit site for the catheter will be. Particularly for abdominal exit sites, the external cuff or exit site should not be placed in areas where clothing could apply pressure, such as beltlines.

Body hair and contamination in the operating field should be considered on the day of the procedure. Body hair does not need to be removed if it does not inhibit the surgical procedure; however, past reports have indicated increased risk of surgical wound infection with shaving using a razor, and so this should be avoided [629]. Surgical clippers should be used as necessary, as ensuring that micro-wounds do not form is important. Old keratinized skin and protein stains cannot be removed with swab-based disinfection and should be removed as much as possible by applying a povidone-iodine soap with a soft brush prior to disinfection. Additionally, the surgical procedure involves placing an artificial catheter into the body and penetrating the abdominal cavity, all while avoiding infection. For these reasons, preventative antibacterial drugs recommended by the ISPD guidelines [563] should be administered immediately prior to surgery to maintain a sufficient blood concentration during surgery.

The space inside the pelvis must be opened wide as the PD catheter is inserted into the tip of the pouch of Douglas. Fecal matter and urine retained in the rectum and bladder, respectively, inhibits catheter insertion, making excretion preparation necessary for surgery, especially in elderly patients where there may be a lot of residual urine even if there is no complaint of urination. Therefore, it is considered necessary to confirm the residual urine and, if necessary, excrete immediately before the operation.

2. Catheter insertion procedure

The insertion procedure is conducted once the preoperative confirmation criteria have been thoroughly reviewed. The optimal anesthetization method is decided according to the procedures of each facility and the insertion procedure type. However, invasive anesthetization methods should be avoided. There are many reports on different implantation methods, but there are currently no RCTs that prove which implantation is superior [563, 631]. A novel systematic review was conducted by this current guideline revision committee, and there have been many discussions on this topic (see Chapter 2). Due to differences in surgical methods, the final catheter insertion method (e.g., insertion angle, cuff fixation) is at the very least thought to largely influence placement abnormalities after surgery, so the catheter insertion design is thought to be significant. However, the use of laparoscopes or other methods that allow for the direct visualization of the insertion location through ventrotomy [632] should be considered for patients with a prior history of abdominal surgery or those where extra care is needed.

2.1. Laparotomy

Laparotomy is the most standardized PD catheter insertion method at the time when this guideline was written. Anesthesia varies according to each facility and includes local anesthesia, lumbar anesthesia, epidural anesthesia, general anesthesia, and transversus abdominis plane block (TAPB). Local anesthesia increases the risk of the abdominal cavity contents coming out due to sudden increases in abdominal pressure. Therefore, fasting or bowel evacuation should be considered prior to surgery.

#From the skin incision to the interior of the abdominal cavity

The catheter insertion area is shown in Fig. 2. In laparotomy, an abdominal midline incision is made directly above the linea alba in order to surgically enter the abdominal cavity. This enables surgery to be conducted

Linea alba

Rectus abdominis

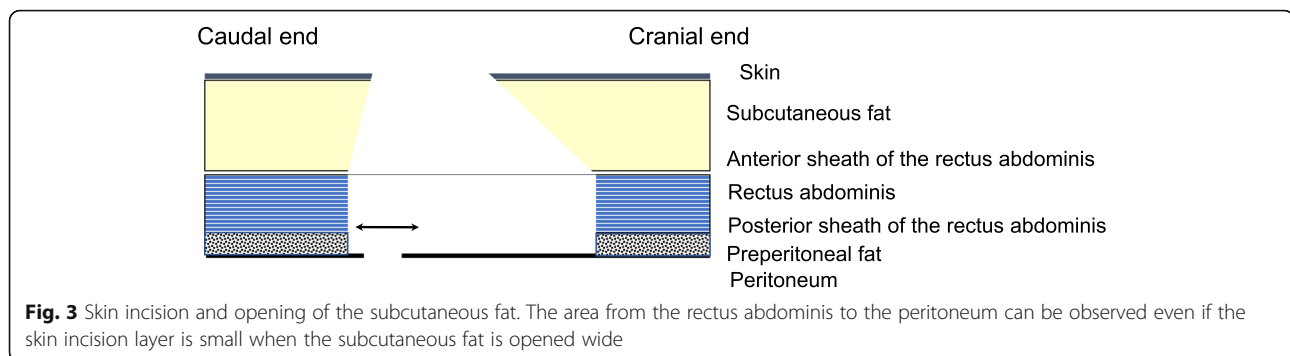Pararectal incision

Transrectal incision

Midline incision
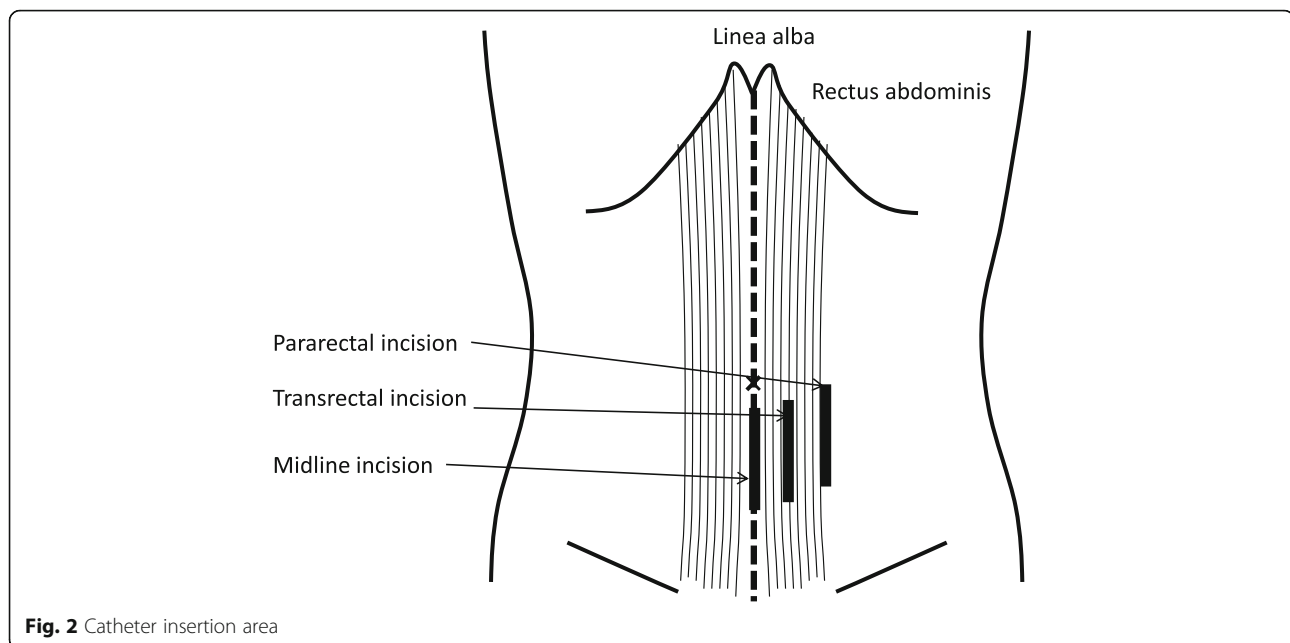
Fig. 2 Catheter insertion area

without the muscles or arteries and veins of the abdominal wall being impacted. However, an insertion using a trans rectus abdominis muscle incision is desirable for PD catheter insertion for two reasons: first, it is important to insert the catheter under the rectus anterior sheath in order to insert the catheter into the abdominal wall, which will be described later, and second, when a tunnel infection occurs, if it penetrates the inside of the rectus abdominis muscle, which has abundant blood flow, it can easily be supplied with factors for protection against infection (white blood cells, globulins, antibiotics, etc.) and resistant to infection. However, in the case of transrectal abdominal muscle technique, the lower abdominal wall arteries and veins may be encountered; therefore, the technique should be exercised with caution.

Regarding the skin incision, the size should be decided according to the skill of the surgeon. As shown in Fig. 3, opening the subcutaneous fat can help enable a wider view of the anterior sheath for the rectus abdominis. This has a large contribution to the positional abnormalities associated with catheter placement, which are discussed later. Next, a long incision should be made in the anterior sheath for the rectus abdominis in the cranial direction. The fibers in the rectus abdominis are longitudinal in direction, so the surgeon can easily reach the posterior sheath by separating the fibers in the left and right directions with a dull muscle hook. Because the wound gradually deepens and the visual field deteriorates, it is recommended to hang a pair of pulling threads on the posterior sheath here caudally. At the same time, it is important that the needle is shallowly moved with sufficient caution because the needle

protruding into the abdominal cavity may cause damage to the organ in the abdominal cavity. By raising this, it is possible to secure a shallow field of view and facilitate subsequent operations. The posterior sheath should be moved into tent-like position, while making sure that the contents of the abdominal cavity are not involved. When confirmed, the posterior sheath is incised with the image of slowly cutting fibers with a scalpel, the peritoneum lining is also cut and reaches the abdominal cavity. This allows the surgeon to reach the abdominal cavity. The usage of scissors should be avoided here as it can result in organ damage if the adhesion of the internal organs occurs on the lower layers of the abdominal cavity. Sometimes, obese patients have thick layers of fat in front of the peritoneum, and it can be difficult to distinguish between peritoneum or omentum tissue. In such cases, tapered forceps should be used to remove the fat steadily and to confirm the peritoneum, which will be a thin membrane in the lower layer. If a blood vessel is encountered at this section, it is highly likely that the omentum or mesentery have adhered, so it is better to switch to insertion from another site so as not to cause damage.

After incising the peritoneum and reaching the abdominal cavity, pulling threads are applied in four directions so as not to damage the abdominal cavity contents (this will be used later for fixing the internal cuff.) It is important to move the needle together with the rectus abdominis sheath because it may cause a postoperative leak or hernia if only the peritoneum is applied. After hanging in four directions, raising it safely increases the distance from the contents of the abdominal cavity. If the incision is applied along the 6 o'clock direction, the

Fig. 3 Skin incision and opening of the subcutaneous fat. The area from the rectus abdominis to the peritoneum can be observed even if the skin incision layer is small when the subcutaneous fat is opened wide

subsequent operation is easy to perform. As purse string sutures sometimes break when sutured, it may take two laps to complete the suture.

#Catheter insertion

Long catheters such as 80-cm catheters are currently available in the market in Japan, and catheters can be selected according to the exit-site position, with each facility choosing and using catheters best suited for their purposes. In making this selection, the use of a catheter with a thick inner cuff to enhance self-recovery should be considered to prevent abnormal catheter position in the future.

Catheter length should be evaluated as an inappropriately long catheter can result in stomach pain and functional failure [633, 634]. A standard insertion method using a stylet is recorded when inserting the catheter in the abdominal cavity. Methods that do not use a stylet will be discussed later.

After injecting sterile glycerin or saline into the catheter to improve the sliding between the stylet and the catheter, the stylet is bent at the tip. This is inserted into the abdominal cavity, bypassing the front wall of the abdominal cavity. In the abdominal cavity, any resistance is an indication of a forceful operation, which may damage the abdominal cavity contents, and should never be performed. There is almost no resistance when inserted in a good gap. When inserted, the bladder hits the posterior pubic surface and resistance develops. Here, the catheter is slightly moved back in the image of the roundness of the bladder wall, and at the same time, the stylet is raised while slowly rotating to about 120°. With this operation, the tip will face the pouch of Douglas while sliding on the outer wall of the bladder. As mentioned above, if there is resistance during this period, it is considered that the contents of the abdominal cavity such as the intestine are obstructed and the procedure is readministered. For patients with a lot of fat in the abdominal cavity, there are few gaps and it is difficult to insert, but in that case, the head to the pouch of Douglas can be opened by slightly lowering the bed and lifting the abdominal wall with a hook. At this time, confirmation by fluoroscopy is not particularly required. Once inserted, the stylet is removed, taking care not to bounce the catheter. Here, we inject about 60 mL of saline and confirm that there is no resistance to infusion and that it can be discharged as a continuous water flow using the siphon principle when the catheter on the body wall side is positioned lower than the body. In case of dripping drainage, it is highly likely that it has not been inserted in a good position, and the catheter must be checked by pulling and inserting it continuously. If a compromise is made in this case, there is a high possibility that the patient will have difficulty with the infusion and drainage later. It is important that the assistant keeps the catheter in place during this operation so that it does not become misaligned.

The cuff is to be fixed once favorable drainage of the injected fluid is confirmed. It is crucial at this stage to ensure that the internal cuff is always placed outside of the abdominal cavity for three reasons: first, if the inner cuff is partially inside the abdominal cavity, the dialysate may leak out of the abdominal cavity due to capillary action until the cuff is covered with fibers and may leak from the tunnel or surgical wound, which could increase the risk of developing tunnel infection. Second, the contents of the abdominal cavity can adhere to the cuff for similar reasons, and lastly, when peritonitis develops in the early stage after the operation, the bacteria will adhere to the Dacron fibers, causing repeated relapsing peritonitis, with a high possibility that the catheter will have to be removed. In order to comply with this, it is important to move the needle to the lower end of the cuff. If the catheter is inadvertently raised when inserting the needle in the 12 o'clock direction, there is a high possibility of causing a positional error. It is important to move the hand so that it does not interfere with the insertion. Once the purse string suture is completed, it is important to be careful to sew under the cuff.

#From subcutaneous tunnel creation to closing the wound

The subcutaneous tunnel is created next. The external (subcutaneous) cuff needs to be anchored in place on the fascia at the correct position, which requires dissection just above the fascia. Separation may be added from the wound of the internal cuff insertion to the head side, or a new skin incision may be placed. Suture to the fascia is not essential because it naturally adheres during the process of wound healing; however, it is important to place it immediately above the fascia. If the cuff is placed in the fat, the risk of escape of the outer cuff increases with time because it is not fixed. If the cuff is positioned too caudally, care must be taken not to bend the catheter. Even if the patient can somehow secure patency in the lying position, it is more likely that the patient cannot inject and drain in the sitting position.

An exit site is created using a tunneler next. This is created from a distance of 2–5 cm away from the external cuff [635–637].

Thereafter, we discuss the repair of the fascia in the insertion section. Care must be taken to ensure that the catheter is smoothly directed to the pouch of Douglas along the abdominal wall, which can be easily achieved by passing the catheter through the lower layers possible in the anterior sheath for the rectus abdominis [638] (Fig. 4). Positional abnormalities are more likely to form if repaired, as shown in (a) if the cuff is inserted in the abdominal cavity in a longitudinal direction. As previously mentioned, insertions, as shown in (b), can result in the immune system becoming stronger due to the activation of white blood cells and immunity factors at the onset of subcutaneous tunneling infections by passing through the muscle interior.

If necessary, the skin is brought closer by an absorbent thread, and then the skin is sewn up to finish.

2.2. Surgery using a laparoscope (this surgical procedure is currently not covered by insurance in Japan, and its implementation should be considered by each facility)

There is debate on whether laparoscopes need to be used in patients who do not have abdominal cavity adhesion. Its surgical application should be considered in patients where such adhesion may have occurred [639–642]. The benefits of this surgical procedure include that the tip can definitively be inserted in the pouch of Douglas by detaching the adhesion as necessary and that it is only minimally invasive due to the small surgical wound [643]. Meanwhile, drawbacks include the requirement of general anesthesia or other specific equipment, specific pneumoperitoneum-related complications (subcutaneous emphysema, and radiating pain in the shoulder area), and new adhesions forming in injuries within the abdominal cavity (trocar insertion areas).

The catheter tip is inserted into the pouch of Douglas through the space created in the pneumoperitoneum via insertion of 1–3 trocars in areas other than the catheter insertion area. Reports have indicated several methods to create a tunnel below the peritoneum in order to minimize catheter placement abnormalities [644, 645] (Fig. 5).

The benefits and drawbacks of ventrotomy and surgery under laparoscopy are analyzed from various perspectives in the clinical questions of this guideline and are recorded in CQ4.

2.3. Non-stylet methods

Methods that do not use a stylet when inserting a catheter inside the abdominal cavity have been discussed in the literature [646]. There is no risk of damaging the internal organs in the abdominal cavity as this method does not use a metallic stylet and is considered to be a much safer method. Meanwhile, insertion can be challenging in patients with high visceral or subcutaneous fat content. Therefore, stylet-based methods should be prepared for these particular patients.

Similar to standard insertion methods, a small hole is first made in the peritoneum. Then, either a muscle hook or forceps is used to elevate the abdominal wall in the 6 o' clock direction. This elevation is extremely important and creates a space in the direction of the pouch of Douglas. Next, an insertion is made within the abdominal cavity from the 12 o' clock direction along the skin. The catheter is then directed towards the pelvis floor along the abdominal wall within the abdominal cavity and inserted into the pouch of Douglas while going along the bladder wall. The catheter used in this method needs to have some degree of stiffness, so a catheter with a reinforced wall thickness in the internal cuff area is preferred as it would be easier to insert. A favorable placement can be quickly confirmed in a manner similar to the standard methods, whereby the absence of resistance is confirmed using a saline injection, indicating continuous drainage.

2.4. Peritoneal wall anchor technique for the catheter

The peritoneal wall anchor technique (PWAT) has been reported in Japan [647, 648], which a method for preventing catheter malposition (Fig. 5b) that is remarkably similar to the concept of the tunneling method described earlier (Fig. 5a). Forcefully matching the catheter with the abdominal wall allows for the tip to be directed towards the pouch of Douglas. Reports have indicated various modifications, such as methods conducted under a laparoscope or pyeloscope (original method) [647], using a PWAT applicator [648], using abdominal wall-
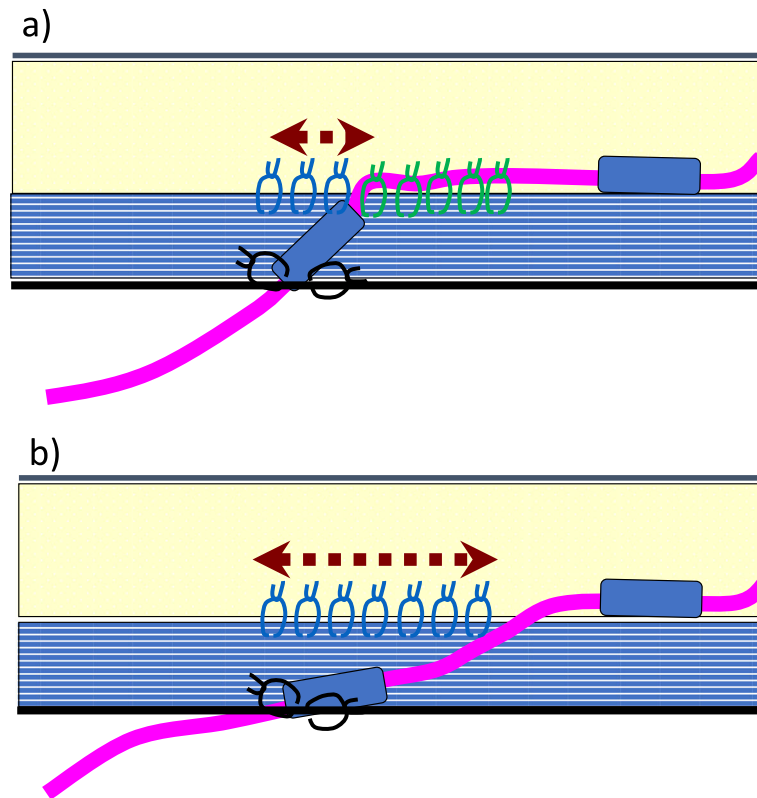
Fig. 4 Internal cuff angle and catheter path within the rectus abdominis. **a** A poor example, and **b** a good example. The cuff naturally goes along the abdominal wall by laying down the internal cuff and placing the suture for the anterior sheath of the rectus abdominis in a central position

fixing equipment [649, 650], and making a large incision wound and fixing the catheter with a wide operating field [651]. There are only few patients in whom this technique has been implemented, and no fixed solution is available. However, reports have indicated that the catheter survival rate is higher than that of the standard insertion methods [652], and as such, further analysis is necessary.

An important aspect when conducting this surgical procedure is that the catheter is said to be "moored" on the abdominal wall and not fixed to it. The following two issues can occur if the catheter is firmly sutured: first, there is a risk that the fixed catheter will be severed when the lower abdominal wall contracts due to the patient coughing, and second, there is the possibility of an intestinal obstruction forming when the intestinal canal wanders between the catheter, which is between the interior cuff insertion area, the PWAT fixed area, and the abdominal wall. A loose placement of the catheter in this situation would allow the catheter to become detached from the PWAT fixed area even if the intestinal canal shifts and prevent complications. A report on 50 patients indicated that no complications had formed [653].

2.5. Embedded catheter implantation (SMAP)

The "catheter insertion method using Moncrief and Popovich's technique" [652], proposed for preventing peritoneal catheter infection and introduced to Japan by Kubota, has been reported as effective [653]. This is in line with the concept of creating an interior shunt before initiation and introducing it as soon as the time is appropriate for patients who plan to be on HD.

#SMAP insertion procedure

Similar to standard surgery, a catheter is inserted, and the external cuff is placed on top of the fascia. The original method uses a tunneler in which the catheter is subdermally embedded without directing the catheter out of the skin [16]. This method keeps the catheter from moving underneath the skin during the embedded period, which enables the faster fibrous formation on the cuff, catheter, and subdermal tissue. The area is furthermore not exposed to external air during the wound healing period, which increases its protection against infection. Meanwhile, this method is thought to increase the possibility of the subdermal leakage of ascites. Therefore, Kubota designed the following modification, in which two tie bands are linked and fixed in the future exit-site section of the catheter, after which they are tightened while injecting an undiluted heparin solution

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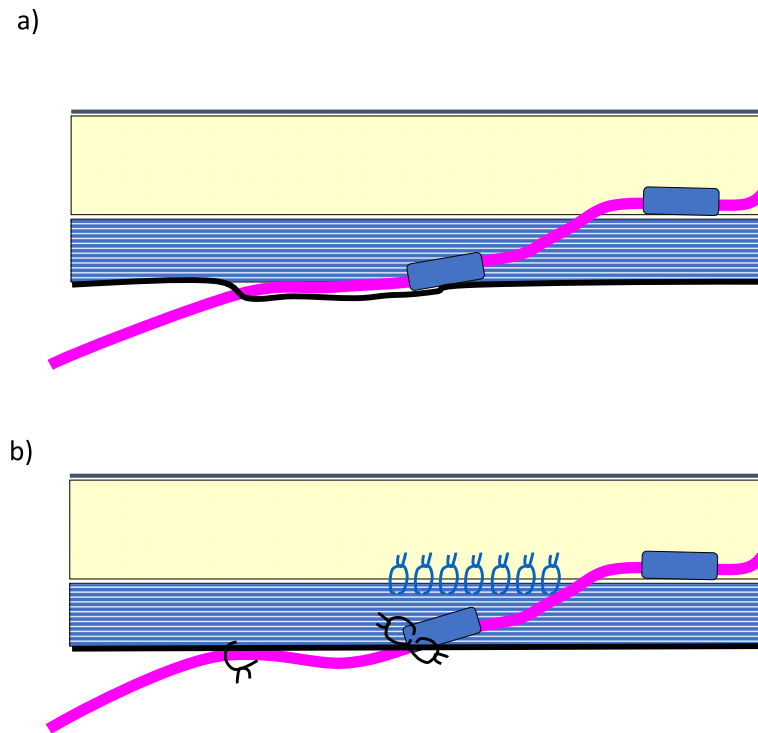
Fig. 5 Modifications to reduce catheter malposition. **a** Tunneling method under the peritoneum using laparoscopy. **b** Peritoneal wall anchor technique (PWAT)

into the catheter. This procedure fills the catheter interior with heparin, preventing the subdermal outflow of ascites. A tunneler is then subsequently used to subdermally embed the catheter [654]. (tie bands are made of 6-6 nylon, which is the same nylon thread material used during surgery, but they have not been approved for clinical use, and its usage depends on the decision of the ethics communities at each facility. This text provides an initiation to this surgical technique and is not a recommendation).

Management during the retention period is conducted during this time. Subsequent management can extend the embedded period for longer.

#Exit-site catheter fixation
The catheter needs to be surgically excavated when catheter initiation becomes necessary. There are few reports on the extension of the embedded period, but this in itself is not thought to lead to substantial problems.

Local anesthesia is applied to the predicted exit-site location when the catheter position is determined by touch or ultrasonography. Then, a micro-incision is made directly on top of the catheter, and the subdermal tissue is separated and incised while taking care not to damage the catheter. Next, the catheter is gently pulled out. The catheter function is confirmed by injecting and draining out saline through the catheter. Coagulated

masses can form inside the catheter during this time due to obstruction duration, but patency can be improved by injecting saline drainage in many of these cases. Initial-stage reports by Kubota indicated that coagulated masses were observed in 6 out of 17 patients but that these were easily removed using a syringe [654]). There was also a single case where the omentum was twisted during the embedding period. However, Moncrief indicated that twisting of the omentum does not occur in cases where there is no dialysis fluid in the abdominal cavity [655].

#Advantages and disadvantages of SMAP
The advantages and disadvantages summarized by Kubota are shown in Table 12 [654].

2.6. Percutaneous insertion methods (this surgical procedure is currently not covered by insurance, and its implementation should be considered by each facility)

New PD catheter insertion methods have been implemented, primarily overseas. A micro-incision is made on the skin, and a catheter is inserted using the Seldinger method [656]. This method is particularly useful when a surgical time frame could not be provided by the surgeon [656].

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Table 12 Advantages and disadvantages of the SMAP method

Advantages	Disadvantages
1. Planned initiation of peritoneal dialysis (PD) can be conducted	1. Intra-abdominal information cannot be obtained until after the catheter is embedded
2. Catheter management is not necessary as the catheter is embedded	2. Two surgeries are necessary
3. Catheter type is not selected	3. Wound management after embedding and exit-site formation is necessary at home
4. Catheter implantation and embedding is safe and straightforward	4. It can be challenging to achieve the 1st class physically disabled classification after implantation
5. Long-term catheter embedding is possible	
6. Comprehensive patient education can be planned	
7. PD can be started at a suitable period	
8. PD can be rapidly commenced	
9. Sufficient dialysis dose can be obtained in a short period of time	
10. No risk of dialysis fluid leakage	
11. Catheter infection is minimal	
12. Hospitalization duration is short	

SMAP Stepwise initiation of PD using the Moncrief and Popovich technique

Many reports have indicated that these procedures are implemented with local anesthesia administered through a sedative [656–658]. A skin incision measuring a few centimeters from the lower transmedian of the abdomen to about 2–3 cm on the external side is made for patients with no prior history of abdominal surgery. Once this has been bluntly separated into the rectus abdominis, a puncture needle is used at an angle towards the pelvis to enter the abdominal cavity. Reports have indicated methods where saline is injected at this point for confirmation [657] and where a contrast agent is injected under X-ray fluoroscopy for further confirmation [658]. A guidewire is then inserted inside the abdominal cavity, and then, a PD catheter is inserted once the space is expanded with a dilator. Care is taken at this stage to ensure that the internal cuff does not extrude into the abdominal cavity.

Comparative analyses with ventrotomy-based insertion methods have indicated that percutaneous insertion groups had higher incidences of primary failure and dialysis fluid leakage from exit sites but a lower incidence of exit-site infection and peritonitis than the ventrotomy group [659]. Results from a meta-analysis also showed that there were no significant differences between the ventrotomy and percutaneous insertion groups for the 1-year catheter retention rate, dialysis fluid leakage from the exit site, and functional failure of the catheter. Meanwhile, the incidence of peritonitis was significantly lower in the percutaneous insertion group, with an incidence rate ratio (IRR) = 0.77; 95% CI 0.62–0.96, p = 0.02 [660]. However, there is a large variation between different reports, which may reflect the different surgical techniques used by each facility. There are no RCTs that prove which technique is superior.

Conclusions

As previously mentioned, PD catheter insertion is a surgical procedure that "creates" function, which makes it different from excisions that "steal" function. As such, its standards and concepts should be thoroughly thought through before implementation. It is important that sufficient training is undertaken prior to implementing the procedure. Catheter stabilization has a large contribution to PD stabilization after initiation. Therefore, access needs to be considered for all patients, as well as stable management. Note that RCTs have not shown a significant difference between each insertion method [563, 631, 660].

(2) Routine care of exit site and subcutaneous tunneling

Key points

(1) Routine care of exit site and subcutaneous tunneling is important to avoid progressive catheter-related infection.
(2) Regular monitoring of the exit site and subcutaneous tunneling is effective for the early detection of catheter-related infections.

Explanation

1. Clinical significance and definition (diagnosis) of catheter-related infections

The objective of routine exit-site care is to avoid catheter-related infections. Because progressive catheter-related infections can result in catheter extraction and fatal refractory peritonitis, preventative approach and early response to any abnormality are essential.

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In this guideline, we have defined catheter-related infection as follows: "pathogenic infection in the outer perimeter of a tissue section where the peritoneal dialysis catheter passed through." We used the term "catheter-related infection" as the collective concept which includes both exit-site infection and tunnel infection.

Regarding exit-site infection and tunnel infection, The ISPD guideline [661] mentioned the following definition:

- Exit-site infection: The presence of purulent discharge, with or without erythema of the skin at the catheter-epidermal interface.
- Tunnel infection: The presence of clinical inflammation or ultrasonographic evidence of collection along the catheter tunnel.

When CKD patients treated with PD exhibit catheter-related infections, its pathogenic infection pathway is generally thought to be (Grade A) exit site → (Grade B) subcutaneous tunnel vicinity → (Grade C) external cuff → (Grade D) internal cuff, with peritonitis occurring when the infection has reached the internal cuff (Fig. 6). The infection can spread to the vicinity of the catheter by scratching wounds near the subcutaneous tunnel and can progress without any infection in the exit site.

Ultrasonography findings are important when conducting the aforementioned grading procedures. As mentioned in the previous chapter, there is an extremely high number of causative agents associated with catheter-related infections. Therefore, the purulent discharge should be collected as a culturing sample, and Gram staining should be conducted.

2. Epidemiology of catheter-related infections

In addition to *Staphylococcus epidermidis*, which is the representative bacterial flora on skin, a wide range of pathogens can also cause catheter-related infections, including Gram-positive cocci, Gram-negative bacilli, corynebacterial, diphtheroid, rapidly growing mycobacteria, and fungi. Longitudinal surveys in facilities conducted on pediatric PD patients in Japan [628] indicated that 59% of causative agents of exit-site/subcutaneous tunneling infections were *S. aureus* (20% were MRSA), and 55% of MRSA-based peritonitis was accompanied by a subcutaneous tunneling infection. Furthermore, catheter-related infections due to *Pseudomonas aeruginosa* were also known to have a high risk of progressing to peritonitis [662]. Therefore, proper attention should be paid to identify pathogen in catheter-based infections.

Meanwhile, reports have indicated an increasing prevalence of rapidly growing mycobacterial infections. The precise reason why these cases are increasing is unknown. However, rapidly growing mycobacteria are

Fig. 6 Onset of catheter-related infections (Shaded areas indicate infected tissue). Grade A: infected tissue is limited to around the exit-site. Grade B: infected tissue has spread to the distant subcutaneous tunnels beyond the external cuffs, but it has not yet reached the external cuff. Grade C: infected tissue has spread to the distant subcutaneous tunnels beyond the external cuffs and has reached the external cuff. Grade D: infected tissue has spread to the distant subcutaneous tunnels beyond the external cuffs and has reached the internal cuff. The accuracy of the grading is improved by using ultrasound measurements

normal bacterial flora that lives within soil or water systems, and previous reports have indicated that infection cases are higher in those with a lower immune capacity [663]. These backgrounds suggest that a factor relating to the decreased immune capacity of dialysis patients (e.g., old age) may be partially contributing to this increase.

3. The necessity of observations during outpatient care

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Monitoring the exit site and tunnel on regular outpatient care is useful in the early detection of catheter-related infections. The quality of regular monitoring can be increased by recording the condition of the exit site and tunnel frequently

A record based on some type of "scoring system" might be ideal for characterizing the exit-site condition in order to maintain objectivity. However, currently, no specific scoring system has been demonstrated to be superior to another for the management of catheter-related infections, at least in adult cases.

4. Exit-site infection prevention

Survey results on Japanese and North American facilities conducted in 1996 indicated that virtually 100% of Japanese facilities conducted povidone-iodine disinfection daily. In contrast, approximately half of North American facilities conducted povidone-iodine disinfection, with the other half using only soap. Furthermore, approximately 20% of North American facilities conducted exit-site care with hydrogen peroxide [664]. Povidone-iodine disinfection was frequently conducted in Japan, but this has decreased now compared to 1996, and longitudinal PDOPPS research on the status of PD in each country indicated that the frequency was about 30% [665]. Regarding soap washing, comparative analyses in Japan on the frequency of catheter-related infections indicated significant differences between no implementation (0.91 times/patient/year) and implementation (0.09 times/patient/year) [666]. At the very least, there is no justification for avoiding soap washing. Previous analyses conducted in Japan [666] indicated that povidone-iodine disinfection presence was not correlated to the incidence of catheter-related infections. Furthermore, various contradictory findings have been reported when comparisons were made between disinfectants and disinfectant usage presence [667–674], and there is no definitive evidence indicating the benefits of using disinfectants. An ISPD guideline [661] statement indicated that "No cleansing agent has been shown to be superior with respect to preventing catheter-related infections." In either case, there is no clear evidence regarding the presence or superiority of disinfection, and there are no particular methods that can currently be recommended. Patients who experience epidermolysis or erosion (i.e., rough skin) in the skin near the exit site while using disinfectants should suspend their usage in order to preserve the barrier function of the skin.

With regard to water quality during showers and bathing, analyses in Japan indicated that no bacteria were detected in tap water. In contrast, there were always bacteria in well or spring water [675], and the pathogens that caused rapidly growing mycobacterial exit-site infection (*Mycobacterium fortuitum*) matched the detected bacteria in the well water used for exit-site care [676]. Given these results, patients should always use tap water and avoid spring water when bathing.

With regard to antibacterial drugs or local coatings of antibacterial substances, the ISPD guideline [661] states that "daily topical application of antibiotic cream or ointment to the catheter exit site" is recommended. Similar recommendations are provided in the guidelines relating to peritonitis prevention and treatment issued by ISPD in 2016, which also stated that "daily topical application of antibiotic (mupirocin or gentamicin) cream or ointment to the catheter exit site" is recommended [395]. These statements are based on multiple analysis results in overseas (not Japanese) reports, including findings indicating that intranasal *S. aureus* presence is a risk factor for catheter-related infections [677], nasal coatings of mupirocin reduced exit-site infections due to *S. aureus* [678], and gentamicin coatings on the exit site reduced the incidence of both exit-site infection and peritonitis [679]. However, reports have also indicated that bacterial resistance can form due to the continuous use of antibacterial ointments and creams, which include mupirocin and gentamicin [680–684]. Meanwhile, coating with both mupirocin and gentamicin has been shown to increase the risk of fungal peritonitis compared to conducting daily coatings of gentamicin [685]. A systematic review has been conducted on this as part of these guidelines (CQ3: Should PD patients use mupirocin and gentamicin ointments as coatings for the exit site?). Mupirocin is applicable only for nasal MRSA disinfection in Japan, and whether the widely used daily coatings of antibacterial ointment/cream can be extrapolated to Japan needs to be researched in the future.

5. Exit-site covering

There is no clear evidence indicating whether exit-site covering using gauze or dressing film is necessary. Questionnaire surveys conducted in facilities in Tokyo, Japan, indicated that exit-site care is recommended in 95% of facilities (of which 97% of patients are indicated to use gauze as a coating material) [686]. Meanwhile, in questionnaire surveys that have been previously conducted in Japan and the USA, while facilities indicated that coating usage is standard practice in Japanese facilities, over 30% of North American facilities do not use coating [663]. A recent Malaysian randomized control trial indicated that there were no significant differences in the incidence of catheter-related infections due to covering presence [687]. However, it is not clear whether this result can be extrapolated to Japan.

(3) Non-surgical treatment for catheter-related infections

Key points

1. Non-surgical treatment should be conducted in patients where the infection has not extended to the external cuff.
2. Antibacterial drugs should be administered in patients where there are apparent inflammation symptoms (e.g., redness/swelling of the exit site and subcutaneous tunnel areas).
3. Culture samples should be collected prior to antibacterial drug administration.
4. Surgical treatment should be considered in refractory cases or where the infection has spread to the external cuff.

Explanation

1. Applications and limits of non-surgical treatment

Systematic and/or local administration of antibacterial drugs is the main strategy of non-surgical treatment for catheter-related infections. Surgical treatment options include unroofing, exit-site alterations, and catheter extraction (and re-insertion).

ISPD guideline [661] defines refractory catheter-related infection as "failure to respond after 3 weeks of effective antibiotic therapy." In such cases, surgical treatment is recommended. However, the possibility of resolution drastically decreases if the infection has spread to the cuff. For such cases in which the infection has been confirmed or assumed to have spread to the external cuff, we recommend surgical treatment in principle. Even if non-surgical treatment is continued, meticulous follow-up is needed.

2. Collection of culture samples

As shown in "Epidemiology of catheter-related infections", there is an extensive number of causative agents for catheter-related infections, so purulent discharge should be collected for culture sample prior to the commencement of treatment, with Gram staining conducted to identify the causative pathogen. Revisions to antibacterial regimens should be based on the actual causative agent, and in that sense, collecting culture samples is crucial. The positivity rate of culture sample after antibacterial drug administration decreases; therefore, culture samples should be collected prior to the administration of antibacterial drugs.

3. Selection principles for antibacterial drugs

Antibacterial drugs should be administered to patients who manifest apparent inflammation symptoms, such as redness or swelling in the exit site and subcutaneous tunneling areas. In principle, the antibacterial drugs administered should be those that *Staphylococcus aureus* and *Pseudomonas aeruginosa* are sensitive to. Based on extensive previous clinical experience, the current recommended antibacterial drug administration pathway is oral. For cases of catheter-related infection whose results of exit-site culture are known from past tests, drugs that are also effective against the detected bacteria should be selected. It is important to use regular surveillance results related to causative agents as a benchmark, as the percentage of causative agents are thought to vary according to the facility.

As to recommended antibiotics, the ISPD guidelines [661] include the following statement: "empiric oral antibiotic treatment of exit-site infections with appropriate *S. aureus* cover such as a penicillinase-resistant penicillin (e.g., dicloxacillin or flucloxacillin) or first-generation cephalosporin, unless the patient has had a prior history of infection or colonization with methicillin-resistant *S. aureus* (MRSA) or *Pseudomonas* species (in these cases they should receive a glycopeptide or clindamycin, or appropriate anti-pseudomonal antibiotic, respectively)."

4. Dose and duration

The administered dose of renally excreted antibacterial drugs should be modified; specifically, the first administration should be the same amount as that of a person with a regularly functioning kidney, with subsequent doses changed according to the drug content. Adjustments to the administered dose should refer to the ISPD guidelines [661] or other relevant manuals [688, 689].

The administered duration should last until the monitoring reveals that the infection in the exit-site or subcutaneous tunneling areas has been resolved. The ISPD guidelines recommend "2 weeks for exit-site infections, and 3 weeks for subcutaneous tunneling or *Pseudomonas aeruginosa* infection." Rapidly growing mycobacteria may require antibacterial drug administration for even more extended periods. If this is the causative agent, ultrasound and CT-based findings may need to be used as decisive indicators for the completion of antibiotic administration.

(4) Surgical treatment for exit-site and subcutaneous tunneling infections

Key points

1. Surgical treatment should be used if medical treatment is not efficacious against subcutaneous tunneling infections.

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2. The surgical procedure varies according to the location of the infection.
3. All treatment should focus on preserving the peritoneum, not continuing PD.

Explanation

As shown in Chapter 3, early-stage diagnosis and medical treatments prevent pathological progress and paracatheter peritonitis. However, if the infection has spread across the external cuff and towards the abdominal cavity, curative medical treatment is no longer possible. In these cases, the area where the infection has spread needs to be accurately diagnosed, and suitable surgical treatment needs to be conducted. There are a number of treatment methods, and a suitable option needs to be chosen according to the degree of subcutaneous tunneling infection progress.

1. Unroofing methods (± cuff shaving methods) (Fig. 7)

This method directs the external cuff of the infected catheter outside of the body and forms a new exit site between the internal and external cuffs [690–692]. Cuff shaving, which removes the external cuff, may or may not be conducted. Anesthesia should be either lumbar or general if the infection is widespread, and catheter extraction is necessary during surgery. Local anesthesia can be used if the infection is deemed to be localized according to ultrasonography.

An incision is made into the entire upper skin layer from the exit site to the subcutaneous tunnel, the infected catheter vicinity is exposed up to the external cuff, and the external cuff is exposed to the external environment [690]. The pus retained in the catheter vicinity is removed and disinfected as much as possible through absorption or disinfectants. Incised fat tissue between the anterior wall of the subcutaneous tunnel and the skin is also present here. Two methods can be used: one where hemorrhaging is stopped with an electronic scalpel and is left as an open wound (Fig. 7a) and one where the wound is closed after sufficient cleaning and disinfection (Fig. 7b). The advantages of the former (Fig. 7a) is that post-operative cleaning and disinfection are easier to conduct and continued infection does not occur. Granulation tissue eventually manifests, and it naturally closes with time. Meanwhile, the latter (Fig. 7b) has the lingering risk of infection, but tissue repair under uninfected conditions is rapid, and the wound itself heals relatively well.

Regarding the external cuff, there is the cuff shaving method [691] (Fig. 7c), in which the dacron fibers are removed with a scalpel or file, and only the silicon tube remains. However, care is needed to ensure that the catheter is not damaged while this procedure is implemented [693]. Generally, the catheter does not become an infection source once it is directed out of the body and dried, regardless of whether there has been an infection.
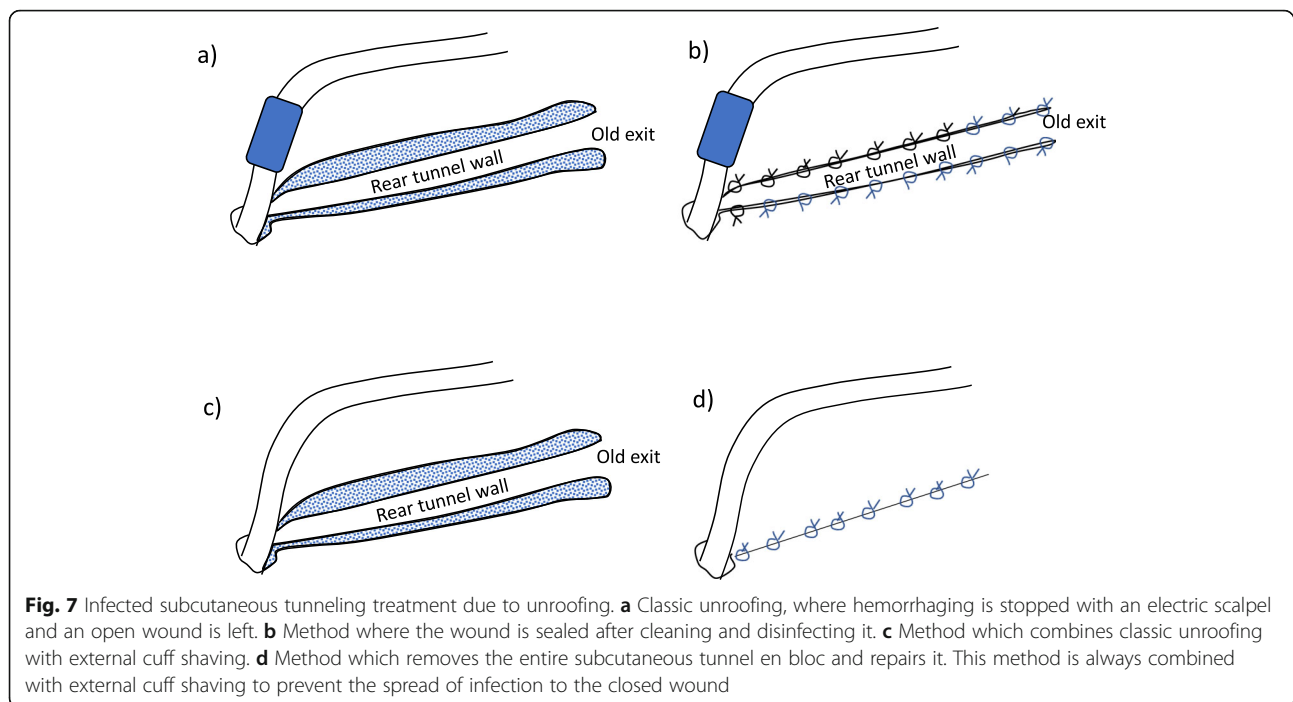
Reports have indicated a method where the entire subcutaneous tunnel en bloc is removed once a skin incision is made directly above the catheter in the non-infected section and the catheter is retained (unroofing-BR method) [692] (Fig. 7d). This is a method that ensures no remaining infected tissue, and reports have indicated favorable infection recovery even in refractory cases of MRSA infections [692]. Clean and rapid wound recovery will occur if the infection does not remain.

The distance to the internal cuff reduces when these unroofing methods are conducted, and paracatheter peritonitis risk is said to increase when subcutaneous tunneling infection progresses. However, as shown in Fig. 4, blood flow is high as the area from this point towards the internal cuff directions passes through the rectus abdominis interior, and infection progress is minimal due to the rapid mobilization of immunity factors and white blood cells. Additionally, pus discharge smoothly exits the body due to the lack of subcutaneous tunnels, even when new exit-site infections occur. This results in minimal subcutaneous tunneling infection progress, and there are many cases where long-term PD continuation is possible. Another significant advantage of this surgical method is that it does not come into contact with the peritoneal region, which allows for the continued use of PD.

2. Exit-site changing procedure (subcutaneous pathway diversion [SPD]) (Fig. 8)

The exit site may be changed to reduce the subcutaneous tunnel length due to the unroofing method or for esthetic purposes following implementation [694–698]. This method was termed subcutaneous pathway diversion (SPD) by Tsuzuki et al. [696]

The infected area is zoned with a dressing film, and surgery is started while ensuring that the infection does not spread into the surgical wound. An incision is made directly above the subcutaneous tunnel in the non-infected area between the internal and external cuff, and the catheter is placed (Fig. 8a). This surgery should be suspended if there is an infection present at this point. In such cases, the unroofing method or replacement surgery should be selected instead. This is because if the infection continues in this area, pus discharge into the exit site no longer becomes possible during relapses and will rapidly spread in the direction of the internal cuff, resulting in an increased risk of paracatheter peritonitis. A new catheter with a titanium extender affixed can be

Fig. 7 Infected subcutaneous tunneling treatment due to unroofing. **a** Classic unroofing, where hemorrhaging is stopped with an electric scalpel and an open wound is left. **b** Method where the wound is sealed after cleaning and disinfecting it. **c** Method which combines classic unroofing with external cuff shaving. **d** Method which removes the entire subcutaneous tunnel en bloc and repairs it. This method is always combined with external cuff shaving to prevent the spread of infection to the closed wound

used (attached catheter, or a catheter where the side hold portion is cut off) (Fig. 8b). A subcutaneous tunnel is then created in the subcutaneous areas where the infection has not spread, while a new exit site is created (Fig. 8c, d).

Next, the new wound is zoned with dressing film, and the spread of infection is prevented, after which the old catheter is extracted. At this time, it is possible to make an incision directly above the tunnel and remove it as if unroofing, but in that case, a large wound will be created. If the catheter that is the source of infection is removed and the drainage is done, the infected wound disappears. Therefore, a method of inserting a Penrose drain into the tunnel after removing the outer cuff is also used. The drainage disappears in about 2 days, so it should be removed.

This method is widely used currently, but there have been reports of the catheter becoming dislodged in the titanium extender area or detached following damage [699, 700]. Therefore, care must be taken to ensure that excessive tension is not applied in this area.

The paragraph in the product attachment for the titanium extender states that "this product is to be used for extending the terminal (external side) of the peritoneal dialysis catheter." There is no mention of using it to extend the catheter inside the body. For this reason, its usage should be carefully considered by the facility and responsible surgeon.

3. Catheter replacement procedure

Often, improvements will not be observed with the above methods in cases where imaging diagnoses confirm the spread of infection from the external cuff and into the center or when the causative agent is *Pseudomonas aeruginosa* [701] or *Serratia*. In such cases and where the patient would like to continue PD, inserting a new catheter from the contralateral side and extracting the infected catheter can be effective. Antibiotic treatment should be prescribed, and a new catheter should be inserted after the infected catheter has been extracted in cases where the patient has peritonitis. In contrast, there is no problem conducting an insertion and extraction together in cases where the patient is affected only by a subcutaneous tunneling infection (as recommended by ISPD) [661]. In these cases, similar to the above scenarios, the infected area is isolated with a dressing film, after which the PD catheter is inserted from the contralateral side. Preventative actions should be taken for dialysis fluid leakage from the internal cuff area.

After a dressing film has been applied to all surgical wounds of the new insertion and the spread of infection has been prevented, a skin incision should be made directly above the internal cuff of the infected catheter. Then, the catheter is first extracted from within the abdominal cavity, after which the peritoneal area is firmly sealed with absorbable threads to prevent leakage. Afterward, the external cuff is removed. It should be noted that the external cuff should not be removed first as this can contaminate the operating field and surgical equipment.

Fig. 8 Subcutaneous pathway diversion (SPD). **a** The central portion of the outer cuff is cut off. **b** Titanium extender is attached to proximal portion of the catheter. **c**, **d** The tissue around the catheter and the catheter are resected together
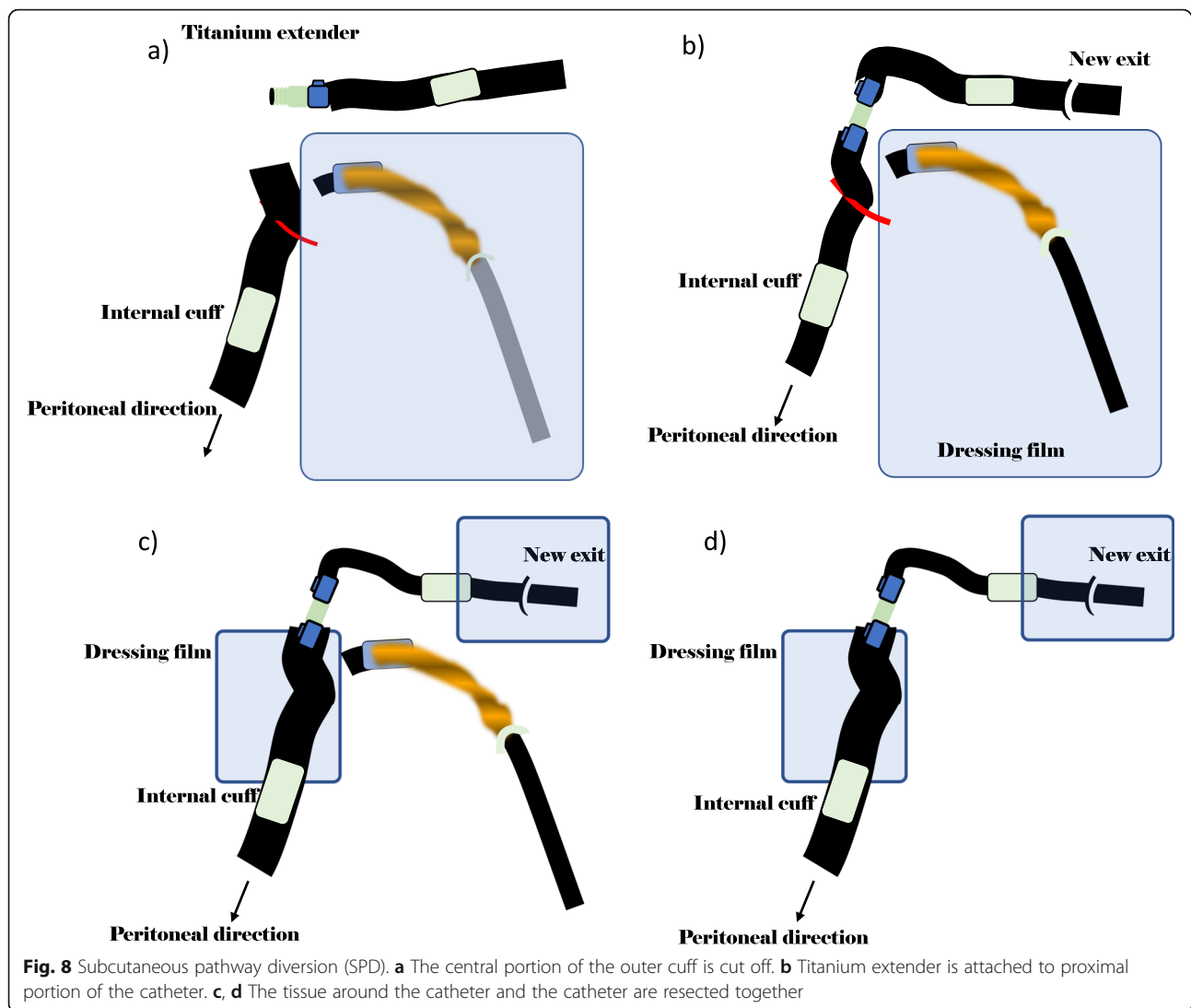
Catheter and exit-site management in pediatric patients

(1) Catheter insertion

Key points

1. Although insertion areas and design are limited, double cuffs are used when possible in pediatric patients.
2. Exit sites in the upward direction should be avoided for children as well.
3. An insertion pathway design that considers growth is essential.

Explanation

Catheter insertion and management in pediatric patients is also important. The extent to which the catheter is safely inserted and managed dictates the success of PD and also affects prognosis of the patient [702]. Insertion areas in children are particularly limited due to their small physique and thin subcutaneous tissue, and designs such as catheter insertion and exit-site creation are limited. It is important to create a thorough plan for catheter insertion as risk factors for peritonitis need to be understood for conducting stable dialysis [703].

The inner diameter of the catheter used for pediatric patients is the same as that used for adults, but its shape, cuff position, and length can vary. These dimensions should be selected after sufficiently understanding their characteristics and in accordance with the physique of the patient or exit-site design. Cuffs decrease the risk of infection, with a double-cuff catheter being selected when possible in pediatric patients in order to fix and stabilize the catheter [238]. A large part of the subcutaneous tunneling portion should be taken and placed so that the subcutaneous cuff and exit site are at least 2 cm

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Table 13 Exit-site scoring (Twardowski)

	0 points	1 point	2 points
Swelling	None	Only at the exit-site (< 0.5 cm)	Includes tunnel area
Crust	None	< 0.5 cm	> 0.5 cm
Redness	None	< 0.5 cm	> 0.5 cm
Pain	None	Slight	Severe
Discharge	None	Serous	Purulent

Note: suspected at 4 points and above

apart [238]. The patient should also be instructed to avoid crying too vigorously immediately after the insertion so as not to apply abdominal pressure. Additionally, shaking of the cuff should be avoided by leaving a space of 2–3 weeks from the time of catheter insertion to dialysis starting [704].

Regarding catheter insertion pathway design, both the full length of the catheter and length from each cuff should be considered and designed using pre-surgical abdominal X-rays so that the tip can be placed in the pouch of Douglas to accommodate possible changes due to growth. Furthermore, the exit site in newborns or infants should not be created within their diaper area to avoid contamination [705], and care should be taken to avoid the belt area in older children. Conventional reports [238] have recommended a downward- or sideways-facing exit site. Observations of 734 pediatric PD patients in the USA 3 years in recent SCOPE (The Children's Hospital Association's Standardizing Care to Improve Outcomes in Pediatric ESRD) reports [627] indicated that the incidence of peritonitis was significantly higher in patients whose exit site was in an upward direction. It is essential to incorporate the opinions of patients and their families and to decide beforehand a design that fits the age and lifestyle preferences of the patient.

(2) Exit-site and subcutaneous tunneling management

Key points

1. It is important to provide ongoing patient education and exit-site care management to prevent the onset of peritonitis. This should be done when the catheter is first inserted and during outpatient visits.
2. A scoring algorithm is used for the observation of exit sites in children.
3. Exit-site infection treatment is conducted as per that in adults, but doses are converted to those appropriate for children.

Explanation

The risk of peritonitis is higher in infants due to contamination from diapers or urinary incontinence [627].

For these reasons, guardians need to observe and care for the exit-site and tunnel areas thoroughly while providing the important management education. A scoring system (Table 13) is used as an objective evaluation of the exit site in children [706, 707]. Reports in Singapore [708] indicated that the incidence of infection improved when a series of patient education programs were implemented, such as when pediatric dialysis nurse specialists directed procedures and observed clinical care. Reports indicated that PD catheter-related infections were significantly improved during a 3-year follow-up period when exit-care management was unified and standardized in 29 pediatric hospitals in the USA [709]. Thus, education to patients and their families during catheter insertion and ongoing follow-up visits is essential. Furthermore, multi-facility research in Italy [587] with home visits and questionnaire surveys indicated that significant re-training was necessary for pediatric patients. An ongoing process of planning, guidance, and evaluation is necessary for the education and training of patients and their families.

Reports on exit-site infection prevention for children indicated that local mupirocin usage combined with sodium hypochlorite solution might reduce the incidence of exit-site infection [672]. However, no clear methods have been established.

Both non-surgical and surgical exit-site infection treatments in children are conducted in accordance with adults. However, the administered dose of antibacterial drugs is reduced for renal excretion and also adjusted in accordance with the child's age, weight, and physique [710]. The administered duration is set at 2–3 weeks in accordance with the culture results [238].

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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