

Comprehensive Review: Diagnosis, Classification, and Risk Factors of Peritoneal Dialysis-Associated Peritonitis

Lingling Guo^{1,2*}, Sairah Abdul Karim^{3*}

¹Post Graduate Centre, Management & Science University, 40100 Shah Alam, Selangor, Malaysia

²School of Nursing, Jiangsu Medical College, 224005 Yancheng, Jiangsu Province, China

³Faculty of Health and Life Sciences, Management & Science University, 40100 Shah Alam, Selangor, Malaysia

*Corresponding authors: Lingling Guo, 295798154@qq.com; Sairah Abdul Karim, sairah@msu.edu.my

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Abstract: Peritoneal dialysis (PD) is a predominant modality of renal replacement therapy (RRT) for individuals suffering from end-stage renal disease (ESRD). Peritoneal dialysis-associated peritonitis (PDAP) represents a frequent complication among patients undergoing PD, significantly contributing to adverse clinical outcomes. This review comprehensively examines the diagnosis, classification, and risk factors associated with PDAP, aiming to offer clinical practitioners essential guidance and a foundational framework for effective clinical management.

Keywords: Research progress; Risk factors; Peritoneal dialysis-associated peritonitis

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1. Introduction

In 2023, the Global Kidney Health Atlas by International Society of Nephrology reported 850 million patients with Chronic Kidney Disease (CKD) worldwide ^[1]. As CKD progresses, the number of patients with end-stage renal disease (ESRD) increases accordingly. Renal replacement therapy (RRT) is the main treatment for ESRD, including hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation (RT) ^[2]. However, due to practical problems such as insufficient donor kidney sources, difficult type matching, and high costs, HD and PD are still the most widely used treatments for ESRD, far more than RT. PD is widely used worldwide, especially in developing countries, due to its simplicity, safety, effectiveness, and suitability for home treatment ^[3]. Peritoneal dialysis-associated peritonitis (PDAP) is the most frequent complication of PD and a primary cause of technical failure. PDAP increases treatment costs, hospitalization rates, and mortality risk ^[4]. Structural changes in the peritoneal membrane are common and detrimental ^[5]. PD catheter removal is necessary in 22% of peritonitis cases ^[6]. PD patients are often switched to HD because of peritonitis. Thus, identifying risk factors is crucial for lowering the incidence of PDAP.

2. Diagnosis of peritoneal dialysis-associated peritonitis

According to the 2022 ISPD guidelines on peritonitis prevention and treatment, peritonitis should be diagnosed if at least two of the following criteria are met ^[7]:

- (1) PD patients have abdominal pain and/or cloudy dialysis effluent, which are clinical features indicative of peritonitis.
- (2) Dialysis effluent white cell count $> 100/\mu\text{L}$ or $> 0.1 \times 10^9/\text{L}$ (after a dwell time of at least 2 hours), with $> 50\%$ polymorphonuclear leukocytes (PMN).
- (3) Positive dialysis effluent culture.

3. Types of peritoneal dialysis-associated peritonitis

According to the 2022 updated prevention and treatment guidelines for PDAP by the International Society for Peritoneal Dialysis (ISPD), PDAP encompasses pre-PD peritonitis, PD catheter insertion-related peritonitis, catheter-related peritonitis, and enteric peritonitis, with specific definitions provided in **Table 1** and **Figure 1** ^[7].

Table 1. Types and definitions of peritoneal dialysis-associated peritonitis (PDAP)

| Type | Definition |
|---|---|
| Pre-PD peritonitis (before PD commencement) | Peritonitis occurs after PD catheter insertion but before the start of PD treatment. |
| PD catheter insertion-related peritonitis | An episode of peritonitis that occurs within 30 days of PD catheter insertion (not graded). |
| Catheter-related peritonitis | Peritonitis occurred at the same period (within 3 months) as catheter infection (outlet or tunnel), and the outlet or tunnel secretion and exudate culture results are the same pathogen, or the above parts are negative after the use of antibiotics. |
| Enteric peritonitis | Due to intestinal diseases, including inflammation, perforation, or ischemia of abdominal viscera. |

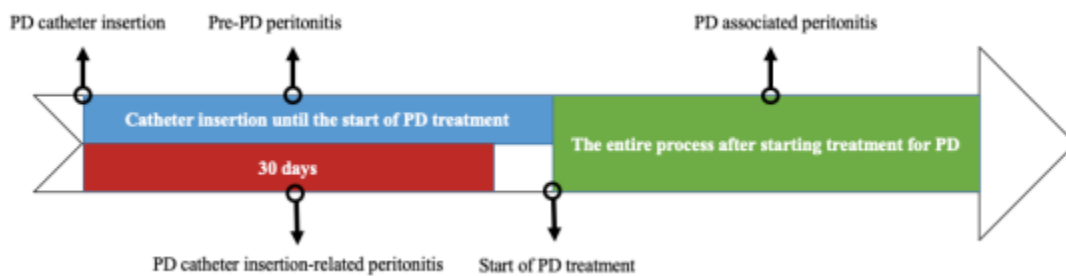


Figure 1. The new classification of PDAP

4. Risk factors of peritoneal dialysis-associated peritonitis

Several risk factors for PDAP have been identified. Non-modifiable factors include older age, male gender, ethnicity, lower socioeconomic status, diabetes mellitus, coronary artery disease, chronic lung disease, and residual renal function. Cognitive impairment and memory loss also independently increase the occurrence of PDAP. Modifiable risk factors include social and environmental factors, medical conditions, dialysis-related factors, and infection-related factors.

4.1. Non-modifiable risk factors

4.1.1. Age

Age-related physiological changes, such as decreased immune function and diminished peritoneal membrane integrity, contribute to the heightened susceptibility to infections among older adults undergoing PD. Studies have consistently shown that advanced age is associated with an increased incidence of PDAP^[8-10].

4.1.2. Gender

The relationship between gender and PDAP remains unclear. Some studies have found gender differences in the incidence of PDAP. A population-based national cohort study of 11,202 PD patients by Mu-Chi Chung *et al.* showed that the female gender had a higher risk (HR 1.21 per patient-year; 95% CI 1.14–1.29)^[10].

4.1.3. Ethnicity

The impact of ethnicity on the occurrence of PDAP is a significant topic in nephrology research. Studies have consistently shown disparities in the incidence and outcomes of PDAP across different racial and ethnic groups^[11,12]. The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS), which included 7,051 adult PD patients from 209 centers across Canada, Japan, Australia, New Zealand, Thailand, the UK, and the USA, revealed significant variations in the occurrence of peritonitis^[12].

4.1.4. Level of education

Several studies have shown that the level of education of PD patients affects the occurrence of peritonitis, with lower education levels associated with higher rates of PDAP^[13,14]. Patients with lower education levels often face challenges in understanding complex treatment plans and infection prevention practices, making them less able to follow medical advice, perform the correct PD procedures, and recognize early symptoms of peritonitis in a timely manner.

4.1.5. Underlying disease

A retrospective cohort study by Risa Ueda *et al.* shows that PD patients with diabetes mellitus are at an increased risk of PDAP^[15]. Other studies on PD patients with cardiovascular diseases, chronic lung diseases, and immunodeficiency states have found similar results. These underlying diseases compromise immune function, impair wound healing, and increase susceptibility to infections, including peritonitis.

4.1.6. Conscientious of PD Patients

Conscientiousness of PD patients refers to their compliance and responsibility with treatment plans, hygiene practices, and follow-up protocols. Studies have found that poor conscientiousness, such as improper hygiene practices during catheter care, failure to strictly follow protocols for dialysis fluid exchange, and failure to maintain aseptic techniques during exchanges, significantly increases the risk of infection.

4.1.7. Climate

Studies show that higher average temperatures and seasonal variations, which can create a more favorable environment for bacterial growth and colonization, may affect the incidence and severity of PDAP^[18,19]. Changes in weather and environmental conditions can impact the immune response and susceptibility to infections among PD patients. However, the results of studies on the effect of humidity on the incidence of PDAP are inconsistent^[18,19], and further research is needed to clarify the impact of humidity on PD patients.

4.2. Modifiable risk factors

4.2.1. Social and environmental factors

4.2.1.1. Smoking

Smoking has been identified as a significant risk factor for the occurrence and development of PDAP. Studies consistently show that PD patients who smoke have a higher incidence of PDAP than non-smokers^[20,21], mainly because smoking damages the immune system, affecting the body's resistance and increasing the chance of infection. Additionally, for PD patients with underlying diseases, smoking can exacerbate conditions such as respiratory or cardiovascular diseases, thereby increasing the risk of PDAP. Long-term exposure to cigarette smoke worsens respiratory function, and impedes wound healing and overall immune function, creating a favorable environment for infection.

4.2.1.2. Domestic pets and zoonotic infection

The influence of domestic pets and zoonotic infection on the occurrence of PDAP is an emerging area of concern in nephrology. Pets, such as dogs and cats, can carry bacteria and parasites that can cause infection in humans through direct contact or environmental contamination^[22]. These pathogens include *Staphylococcus aureus*, *Streptococcus*, and various opportunistic pathogens that multiply in animal hosts. Moreover, interference by pets or improper hygiene practices during peritoneal dialysate exchange can accelerate the spread of these pathogens to PD patients. Factors such as the pet's hygiene habits, sandbox maintenance, and household cleaning derived from pet ownership play an important role in reducing the risk of zoonotic infections in susceptible patient populations^[7].

4.2.1.3. Distance from peritoneal dialysis center

The distance between the patient and the PD center indicates the availability of medical facilities and assistance for PD patients, which plays a crucial role in the follow-up management and prognosis of PD patients who are cared for at home and need regular follow-up, especially for infection prevention and timely medical intervention^[23]. Patients who live far away from PD centers often struggle to adhere to regular follow-ups due to factors such as inconvenient transportation, long travel times, and the inability to seek timely medical attention when peritonitis symptoms or complications occur. This can lead to the aggravation of infection and deterioration of the condition. Some working PD patients may also experience reduced frequency and quality of follow-up due to business trips and other commitments.

4.2.2. Medical factors

4.2.2.1. Body weight and body mass index

Body weight and body mass index (BMI) are important indicators of the nutritional status, body composition, and overall health of PD patients, influencing their susceptibility to infection. Research shows that PD patients with obesity and/or higher BMI are at greater risk of peritonitis because excess fat can lead to chronic inflammation and impair immune function^[9,18]. At the same time, obesity also increases the risk of underlying diseases such as diabetes and cardiovascular disease in PD patients. However, poor nutrition or a low BMI can also decrease the body's resistance and increase the risk of infection. The relationship between body weight, BMI, and PDAP needs further exploration in the future.

4.2.2.2. Serum albumin level and albumin/globulin ratio

Serum albumin levels and the albumin/globulin (A/G) ratio are important biomarkers that can influence the occurrence of PDAP^[24,25]. Albumin is the most important protein in human plasma, maintaining the body's

nutrition and osmotic pressure. It is an indicator of nutritional status and systemic inflammation, affecting immune function and wound healing. The A/G ratio reflects the balance between albumin and globulin in the blood. A reduced A/G ratio may indicate underlying chronic inflammation or immune disorder, predisposing PD patients to infections such as peritonitis. Studies have shown that PD patients with hypoalbuminemia and an unbalanced A/G ratio have a higher risk of developing PDAP, leading to delayed wound healing, impaired peritoneal function, and compromised defense mechanisms against bacterial pathogens ^[24,25].

4.2.2.3. C-reactive protein

C-reactive protein (CRP) is a sensitive marker of inflammation. A retrospective study shows that high baseline CRP levels are associated with an increased risk of PDAP ^[24]. Chronic inflammation, indicated by persistently elevated CRP levels, can impair peritoneal membrane function and compromise host defenses against microbial invaders, creating a favorable environment for peritonitis episodes.

4.2.2.4. Serum IgG or peritoneal dialysate IgG

The relationship between dialysate or serum IgG and peritonitis remains inconclusive ^[26]. A prospective study of 240 consecutive PD patients found that low serum IgG was associated with an increased risk for peritonitis ^[27]. Another study of 479 PD patients showed lower baseline dialysate IgG concentrations in 16 patients with frequent peritonitis during follow-up than in the 28 who remained peritonitis-free during a similar follow-up period ^[28].

4.2.2.5. Parathyroid hormone, calcium, and phosphorus levels

Parathyroid hormone (PTH), calcium, and phosphorus levels play a critical role in mineral and bone metabolism. Abnormal PTH, calcium, and phosphorus levels are common in patients with ESRD due to impaired kidney function and disrupted mineral metabolism. Chronic elevation of iPTH may lead to systemic inflammation and immune dysfunction, leaving PD patients vulnerable to infections, including peritonitis ^[29]. Similarly, disturbances in calcium and phosphorus levels can affect immune response and peritoneal integrity. Hypocalcemia or hypercalcemia, as well as abnormal phosphorus metabolism, may impair immune function in PD patients and increase susceptibility to infection ^[30].

4.2.2.6. Iron status

Iron status plays a crucial role in immune function and infection susceptibility among PD patients. Iron is an important carrier for oxygen transport in the body and an essential element for maintaining energy and immune cell function. Patients with iron metabolism disorders have an increased risk of peritoneal dialysis-related peritonitis ^[31]. Excess iron accumulation may impair immune cell function, disrupt microbial defense mechanisms, and increase the risk of infection by promoting oxidative stress and inflammatory responses.

4.2.2.7. Hypokalemia

Potassium is an essential electrolyte crucial for maintaining cellular function, nerve conduction, and muscle contraction, including the smooth muscles of the peritoneal membrane. Studies have shown that hypokalemia (HK) may impair peritoneal function, making it more susceptible to microbial invasion and resulting in peritonitis ^[32,33]. In addition, electrolyte imbalances, including HK, can lead to systemic inflammation and immune dysfunction, further exacerbating the risk of infection in PD patients.

4.2.2.8. Vitamin D deficiency

In patients with PD, vitamin D deficiency can be caused by a variety of factors such as insufficient sunlight, impaired kidney conversion of vitamin D to its active form, and inadequate diet. Low vitamin D levels are associated with immune dysfunction, chronic inflammation, and impaired inflammatory responses, which increase the risk of peritonitis in PD patients. Studies show that vitamin D deficiency may negatively affect the integrity of the peritoneum, making it more susceptible to microbial invasion, which in turn can lead to the development of peritonitis ^[34]. Vitamin D receptors present in immune cells play a pivotal role in innate and adaptive immune responses, influencing the body's ability to fight off infections effectively.

4.2.3. Dialysis-related factors

Dialysis-related factors influencing PDAP include dialysis techniques and practices, characteristics of dialysis solution, dialysis prescription and frequency, the number of PD bags connected per 24 hours, higher peritoneal transport status, and using devices for PD fluid exchange are high-risk factors for PDAP ^[24,34,35].

4.2.4. Infection-related factors

Touch contamination (23.9%), intra-abdominal infection (10.7%), and exit-site tunnel infection (10.1%) are the three primary causes of peritonitis, as reported by the Japanese Society for Peritoneal Dialysis. However, a significant proportion (38.1%) of peritonitis episodes are of unknown origin, often classified as culture-negative peritonitis ^[37]. Key measures to prevent infection-related factors of PDAP include strictly following aseptic practices, regularly inspecting and keeping the exit site clean, and avoiding contact with infectious sources. Additionally, timely treatment of skin infections and adhering to reasonable antibiotic use principles are crucial measures to prevent peritonitis ^[38].

5. Conclusion

Most of the current studies on the risk factors of PDAP are retrospective cohort studies. The influencing factors are numerous and complex, and there is essentially no deterministic relationship between the controllable factors and the occurrence of PDAP. It is necessary to conduct prospective studies on specific risk factors to determine their relationship under the premise of controlling confounding factors.

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Author contribution

Conceptualization: Lingling Guo, Sairah Abdul Karim

Investigation: Lingling Guo, Sairah Abdul Karim

Formal analysis: Lingling Guo

Writing – original draft: Lingling Guo

Disclosure statement

The authors declare no conflict of interest.

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