

INCIDENCE, CLINICAL OUTCOME AND CHANGES OF PERITONEAL MEMBRANE TRANSPORT STATUS IN TREATED CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD) RELATED PERITONITIS

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Abstract

Peritoneal dialysis-related peritonitis remains the most common complication and a key barrier to peritoneal dialysis' long-term success. The present study aimed to report on the incidence of peritonitis and clinical outcomes in CKD patients on CAPD at a hospital in Vietnam's south and evaluate the peritoneal membrane transport status before and after peritonitis therapy. This study was a cross-sectional study involving 141 participants sampled from the warded adult patients at An Giang center general hospital, in Vietnam. Peritonitis rate was measured in terms of incidences per patient-year. Dialysis fluid was drawn under aseptic conditions and treated using a culture approach to identify bacteria. The response treatment time for each episode of peritonitis after receiving empirical antibiotic medication. We use Peritoneal Equilibration Test (PET) to determine the peritoneal transport status. Peritonitis was found in 29.8% of the cases. The number of episodes of peritonitis per patient-year was 0.035. Negative bacteria account for 81.0 percent of all cases tested. It took an average of 3 to 5 days for a clinical response. Before and after peritonitis, there was no statistically significant connection between transport status groups. The rate of peritonitis identified in this study was significantly lower than that recommended by the International Society for Peritoneal Dialysis (ISPD) recommendations. More research is needed to fully understand the variables that influence the clinical outcomes of peritonitis and the remaining function of the peritoneal membrane.

Keywords: CAPD, CKD, Peritonitis

Introduction

Chronic kidney disease (CKD) is becoming a more significant public health issue worldwide, especially in developing nations. Patients with end-stage kidney disease (ESKD) requiring renal replacement therapy (RRT) (eGFR < 15) constitute 0.1 % of the global estimated CKD incidence (1). End-stage renal disease is stage-5-CKD, with a Glomerular filtration rate (GFR) of less than 15 mL/min/1.73 m², and hemolytic uremic syndrome, which is fatal unless renal replacement therapies are used, according to the Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease KDIGO (2012) (2). In Vietnam, the prevalence of CKD and end-stage renal disease (ESRD) has been continuously increasing, reaching nearly 90,000 patients with ESRD annually. In fact, by the end of 2016, only about 21,000 patients were being treated with maintenance hemodialysis (MHD), peritoneal dialysis (PD), or renal

transplantation (3). For those with early-stage PD, CAPD is the most prevalent treatment choice. Its effects are equivalent to hemodialysis (HD) and, in certain cases, may be better in the first few years (4).

Peritonitis, a common and significant consequence of CAPD due to peritoneal membranes to treat renal failures, directly causes mortality for 16 % of PD patients, despite less than 5% of peritonitis episodes ending in death (5). Additionally, it is the main cause of CAPD method failures, catheter removal, higher hospitalization rates, death, or hemodialysis (6). Furthermore, severe or persistent peritonitis causes a change in the structure of the peritoneal membrane and function, leading to membrane breakdown and encapsulating peritoneal sclerosis (7). Last but not least, peritonitis is a common cause of PD method failures and long-term hemodialysis conversions (8).

Studies on clinical outcomes of CAPD patients with peritonitis have been conducted worldwide (3-4, 9-11); However, a study on this topic was limited in Vietnam. The Ministry of Health in Vietnam reported that over 80,000 ESKD patients are in current need of PD treatments, and this number is increasing. To our knowledge, no study on the combination of peritoneal membrane transport status and peritonitis by using the Peritoneal Equilibration Test (PET) approach has been reported in Vietnam. Consequently, we decided to conduct a study on the incidence of peritonitis and clinical outcomes in CAPD patients by assessing the peritoneal membrane transport status before and after the peritonitis treatment.

Material and methods

Study population

In this study, only patients diagnosed with end-stage kidney disease had undergone CAPD. They attended regular follow-ups in An Giang center general hospital, Vietnam. Patients with ESRD were defined based on KDIGO criteria (2012), eGFR < 15 mL/min/1.73 m², particularly (2), initiations of CAPD > 4 weeks, and agree to participate in the study. The exclusion criteria were as follows: Patients who did not have their membrane function tested before and after peritonitis therapy, patients who had a communication issue, patients who were suffering acute illnesses, and patients who had a mental disorder.

Study design

A cross-sectional research was performed in An Giang center general hospital, Vietnam from March 2018 to March 2019.

Sample size

The formula used to estimate the required sample size was $n = \frac{(Z_{1-\alpha/2})^2 \times p(1-p)}{d^2}$. Where, n is the sample size; α is confidence level, with $\alpha = 0.05$; p is expected incidence (peritonitis incidence of the previous study) (7), with p = 0.16; d is precision, with d = 0.07.

Sampling method

The convenience sampling method was used to choose patients for the study based on the availability of their medical records.

Measurement and variables

The study's primary result was the incidence and clinical outcomes of peritonitis therapy and transport status following treatment. Patients who had at least two

criteria for Peritoneal Dialysis (ISPD) (2) recommended by The International Society were 1) clinical features consistent with peritonitis, i.e., abdominal pain and/or cloudy dialysis effluent; 2) dialysis effluent white cell counts more than 100/ μ L or 50% polymorphonuclear; and 3) positive dialysis affluent culture.

The incidence of peritonitis is calculated using the percentages of patients who had at least one episode of peritonitis during CAPD. The peritonitis rate was estimated by adding all occurrences of peritonitis that occurred throughout the study period for all patients enrolled in the program. This sum was split by the number of years spent at risk. The rate of peritonitis was calculated as incidents per patient-year. The percentages of primary causative organisms: *Enterobacter*, *candidiasis*, *Staphylococcus aureus*, and *Streptococcus alpha*.

A 4-hour peritoneal equilibration test (PET), as described by Twardowski et al, was done on each patient in the first one to three months following CAPD to establish peritoneal transport status (8). Dialysate (D) creatinine concentrations at 4h after the start of PET were divided by plasma (P) creatinine concentrations (4h D:P cr) to calculate D:P creatinine ratios. According to the 4h D:P cr, peritoneal transport status was classified as follows: low (0.50); low-average (0.50–0.64); high-average (0.65–0.80); high (> 0.81).

Regarding demographic characteristics, the participating patients were divided into groups with their respective subgroups: 1) gender (male, female); 2) age (41-50 years, 51-60 years, 61-70 years, and > 70 years old); 3) CAPD-time (< 24 months; 24 -47 month; \geq 48 months). Besides, the mean age and mean CAPD-time were figured.

Statistical analyses

For statistical analysis, the SPSS 18.0 program was employed. We used frequencies and percentages to represent qualitative variables, and means and standard deviations to express quantitative data. The Chi-square test was used to assess the differences between the two groups. With a p < 0.05 significance level, the difference was statistically significant.

Ethical considerations

This study was approved by the Ethics and Review Board Can Tho University of Medicine and Pharmacy and accepted for performance at the study hospital in Vietnam in 2018 (Approbations QD-DHYDCT-2018.638). All study participants were allowed to give their informed consent. In total, 141 participants were included based on medical records were identified and screened.

Results

Baseline characteristics of study participants

There were 141 CAPD patients, with 87 (61.7%) males. The average age was 45.5 ± 10.8 years, with the majority between 40 and 59 (56.7%). The mean follow-up time was 41.14 months, with 39.01% of patients having a follow-up time of fewer than 24 months and 31.21% having a follow-up time of more than 48 months (Table 1).

Table 1: Characteristics of the study population.

Characteristics		Frequency (n = 141)	Percentage
Gender	Male	87	61.7
	Female	54	38.3
Age	Age (years) Mean ± S.D.	45.5 ± 10.8	
	< 40 years	47	33.3
	40-59 years	80	56.7
	≥ 60 years	14	10.0
	CAPD duration	Mean PD duration (months)	41.14
	< 24 months	55	39.0
	24 - 47 months	42	29.8
	≥ 48 months	44	31.2

S.D. = standard deviation
 Mean PD duration = mean peritoneal dialysis duration
 CAPD = Continuous ambulatory peritoneal dialysis

Incidence and clinical outcomes of peritonitis

Peritonitis occurred in 42 patients (29.8%). Patients were categorized into the peritonitis and non-peritonitis groups (Table 2). Peritonitis was the highest concentration among over-60-year-olds (50%). Peritonitis was seen in 12 (21.8 %), 16 (38.1 %), and 14 (31.8 %) patients on peritoneal dialysis from 0 to 24 months, 24 to 47 months, and ≥ 48 months, respectively. The peritonitis group had a mean peritoneal dialysis time of 41.21 ± 23.59 months, while the non-peritonitis group had a mean peritoneal dialysis time of 41.11 ± 34.96 months. With 60 occurrences, 42 patients (29.8%) had at least one episode of peritonitis. Twelve patients had two episodes, three had three episodes, two had four episodes, and one had five episodes. There was no statistically significant relationship between age and CAPD duration and the occurrence of peritonitis (Table 3). The rate of peritonitis was 0.035 per patient-year.

Table 2: Peritonitis incidence varies by age group and CAPD duration.

		Peritonitis	Non-peritonitis	p-value
Peritonitis incidence	Frequency	42	99	-
	Percentage	29.8	70.2	
Age				
< 40 years	n	11	36	0.16
	%	23.4	76.6	
40 - 59 years	n	24	56	
	%	30.0	70.0	
≥ 60 years	n	7	7	
	%	50.0	50.0	
CAPD duration				
< 24 months	n	12	43	0.2
	%	21.8	78.2	
24 - 48 months	n	16	26	
	%	38.1	61.9	
≥ 48 months	n	14	30	
	%	31.8	68.2	
Mean PD duration (months)		41.21 ± 23.59	41.11 ± 34.96	-

S.D.= standard deviation
 Mean PD duration = mean peritoneal dialysis duration
 CAPD = Continuous ambulatory peritoneal dialysis

Table 3: Peritonitis rate

Episode	1	2	3	4	5	Total
Value	42	12	3	2	1	60 episodes
The total number of months						1692 months
Peritonitis episode per patient-year						0.035

The bacteria that cause CAPD-related peritonitis are listed in Table 4. Peritoneal peritonitis with no culture accounted for 34 (81.0%) of all occurrences. *Enterobacter* and *S. aureus* species were typically found in culture-positive peritonitis (7.1%, equally). *Fungal* was found in one case (2.4%) of all peritonitis episodes, and *S. alpha* was found in one case (2.4%).

Table 4: Microorganisms causing CAPD-related peritonitis

	Frequency	Percentage
Culture negative	34	81.0
Enterobacter	3	7.1
Fungal	1	2.4
Staphylococcus aureus	3	7.1
Streptococcus alpha	1	2.4

The mean time it took for a clinical response was three to five days. The maximum response treatment time for the first episode was up to 10 days (Table 5). Sixty percent of the patients in that incidence responded to therapy within five days (Table 6). The percentage of patients who responded to treatment after receiving empirical antibiotic medication is shown in Table 7, with most patients responding for the first time (83.3%). Throughout the subsequent episodes, the rate of antibiotic treatment response declined.

Table 5: Response treatment time

Episode	Response treatment time			
	Minimum (days)	Maximum (days)	Mean (days)	S.D.
1 (n = 42)	0	10	3.86	2.543
2 (n = 12)	0	8	2.92	2.275
3 (n = 3)	3	8	5.00	2.646
4 (n = 2)	4	5	4.50	0.707
5 (n = 1)	3	3	3.00	

S.D. = standard deviation

Table 6: Response treatment percentage in the first episode

Response treatment time (days)	Frequency	Percentage
2	2	4.8
3	12	28.6
4	7	16.7
5	4	9.5
6	3	7.1
7	2	4.8
8	4	9.5
10	1	2.4
No response	7	16.7

Table 7: Response treatment percentage in each episode

Treatment episode	Frequency	Percentage
Ep 1 (n = 42)	Yes	35
	No	7
Ep 2 (n = 12)	Yes	9
	No	3
Ep 3 (n = 3)	Yes	3
	No	0
Ep 4 (n = 2)	Yes	2
	No	0
Ep 5 (n = 1)	Yes	1
	No	0

Peritoneal membrane transport status after peritonitis treatment

As per the standard definition, transport status was categorized as low, low average, high average, and high. As can be seen from Table 8. The PET demonstrated that there were seven high transporter patients (20.0%), eight high average transporters (22.9%), 15 low average transporters (42.9%) and five low transporters (14.3%) in the before-treatment group. In the after-treatment group, there were more patients with high transporters 19 (54.3%) and high average transporters nine (25.7%), and low average transporters seven (20.0%) and no low transporters. Low average transporters were the most prevalent in groups ($p < 0.05$).

Table 8: Peritoneal membrane transport status before and after peritonitis treatment

Transport status	Before		After		p-value
	Number	Percentage	Number	Percentage	
High	7	20.0	19	54.3	< 0.05
High average	8	22.9	9	25.7	
Low average	15	42.9	7	20.0	
Low	5	14.3	0	0.0	

Discussion

Baseline characteristics of study participants

Our study comprised 141 participants, with 61.7% of men being taller than women, which is comparable to Wu et al. (2020) on Incidence and risk factors of peritoneal dialysis-related peritonitis in elderly patients (59.7% males) (14). The findings of Tan et al. (2019) were the polar opposite of ours, indicating that females are taller than men (40.7% of males). These discrepancies in the results might be due to sampling size disparities; our sample size was 2.5 times larger than Tan et al. (11). The mean age in our study was 45.5 ± 10.8 , which is similar to Tang et al. (2019) in Malaysia (45.5 ± 15.1 years), as well as two other studies: Wu et al. (2020) in China (47.3 ± 15.2 years) and Pindi et al. (2020) in India (45 ± 6 years) (9, 11, 12); CAPD may assist these patients in continuing to work. The mean CAPD-time was 41.14 months, and the CAPD-time < 24 months was the highest, accounting for 39%.

Incidence and clinical outcomes of peritonitis

Peritonitis morbidity was 29.2%, patients of the group aged > 60 years have peritonitis incidence higher than the others (50%). This is in line with our hospital's

patients, largely elderly folks. In China, Wu et al results also reveal that incidence was 29.7%, ≥ 65 years group account for 33.2% higher than the other group. Their result is rather consistent with our result. In their research, Wu et al explained that elderly patients could be more susceptible to peritonitis because of functional impairments, immune deficiency, and diverticulitis (14).

The mean CAPD time of the peritonitis group was 41.21 ± 23.59 months, which was equivalent to that of the no-peritonitis group. A retrospective multicentre study in Korea by Gweon et al. has CAPD durations were 33.9 and 51.4 months, respectively. However, statistical significance was not attained ($p = 0.207$) (15).

Additionally, we found that the < 24 months CAPD durations patient has a peritonitis incidence lower than the ≥ 24 months CAPD patient. The author reports that from 0–12 months, 12–24 months, and > 24 months, the number of initial episodes of peritonitis seen was 58 (33.3%), 41 (23.6%), and 75 (43.1%), respectively, at Central South University's Third Xiangya Hospital (6). However, in recent-5-years of research, the relationship between peritoneal incidence and CAPD durations remains unclear. Peritonitis is the most common complication of peritoneal dialysis (PD). Peritonitis occurs worldwide at 0.06–1.16 per patient-year in various peritoneal dialysis facilities (16). The International Society for PD guidelines (ISPD) recommend the standard peritonitis rate was 0.5 episodes per patient-year (2). Our peritonitis rate was lower than the ISPD peritonitis guidelines (0.035 episodes per patient-year). Forty-two patients had one incident of peritonitis, 12 patients had two episodes, three patients had three episodes, two patients had four episodes, and one had five episodes. The peritonitis rate in our study area was much lower, compared to 0.184 episodes per patient-year reported by Tang et al. at Miri General Hospital in Malaysia (13 patients had a single episode, nine patients had two episodes, one patient had three episodes, and one patient had four episodes of peritonitis) (9). The peritonitis rate was also 0.154 episodes per patient-year at the PD center of Sun Yat-sen University's First Affiliated Hospital in China (14). In a multicenter cohort study in Japan, patients with CAPD had 0.12 incidents per patient-year (17). Our patients' improved adherence to the aseptic approach during PD exchange might explain the disparities. Alternatively, our research location may have been Provincial General Hospital, with far fewer CAPD patients.

Many causes lead to PD-related peritonitis, mainly including 1) contamination, which is most likely due to skin or environmental organisms. 2) Catheter-related infections, which *S. aureus* or *P. aeruginosa* often causes. This includes biofilm on the internal portion of the catheter and exit-site and tunnel infection. 3) Bowel source enteric organisms, including gram-

negative rods, *Candida*, and anaerobes. 4) Bacteremia, which *Streptococcus* or *Staphylococcus* often caused. 5) Gynecologic source was often caused by *Streptococcus*, *Candida*, and some gram-negative rods (18). Almost all of the explanations described above are caused by bacterial infections. The main cause of peritonitis (54.7%) was gram-positive microorganisms. Over the years, there was a change in the causative microorganism profile: predominance of gram-negative bacilli between 1996 and 2000, then the emergence of gram-positive cocci with a constant progressive rise from 2001 till 2017. Such findings of the predominance of gram-positive bacteria were similar to studies conducted in Scotland, Canada, the United States of America, and Hong Kong in which gram-positive microorganisms comprised up to 66% of causative pathogens of peritonitis (19).

In the peritonitis group, positive-culture percentage accounts for 19%, with gram-positive microorganisms such as *S. aureus* (9.5%), and *S. alpha* (2.4%) having a higher percentage than gram-negative microorganisms (7.1%) and *Fungal* (2.4%), similar to studies (10, 16, 20-21). At Osmania General Hospital in India, Pindi et al. discovered that Gram-positive cocci constituted the majority of exit-site infections, *S. aureus* and *P. aeruginosa* exit-site infections are associated with tunnel infections and cause catheter infection-related peritonitis requiring aggressive management (10). As a result, aseptic catheter insertion, frequent effluent replacement, and patient care must all be done with caution to limit the risk of Gram-positive infections. The most considerable difference between our study about microorganisms and others was negative culture accounted for 81%. But ISPD Guidelines recommend a benchmark of less than 20% culture-negative cases (22). Antibiotic treatment prior to peritoneal fluid cultures and poor handling or processing of cultures or procedures are the most prevalent reasons for negative cultures. Furthermore, some of our patients originate from remote areas and may travel for several hours or days to reach our hospital. As a result, those patients may begin antibiotic therapy at a lower-level hospital. *Fungal* peritonitis is uncommon compared to bacterial peritonitis, accounting for just 1–12% of total peritonitis in PD disease patients. However, it is severe, with greater catheter loss, morbidity, and death rates (11).

For the treatment of peritonitis, early empirical antibiotic therapy is suggested. After diagnosing peritonitis, empiric antibiotic therapy was started as soon as possible. It took three to five days for clinical response in all our cases. The ISPD guidelines were followed: clinical improvement generally occurs within 72 hours after starting antibiotic therapy. Refractory peritonitis episode is now defined as failure of the effluent to clear after five days of appropriate antibiotics. In contrast, relapsing peritonitis refers to the episode that occurs within four

weeks of completion of therapy of a prior episode with the same organism or being culture negative. But in some cases, the maximal response treatment time for the first episode was up to ten days. The cloudy fluid may improve slowly due to this. A repeat peritoneal fluid sample should be cultured for atypical microorganisms if the patient has not reacted clinically after three to five days (22). A 8-year- research by Whitty et al. (2017) at a single major PD facility examined the outcomes of 339 peritonitis events and reveal that almost half of the patients were admitted to the hospital for the peritonitis therapy, and the average antibiotic treatment time was 22 days, and the intraperitoneal white cell count was resolved in three to four days on average (23). According to Continuous Ambulatory Peritoneal Dialysis Peritonitis Guidelines – Consensus Statement of Peritoneal Dialysis Society of India – 2020, the peritonitis should be treated for at least two to three weeks with suitable antibiotics, depending on the bacteria detected (24). A prompt fluid analysis and initiation of empirical antibiotic therapy improved outcomes. However, much of what is known about treating the peritonitis is based on the expert's opinion rather than the research. The evidence on how to treat the peritonitis is still quite limited (16).

The intraperitoneal antibiotics were preferred in our investigation into the peritonitis therapy. The intraperitoneally administered antibiotics have several advantages, including delivering a high concentration of antibiotics at the site of infection, antibiotics being absorbed into the systemic circulation and diffusing back into the peritoneum, allowing daily or less frequent administration, and eliminating the need for intravenous access, which would be required for weeks. As a result, the therapeutic response time was brief. Consequently, 60% of the patients responded to therapy in less than five days. The length of the antibiotic therapy necessary to treat the peritonitis episodes safely and successfully has also not been well investigated. Treatment should be continued for at least two weeks and prolonged to three weeks for more severe infections such as *S. aureus*, Gram-negative, and *enterococcal peritonitis*, according to the ISPD Peritonitis Guidelines (25).

Peritoneal membrane transport status after peritonitis treatment

Peritoneal transport status refers to the rate of peritoneal solute transport. It is determined by the peritoneal equilibration test (PET) and is an important basis for peritoneal dialysis prescription. In the pre-treatment group, there were seven high transporter patients (20.0%), eight high average transporters (22.9%), 15 low average transporters (42.9%), and five low transporters (14.3%). All patients' transport status and D4/P creatinine levels are greater in the post-treatment group than in the pre-treatment group. High

transporters were the most common in groups (54.3%), and no patients were found in the low transporters group.

There was no statistically significant link between transport status groups before and after peritonitis. According to several studies, there is a statistically significant link between peritoneal dysfunction and peritonitis. According to a study conducted by Jing Hu et al on peritonitis in PD duration, there was a statistically significant difference in peritonitis rate between low and high transport ($p < 0.001$; HR = 1.765) (6). The relationship between peritonitis treatment and the change in transport status was still a point for discussion. Higher peritoneal transport is often associated with less ultrafiltration and high albumin loss. Studies have shown that the peritoneal transport status is closely related to the mortality of PD patients. Still, few studies have explored the relationship between the peritoneal transport status and the treatment of peritonitis episodes.

Strengths and limitations

There were strengths and limitations to this study. This is one of the few studies that precisely examines the incidence of peritonitis and clinical outcomes in CKD patients on CAPD and the peritoneal membrane transport status before and after peritonitis treatment. Our study's strength was that the data included all CAPD patients at An Giang Center General Hospital, allowing easy management and long-term follow-up. The demographic information and results described are exclusive to our study population, and it also demonstrates the relationship between several patient factors and the incidence of peritonitis. Our findings also describe the peritoneal membrane following peritonitis therapy, allowing clinicians to better care for patients.

Our participants were all from a single center and therefore might be subjected to selection bias. Although this was a single-center trial, the doctors and nurses treated all patients according to standard operating procedures to prevent potential confounders from other locations. Being a cross-section study, there could be other confounding factors or covariates that were not considered in our analyses. Also, because of the cross-section study, data for illness groups could not be evaluated, and the cause-effect link between disease factors and peritonitis incidence remained unexplored. Furthermore, due to the small number of patients, the proportion of culture-negative events exceeded the ISPD's advised upper limit of 20%. Therefore, we were unable to further investigate the characteristics of organism-specific occurrences. Results following peritonitis therapy revealed improved transport status. The purpose of performing PET after peritonitis treatment is to select the next method of

PD filtration. The question is: is it necessary to change the filtration method after peritonitis? At last, make recommendations to patients after peritonitis in the next stage. In the future, we will conduct research about choosing the next RRT recommendations for patients after CAPD-related peritonitis.

The incidence of peritonitis in CAPD patients is linked to socioeconomic factors, caregiver status, education level, and antibiotics. However, this characteristic has yet to be described. Finally, the findings of this study in a Vietnamese community may not apply to people in other nations. Many crucial problems need to be answered by high-quality, multicenter, randomized, controlled studies. Further studies of Quality of life, the cost of treatment, and Quality of hospital or environment are needed to assess and prevent peritonitis-related in CAPD patients. Hence, despite its limitations, our findings might yield useful information. The findings will set the tone for future research and the formulation of clinical practice recommendations that will concentrate on the development and implementation of novel techniques and the improvement of current illness management.

Conclusion

Our study detected the rate of peritonitis was lower than that recommended by the International Society for Peritoneal Dialysis (ISPD) recommendations. Additionally, the treatment response rate is quite positive. This is a promising method for CKD patients who desire to employ a low-risk dialysis procedure. Otherwise, the percentage of cases with peritoneal peritonitis with a negative culture was substantially greater than the ISPD guidelines. As a result, physicians may find it challenging to select an initial antibiotic that matches the microbiological culture. More research is needed to fully understand the variables that influence the clinical outcomes of peritonitis and the remaining function of the peritoneal membrane.

Acknowledgement

The authors express their gratitude to all of the participants who made significant contributions to this study and all of the personnel at the An Giang center general hospital in Vietnam.

Conflict of interest

There is no conflict of interest declared by the authors.

Financial support

This research received no financial support from any funding agency, commercial, and/ or not-for-profit sectors.

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