Intraperitoneal Antibiotic Utilization among Continuous Ambulatory Peritoneal Dialysis (CAPD) Patients with Peritonitis at a Tertiary Hospital Setting in Malaysia

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Introduction: Patients receiving continuous ambulatory peritoneal dialysis (CAPD) are commonly associated with peritonitis. However, little is known about the utilization of antibiotics for the treatment of peritonitis in these patients. Objectives: This study aimed to evaluate the patterns of intraperitoneal (IP) antibiotic utilization for the treatment of peritonitis in CAPD patients. Materials and Methods: This is a retrospective study conducted at a tertiary hospital setting in Malaysia. Medical records of CAPD patients who were diagnosed with peritonitis and registered with National Kidney Registry from 2013 to 2018 were reviewed. Types of antibiotics used and its dose and duration were recorded and reported using the anatomical therapeutic chemical/defined daily dose (ATC/DDD) system. Results: A total of 105 peritonitis episodes were recorded from 72 patients. The most common first-line empirical antibiotic combinations used were ceftazidime/cefazolin (40%, n = 42), followed by cefepime/cefazolin (30.5%, n = 32) and ceftazidime/cloxacillin (25.7%, n = 27). The definitive therapy for culture-proven CAPD-related peritonitis (CAPD-P) showed that vancomycin was the most frequently prescribed antibiotic (31.7%, n = 26/82), followed by amikacin (14.6%, n = 12/82), meropenem (11%, n = 9/82) and ampicillin (11%, n = 9/82). Ciprofloxacin was among the least prescribed definitive antibiotics for CAPD-P (2.4%, n = 2/82) but the DDD/100 patient-days estimates showed that it had the highest therapeutic intensity. Conclusion: There are various IP antibiotics used for CAPD-P and the most common empirical therapy was the combination of ceftazidime and cefazolin while vancomycin is predominantly used for definitive therapy. Future studies to evaluate the clinical outcomes of the antibiotic use should be conducted to have a better insight on the efficacy of the peritonitis treatment.

Keywords: Antibiotics, continuous ambulatory peritoneal dialysis, intraperitoneal, peritonitis, utilization

INTRODUCTION

Continuous ambulatory peritoneal dialysis (CAPD) is one of the treatments for patients with end-stage renal failure, whose kidney function deteriorates or suffered permanent damage. However, this modality is commonly associated with peritonitis, which is a...
significant cause of morbidity and mortality in these patients.\textsuperscript{[1]}

Early empirical antibiotic therapy for the treatment of peritonitis is recommended, with the choice of agents guided by local resistance patterns.\textsuperscript{[2]} Despite the increasing concern surrounding this issue, little is known about the utilization of intraperitoneal (IP) antibiotic for the treatment of peritonitis in patients receiving CAPD. This is a topic of pivotal importance in managing the peritonitis infection as the appropriate type of IP antibiotics administered may lengthen the use of CAPD modality, which has been proven to produce better quality of life,\textsuperscript{[3]} less economic burden,\textsuperscript{[4]} and better clinical outcomes compared to another complicated modality for ERSF, which is hemodialysis.\textsuperscript{[5]}

As routine use of specific antibiotic agents can drive resistance due to its inherent selective pressure,\textsuperscript{[6]} therefore, regular assessment of IP antibiotic utilization is essential for early detection on center-specific bacterial resistance and antibiotic susceptibility. As such, this study aimed to describe the patterns of IP antibiotic utilization for the treatment of peritonitis in CAPD patients.

Materials and Methods

Study design

This is a retrospective, observational study of IP antibiotic utilization conducted at the CAPD Unit, Hospital Tengku Ampuan Afzan (HTAA), Kuantan, Pahang, a tertiary hospital setting in Malaysia. This study was conducted between February 2018 and June 2019.

All CAPD patients who were diagnosed with peritonitis and had their cases registered with the National Kidney Registry between 2013 and 2018 were included. Those patients who were transferred to other institutions were excluded. Those included in the study had their medical records reviewed for demographic, clinical, laboratory, and medication data. The following records on CAPD-related peritonitis (CAPD-P) events were extracted: the results of peritoneal dialysis effluent (PDE) microbiological culture and sensitivity (C&S) report prior to starting IP antibiotics, the initial IP empirical antibiotic used and its dose, titration of IP antibiotic treatment following C&S results, and duration of IP antibiotics used.

Antibiotic classification and defined daily dose

The antibiotics were classified using the Anatomical Therapeutic Chemical (ATC) classification system. A reference defined daily dose (DDD) was obtained for each antibiotic from the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology 2019.\textsuperscript{[7]} The IP antibiotic utilization measures were reported in DDD/100 patient-days and the mean dose per patient per day.

The DDD/100 patient-days is a commonly used measure for the comparison of antibiotic consumption\textsuperscript{[6]} and provides an estimate of therapeutic intensity for in-patients.\textsuperscript{[9]} The DDD/100 patient-days was calculated using the following formula:\textsuperscript{[9]}

$$\text{DDD/100 patient-days} = \frac{\text{The number of DDD of a given antibiotic} \times 100}{\text{Duration of treatment (days) × Number of beds × Bed-occupancy rate}}$$

The mean dose per patient per day provided specific information on the patient-level dose used for the treatment of peritonitis in this cohort. It was calculated by dividing the total dose of prescribed antibiotic by the total number of days on therapy for each patient during the hospital stay.

Descriptive statistics were used to report the outcome measures. Categorical variables were presented as frequencies and percentages. Analyses of the findings were stratified based on C&S results; that is, the culture-negative peritonitis (CNP) and the culture-positive peritonitis (CPP) groups. The overall IP antibiotic consumption was reported as an aggregated data. Chi-squared test of independence was used to compare proportions (categorical variables) between the two groups. Alternatively, Fisher’s exact test was used when one of the cells in its contingency table has an expected frequency of less than 5. All data analyses were performed using Microsoft Excel and SPSS Statistics for Windows, version 23 (IBM Corporation, Armonk, New York).

This study was registered with the National Medical Research Registry (NMRR-16-2755-33413) and has been granted approval by the Malaysian Research Ethical Committee (MREC), Ministry of Health Malaysia. The data on patient information were made confidential and only aggregate results were reported.
RESULTS

Patient demographics
A total of 72 patients’ medical records were reviewed, which presented 105 peritonitis episodes between 2013 and 2018. The mean age of the patients was 50 ± 14.1 years. The proportion of genders was nearly equal and the majority of them were Malay (88.9%, n = 64/72).

Type of IP antibiotics for initial empirical treatment
The relationship between the initial empiric antibiotic treatment strategy and the types of antibiotics given was statistically significant in all peritonitis cases, based on a chi-squared test of independence (P = 0.001). This was similarly seen when stratified into the CNP/CPP cases [Table 1]. The most common first-line empirical antibiotic combinations used were ceftazidime/cefoxitin, ceftazidime/cefazolin, cefepime/cefoxitin, cefepime/cefazolin, cefepime/moxifloxacin, and cefepime/imipenem.

Table 1: Comparison of intraperitoneal antibiotic types and treatment strategy and microbiological findings in culture-negative and culture-positive peritonitis cases (n = 103)

| Peritonitis group variable | CNP (n = 29) | CPP (n = 74) | P value | Total patients |
|----------------------------|--------------|--------------|---------|----------------|
| Number of patients         | 29 28.2      | 74 71.8      |         | 103 100.0      |
| Initial empiric treatment strategy |               |              |         |                |
| Single IP antibiotics      | - -          | 2 2.7        | 0.514a  | 2 1.9          |
| Combination IP antibiotics | 29 100.0     | 72 97.3      |         | 101 98.1       |
| Single IP antibiotics      |              |              |         |                |
| Cefepime                   | - 1.4        | 1 1.4        | 0.537a  | 1 1.0          |
| Amikacin                   |              |              |         |                |
| Dual IP antibiotics        |              |              |         |                |
| Ceftazidime + cefoxitin    | 9 31.0       | 18 24.3      |         | 27 25.7        |
| Ceftazidime + cefazolin    | 13 44.8      | 28 37.8      |         | 42 40.0        |
| Cefepime + cefazolin       | 6 20.7       | 25 33.8      |         | 32 30.5        |
| Cefepime + meropenem       | 1 3.4        | - -          |         | 1 1.0          |
| Ceftazidime + gentamicin   | - 1.4        |              |         | 1 1.0          |
| Streamlining of antibiotics after C&S results were received |              |              |         |                |
| With a different antibiotic | 13 44.8     | 58 78.4      | 0.084b  | 71 68.9        |
| With the same initial empirics | 16 55.2    | 16 21.6      |         | 32 31.1        |
| IP antibiotics used to substitute initial empirical antibiotics |              |              |         |                |
| Vancomycin                 | 10 40.0      | 26 31.7      | 0.489b  | 36 33.6        |
| Meropenem                  | 7 28.0       | 9 11.0       |         | 16 15.0        |
| Amikacin                   | - -          | 12 14.6      |         | 12 11.2        |
| Piperacillin/tazobactam    | 3 12.0       | - -          |         | 3 2.8          |
| Others                     | 5 20.0       | 35 42.7      |         | 40 37.4        |
| Causative microorganism    |              |              |         |                |
| Gram-positive bacteria      |              |              |         |                |
| MRCoNS                     | - -          | 13 15.3      | <0.001a | 13 15.3        |
| Streptococcus sp.          |              | 11 12.9      |         | 11 12.9        |
| Enterococcus sp.           |              | 10 11.8      |         | 10 11.8        |
| Other Gram-positive bacteria|             | 19 22.4      |         | 19 22.4        |
| Gram-negative bacteria      |              |              |         |                |
| Klebsiella pneumoniae      | 7 8.2        |              |         | 7 8.2          |
| Acinetobacter baumannii    | 4 4.7        |              |         | 4 4.7          |
| Escherichia coli           | 4 4.7        |              |         | 4 4.7          |
| Other Gram-negative bacilli| 13 15.3      |              |         | 13 15.3        |
| Others                     | - -          | 2 2.4        |         | 2 2.4          |
| Candida sp.                | 2 2.4        |              |         | 2 2.4          |
| Trichosporon asahii        | 1 1.2        |              |         | 1 1.2          |
| Polymicrobial              | 1 1.2        |              |         | 1 1.2          |

CNP = culture-negative peritonitis, CPP = culture-positive peritonitis, IP = intraperitoneal, MRCoNS = methicillin-resistant coagulase-negative Staphylococcus

*aFisher’s exact test

*bPearson’s chi-squared test of independence
cefazolin (40%, \( n = 42/105 \)), cefepime/cefazolin (30.5%, \( n = 32/105 \)), and ceftazidime/cloxacillin (25.7%, \( n = 27/105 \)) in overall cases. The same trend was demonstrated in the CNP/CPP cases.

**Empirical IP antibiotics used for culture-negative peritonitis**

Data on PDE microbiological C&S results were available for 103 cases [Table 1]. There was a positive culture in 71.8% of the cases, whereas the remaining cases showed negative culture results. In total, 55.2% of CNP cases were sustained with initial empirical antibiotic treatment, whereas 44.8% of CNP cases had their initial empirical antibiotics substituted after C&S results were reported [Table 1]. Vancomycin (40%) and meropenem (28%) were highly used as empirical antibiotic substitutes.

**Definitive IP antibiotics used for CAPD-related peritonitis**

Table 1 indicates that 21.6% of CPP cases’ initial empirical antibiotic treatments were retained, whereas the other 78.4% of cases had their initial empirical antibiotic streamlined based on the C&S report. The most prescribed antibiotics used for CPP was vancomycin (31.7%), because the predominant causative pathogens for CAPD-P were Gram-positive bacteria (62.4%, \( P < 0.001 \)), mainly methicillin-resistant coagulase-negative *Staphylococcus* (MRCoNS) (15.3%), *Streptococcus* sp. (12.9%), and *Enterococcus* sp. (11.8%). Meanwhile, amikacin (14.6%) and meropenem (11%) were prescribed for susceptible and resistant Gram-negative bacteria isolates, respectively.

**Antibiotic utilization**

Table 2 revealed that cloxacillin and ciprofloxacin exerted the highest antibiotic utilization (0.00076 DDD/100 patient-days). High consumption of cloxacillin was reasonable because it was used as an empirical and definitive treatment. Our findings were somewhat surprising for ciprofloxacin because contrary to cloxacillin, ciprofloxacin was only prescribed in two cases of CAPD-P; therefore, it should result in a low utilization. However, ciprofloxacin produced a high number of DDD within a short treatment duration, which led to a surge in ciprofloxacin DDD/100 patient-days. In terms of mean dose per patient per day, all antibiotics were prescribed within the recommended doses.[2] IP vancomycin, which was administered intermittently, was prescribed at the mean dose of 650 mg/day.

**Discussion**

The choice of initial antimicrobial treatment (prior to the results of microbiological tests) is a crucial determinant for a favorable clinical outcome.[2,6,10,11] Our study demonstrated that the top three common empirical combinations used in this center (ceftazidime/cefazolin, cefepime/cefazolin, and ceftazidime/cloxacillin) which covers both Gram-positive and Gram-negative bacteria, adhered to the recommendation by the ISPD guideline.[2,11] Our prominent initial empiric combination (ceftazidime/cefazolin) was also reported to be the initial empirical antibiotic of choice in another center in Malaysia.[12] Both achieved a resolution rate of more than 70%. On the contrary, studies in other countries had reported the use of an aminoglycoside with vancomycin or cefazolin as their first-line initial empirical antibiotics.[13-17] The combination of ceftazidime/cefazolin was also used, but to a lesser extent in Australia, New Zealand, and Brazil.[13-15] The different choice of antibiotics in an

**Table 2: Intraperitoneal antibiotic utilization for continuous ambulatory peritoneal dialysis-related peritonitis between 2013 and 2018**

| Antibiotics            | ATC code | DDD (g) | Number of DDD | Number of days on therapy | DDD/100 patient-days (\( \times 10^{-5} \)) | Mean dose per day (g) |
|------------------------|----------|---------|---------------|----------------------------|---------------------------------------------|-----------------------|
| Cloxacillin            | J01CF02  | 2       | 119           | 238                        | 76                                          | 1                     |
| Ciprofloxacin          | J01MA02  | 0.8     | 17.5          | 35                         | 76                                          | 0.4                   |
| Piperacillin/tazobactam | J01CR05  | 14      | 32.46         | 92                         | 53.6                                        | 4.9                   |
| Cefazolin              | J01DB04  | 3       | 208.33        | 625                        | 50.7                                        | 1                     |
| Meropenem              | J01DH02  | 3       | 55.67         | 167                        | 50.7                                        | 1                     |
| Vancomycin             | J01XA01  | 2       | 59.5          | 183                        | 49.4                                        | 0.650                 |
| Cefepime               | J01DE01  | 4       | 78.25         | 313                        | 38                                          | 1                     |
| Ceftazidime            | J01DD02  | 4       | 145.5         | 582                        | 38                                          | 1                     |
| Gentamicin             | J01GB03  | 0.24    | 10.07         | 58                         | 26.4                                        | 0.04                  |
| Ampicillin             | J01CA01  | 6       | 21.83         | 131                        | 25.3                                        | 1                     |
| Amikacin               | J01GB06  | 1       | 13.42         | 133                        | 15.7                                        | 0.1                   |
| Benzylpenicillin       | J01CE01  | 3.6     | 1.52          | 44                         | 5.3                                         | 0.1                   |

DDD = defined daily dose
individual center is determined by the prevalence and types of bacteria isolated, hence this explains the use of different initial empirical antibiotic in Malaysia compared to other countries.

In our setting, CNP accounted for 28.2% of the overall peritonitis cases, which was similarly reported in another center in Malaysia (28.2%) and in the United Kingdom (>20%). Whereas the other centers reported a lower incidence of CNP rates (<15%). High CNP incidence in our center may be attributed to recent antibiotic usage and technical problems of culturing PDE specimen. A close liaison with the microbiology laboratory should be instigated to review and improve sampling and culture methods of PDE, as recommended by Szeto.

From the microbiological aspect, our study found that Gram-positive bacteria, namely CoNS, were the prime causative pathogen, as similarly reported by previously published studies. CoNS are considered the most common etiological pathogens for CAPD-P, based on the close agreement in multiple centers. Possible sources of infection include touch contamination and migration of skin organisms. The finding on prominent Gram-positive bacteria isolates is a matter worth scrutinizing because it has great propensity to relapse and leads to high peritoneal dialysis failure.

In terms of definitive treatment of a culture-proven peritonitis, our study revealed that vancomycin was the most frequently used, followed by amikacin and meropenem. This observation is rational as vancomycin is the antibiotic of choice for methicillin-resistant Staphylococcus aureus, MRCoNS, and a broad-spectrum of Gram-positive bacteria. Amikacin was mainly used for the treatment of susceptible broad-spectrum Gram-negative bacilli, as was in other studies, whereas meropenem was used to combat multiresistant Gram-negative bacterial strains, as well as the highly resistant extended-spectrum β-lactamase-producing Enterobacteriaceae.

In summary, our center had used antibiotics accordingly for definitive treatment of peritonitis, based on the prescribing adherence to the ISPD guideline and fairly high resolution was achieved. The choice of antibiotics is non-debatable as the choice of antibiotic use should be based on the center’s causative bacteria susceptibility.

In terms of the antibiotic utilization, ciprofloxacin, cloxacillin, and piperacillin/tazobactam were the highest prescribed, based on its resultant DDD/100 patient-days. This showed that antibiotic with high usage frequency (used for both empirical and definitive treatment) does not necessarily result in high DDD/100 patient-days because this indicator relies on both the number of DDD and duration of therapy. As such, those with a low number of DDD may present a high therapeutic intensity when the duration of therapy is short, as seen by the high DDD/100 patient-days of ciprofloxacin compared to other antibiotics.

In view of dosing, all IP antibiotics were prescribed according to the recommended daily dose outlined in the ISPD 2016, except for vancomycin. Vancomycin was administered using an intermittent dose of 1–2 g every 5–7 days in our center. Hypothetically assuming the treatment is for 5 days, the indicated vancomycin dose is 200–400 mg/day. However, vancomycin dose prescribed in our center (650 mg/patient-day) was higher than the hypothetical dose. Increased vancomycin usage has been purported to lead to bacterial resistance via selective pressure. However, we can neither assume nor conclude that the use of vancomycin in our center has affected the bacterial resistance pattern because vancomycin susceptibility test was not performed.

In summary, IP antibiotic utilization evaluation is scarce because studies on drug evaluation are focused in other critical clinical areas, such as the intensive care units and the surgical departments. To the best of our knowledge, this is the first reported IP antibiotic utilization in this country; therefore, the data presented here can be used for benchmarking to detect injudicious antibiotic consumption in this clinical area.

This study is limited in view of its retrospective design; therefore, a thoroughgoing patient-level drug utilization assessment cannot be accomplished. The reference DDD was derived from DDD for parenteral administration; hence, the DDD/100 patient-days values were ultra-small, which makes interpretation a challenge, yet possible. Another alternative approach using days of therapy per 1000 patient-days (DOT/1000 patient-days) has been suggested. Therefore, using DDD/100 patient-days methodology to assess antibiotic utilization in this cohort may be arguable. Still, this does not undermine the results of this study for inter-center IP antibiotic utilization comparison if the same reference DDD is applied.

**Conclusion**

The most common initial empirical IP antibiotic used in this study was ceftazidime/cefarolin, whereas vancomycin was mainly used for CNP and definitive treatment for CAPD-P at 650 mg/day. Cloxacillin and ciprofloxacin wielded the highest DDD/100 patient-days.
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Conflicts of interest
There are no conflicts of interest.

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