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CKJ REVIEW

# Stability and compatibility of antibiotics in peritoneal dialysis solutions

Simon Wai Yin So[1], Lu Chen[1], Alex Yuk Hei Woo[1], Derek Man Him Ng[2], Jennifer Ka Wah Wong[2], Kai Ming Chow[3], Naomi Runnegar[4], David W. Johnson[4] and Philip Kam-Tao Li[3]

[1]Pharmacy Department, Alice Ho Miu Ling Nethersole Hospital, Tai Po, Hong Kong, [2]Pharmacy Department, Prince of Wales Hospital, Shatin, Hong Kong, [3]Department of Medicine and Therapeutics, Carol and Richard Yu Peritoneal Dialysis Research Centre, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong and [4]University of Queensland at Princess Alexandra Hospital, Brisbane, QLD, Australia

Correspondence to: Philip Kam-Tao Li; E-mail: philipli@cuhk.edu.hk

## ABSTRACT

Intraperitoneal (IP) administration of antibiotics is a preferred treatment of peritoneal dialysis (PD)-related peritonitis. Given the treatment duration of up to 2–3 weeks, it is important that robust data on antibiotic stability and compatibility are available to achieve notable treatment success. This article provides a comprehensive review of recent stability and compatibility studies pertaining to a wide range of antibiotics admixed in various PD solutions.

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## GRAPHICAL ABSTRACT

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# Stability and compatibility of antibiotics in peritoneal dialysis solutions

**Comprehensive review of stability and compatibility studies relating to intraperitoneal (IP) antibiotic administration in different peritoneal dialysis (PD) solutions under various storage conditions**

**Methods**

Literature review
2016–2021

**Use of IP antibiotics in different solutions:**
- Dextrose
- Icodextrin
- pH neutral

**Results**

**Stability of antibiotics in various PD solutions**

| | PD solution | Room temperature | Refrigerated |
|---|---|---|---|
| Gentamicin | Icodextrin | 14 days | 14 days |
| Cefazolin | Icodextrin | 7 days | 14 days |
| Ceftazidime | Icodextrin | 2 days | 14 days |
| Cefepime | pH-neutral (bicarbonate component) | 4 days | 7 days |
| Vancomycin | Icodextrin | 14 days | 14 days |

**Compatibility of antibiotics for IP administration**

| | Gentamicin | Ceftazidime | Cefazolin | Vancomycin |
|---|---|---|---|---|
| Gentamicin | | N/A | ✓ | ✓ |
| Ceftazidime | N/A | | ✓ | ✓ |
| Cefazolin | ✓ | ✓ | | N/A |
| Vancomycin | ✓ | ✓ | N/A | |

The stability data of other antibiotics, including amoxicillin, ampicillin, piperacillin/tazobactam, meropenem, imipenem and ciprofloxacin, were also reviewed.

**Conclusion:** The review provides an extended scope of antibiotic stability data for common antibiotics in PD solutions. Future research is required regarding the impact of administration of antibiotics in different compartments of dual-chamber bags, the stability data of antifungal agents and narrow-spectrum antibiotics in PD solutions.

So, SWY., et al.
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philipli@cuhk.edu.hk
@CKJsocial

**Keywords:** antibiotics, compatibility, dialysis, intraperitoneal, peritoneal, peritonitis, stability

In the treatment of peritoneal dialysis (PD)-related peritonitis, the International Society for Peritoneal Dialysis (ISPD) guidelines/recommendations: 2016 update recommends that intraperitoneal (IP) administration of antibiotics is preferred unless the patient has features of systemic sepsis [1]. IP antibiotic therapy ensures maximal antibiotic concentrations in the peritoneal cavity, which is the principal site of infection. In clinical practice, antibiotics are added to the PD solution and allowed to dwell in the peritoneal cavity for at least 6 hours while performing continuous ambulatory PD (CAPD). IP antibiotic therapy enables the continuation and completion of peritonitis treatment on an outpatient basis, which facilitates earlier hospital discharge with benefits to both the patient and the healthcare system. For the treatment duration of PD-related peritonitis of up to 2–3 weeks, patients are often required to complete the IP antibiotic therapy at home. Some patients are trained to reconstitute antibiotic vials and add the antibiotics to their PD bags, while others rely on community nurses to premix the antibiotics with all PD solutions on a daily basis. Without robust stability and compatibility data that would permit preparation and storage of antibiotic-loaded bags days in advance, patients may require frequent home nursing visits for the administration of antibiotics into PD solutions.

Although the stability and compatibility of some antibiotics added to PD solutions are available in the ISPD guidelines 2016 update, there are limited data regarding the stability and compatibility of commonly used antibiotics in different formulated PD solutions. Antibiotic activity in a variety of PD solutions and storage conditions may vary over a period of time. Thus data on antibiotic stability and compatibility over time are a prerequisite for treatment success. Given the paucity of stability and compatibility data of antibiotics in PD solutions, this article aims to comprehensively review available stability and compatibility studies relating to IP antibiotic administration in different PD solutions under various storage conditions, as recommended by ISPD guidelines from 2016 to 2021. In addition, the present review of all published stability data on antibiotics in various PD solutions is summarized in Table 1.

## AMINOGLYCOSIDES

Aminoglycoside antibiotics have coverage for Gram-negative bacteria. They are suggested by the ISPD guidelines 2016 update to be administered intermittently via the IP route for better safety and efficacy [1].

Table 1. Stability of antibiotics in PD solutions

| Drug | Type of treatment[a] | Concentration (mg/L) | PD solution | Drug stability in hours (h) or days (d) | | | | | | Assay | Remarks | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aminoglycosides | | | | | | | | | | | | |
| Gentamicin | Intemittent | 20 | Extraneal | >14 d | @4°C | >14 d | @25°C | >14 d | @37°C | LCMS/MS | | [2] |
| Cephalosporins | | | | | | | | | | | | |
| Cefazolin | LD | 500 | Extraneal | >14 d | @4°C | 7 d | @25°C | 1 d | @37°C | HPLC | | [2] |
| | MD | 125 | Physioneal 40 1.36%, mixed | | | | | >1 d | @37°C | HPLC | | [3] |
| | | | Physioneal 40 3.86%, mixed | | | | | >1 d | @37°C | HPLC | | |
| | | | Extraneal | | | | | >12 h | @37°C | HPLC | First stored at 22°C ± 2°C for 12 h, then 37°C for 12 h | [5] |
| Ceftazidime | LD | 500 | Dianeal 1.5% | | | | | 2 h | @37°C | HPLC | Stability data provided only | |
| | | | Dianeal 2.5% | | | | | 2 h | @37°C | HPLC | included those with generation | |
| | | | Dianeal 4.25% | | | | | 2 h | @37°C | HPLC | of pyridine level <2 mg/d, | |
| | | | Physioneal 1.36%, mixed | | | | | 2 h | @37°C | HPLC | assuming 1 bag/d | |
| | | | Physioneal 2.27%, mixed | | | | | 2 h | @37°C | HPLC | | |
| | | | Physioneal 3.86%, mixed | | | | | N/A | @37°C | HPLC | | |
| | | | Extraneal | >14 d | @4°C | 2 d | @25°C | 6 h | @37°C | HPLC | | [2] |
| | MD | 125 | Dianeal 1.5% | | | | | 6 h | @37°C | HPLC | Stability data provided only | [5] |
| | | | Dianeal 2.5% | | | | | 6 h | @37°C | HPLC | included those with generation | |
| | | | Dianeal 4.25% | | | | | 6 h | @37°C | HPLC | of pyridine level <2 mg/d, | |
| | | | Physioneal 1.36%, mixed | | | | | N/A | @37°C | HPLC | assuming 4 bags/d | |
| | | | Physioneal 2.27%, mixed | | | | | N/A | @37°C | HPLC | | |
| | | | Physioneal 3.86%, mixed | | | | | N/A | @37°C | HPLC | | |
| | | | Physioneal 40 1.36%, mixed | | | | | 12.8 h | @37°C | HPLC | | [3] |
| | | | Physioneal 40 3.86%, mixed | | | | | 6 h | @37°C | HPLC | | |
| | | | Extraneal | | | | | >12 h | @37°C | HPLC | First stored at 22°C ± 2°C for 12 h, then 37°C for 12 h | |
| Ceftazidime + Heparin | MD | 125 mg/L + 500 IU/L | Dianeal 2.5% | >5 d | @4°C | >6 h | @25°C | >12 h | @37°C | HPLC | First stored at 4°C for 5 d, then 25°C for 6 h, then 37°C for 12 h | [7] |
| | | | Dianeal 4.25% | >5 d | @4°C | >6 h | @25°C | >12 h | @37°C | HPLC | | |
| | | | Extraneal | >5 d | @4°C | >6 h | @25°C | >12 h | @37°C | HPLC | | |

Table 1. Continued

| Drug | Type of treatment[a] | Concentration (mg/L) | PD solution | Drug stability in hours (h) or days (d) | | | | | | Assay | Remarks | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 125 mg/L + 500 IU/L | Balance 2.3%, mixed | | | | | >12 h | @37°C | HPLC | | |
| | | 250 mg/L + 1000 IU/L | Bicarbonate compartment 1 L of Balance 2.3% 2 L, not mixed | >5 d | @4°C | >6 h | @25°C | | | HPLC | | |
| Cefepime | MD | 250 | Bicarbonate compartment 1.25 L of Balance 1.5% 2.5 L, not mixed | 7 d | @4°C | 4 d | @25°C | | | HPLC | | [10] |
| | | 125 | Balance 1.5%, mixed | | | | | 12 h | @37°C | HPLC | | |
| | | | Physioneal 40 1.36%, mixed | | | | | 10 h | @37°C | HPLC | | [3] |
| | | | Physioneal 40 3.86%, mixed | | | | | 5 h | @37°C | HPLC | | |
| | | | Extraneal | | | | | >12 h | @37°C | HPLC | | |
| Penicillins | | | | | | | | | | | | |
| Ampicillin | MD | 125 | Dianeal PD-4[b] | 14 d | @4°C | 3 d | @25°C | 1 d | @37°C | HPLC | | [11] |
| | | | Balance[b,c] | 14 d | @4°C | 2 d | @25°C | 12 h | @37°C | HPLC | | |
| | | | Extraneal | 14 d | @4°C | 2 d | @25°C | 1 d | @37°C | HPLC | | |
| Amoxicillin | | 125 | Dianeal PD-4[b] | 14 d | @4°C | 3 d | @25°C | 1 d | @37°C | HPLC | | |
| | | | Balance[b,c] | 14 d | @4°C | 2 d | @25°C | 12 h | @37°C | HPLC | | |
| | | | Extraneal | 14 d | @4°C | 2 d | @25°C | 1 d | @37°C | HPLC | | |
| Piperacillin/ tazobactam + Heparin | MD | 500/62.5 mg/L + 500 IU/L | Dianeal 1.5% | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | First stored at 4°C for 7 d, then 25°C for 3 h, then 37°C for 10 h | [12] |
| | | | Dianeal 2.5% | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |
| | | | Dianeal 4.25% | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |
| | | 1000/125 mg/L + 1000 IU/L | Bicarbonate compartment 1 L of Balance 2.3% 2 L, not mixed | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |
| | | 1380/172.5 mg/L + 1400 IU/L | Dextrose compartment 0.725 L of Physioneal 1.36% 2 L, not mixed | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |
| | | | Dextrose compartment 0.725 L of Physioneal 2.27% 2 L, not mixed | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |

**Table 1. Continued**

| Drug | Type of treatment[a] | Concentration (mg/L) | PD solution | Drug stability in hours (h) or days (d) | | | | | | Assay | Remarks | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Dextrose compartment 0.725 L of Physioneal 3.86% 2 L, not mixed | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |
| | | 500/62.5 mg/L + 500 IU/L | Extraneal | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |
| Imipenem | | 200 | Physioneal 40 1.36%, mixed | | | | | 2 h | @37°C | HPLC | | [3] |
| | | | Physioneal 40 3.86%, mixed | | | | | 2 h | @37°C | HPLC | | |
| | | | Extraneal | | | | | N/A | @37°C | HPLC | First stored at 22°C ± 2°C for 12 h, then 37°C for 12 h | |
| | MD | 50 | Physioneal 40 1.36%, mixed | | | | | 2 h | @37°C | HPLC | | [3] |
| | | | Physioneal 40 3.86%, mixed | | | | | 2 h | @37°C | HPLC | | |
| | | | Extraneal | | | | | N/A | @37°C | HPLC | First stored at 22°C ± 2°C for 12 h, then 37°C for 12 h | |
| Meropenem + Heparin | Intermittent | 500 mg/L + 500 IU/L | Dianeal 1.5% | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | First stored at 4°C for 7 d, then 25°C for 3 h, then 37°C for 10 h | [12] |
| | | | Dianeal 2.5% | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |
| | | | Dianeal 4.25% | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |
| | | 1000 mg/L + 1000 IU/L | Bicarbonate compartment 1 L of Balance 2.3% 2 L, not mixed | >1.5 d | @4°C | >3 h | @25°C | N/A | @37°C | HPLC | | |
| | | 500 mg/L + 500 IU/L | Extraneal | >7 d | @4°C | >3 h | @25°C | >10 h | @37°C | HPLC | | |
| Others | | | | | | | | | | | | |
| Ciprofloxacin | MD | 50 | Physioneal 40 1.36%, mixed | 14 d | @6°C | N/A[d] | @25°C | >1 d | @37°C | HPLC | | [13] |
| | | | Physioneal 40 2.27%, mixed | 14 d | @6°C | 2 d | @25°C | >1 d | @37°C | HPLC | | |
| | | | Physioneal 40 3.86%, mixed | 14 d | @6°C | 2 d | @25°C | >1 d | @37°C | HPLC | | |
| | | | Extraneal | 14 d | @6°C | 7 d | @25°C | >1 d | @37°C | HPLC | | |
| Vancomycin | LD/intermittent | 1000 | Extraneal | >14 d | @4°C | >14 d | @25°C | 4 d | @37°C | HPLC | | [2] |

HPLC, high-performance liquid chromatography; LCMS, liquid chromatography mass spectrometry; N/A, not applicable.

[a] Treatment dosage per recommendations from the ISPD guidelines 2016 update. Intermittent dosage assumes the patient's body weight is between 60 and 70 kg.

[b] Dextrose concentration was not provided.

[c] Methodology on the sequence of antibiotic injection in compartments and mixing of compartment solutions was not provided.

[d] Stability was considered inconclusive, presumably due to drug adsorption.

### Gentamicin

Gentamicin is an aminoglycoside commonly used in combination with cefazolin or vancomycin for empirical treatment of PD-related peritonitis prior to identification of the responsible organism from PD effluent cultures. It is also used for specific treatment of PD-related peritonitis known to be caused by *Pseudomonas* species or severe peritonitis caused by *Enterococcus* species. Aminoglycosides are well known to be incompatible with penicillins [1]. Ranganathan *et al.* [2] investigated the stability of gentamicin and in combination with vancomycin and cefazolin in icodextrin-based PD solution (Extraneal, Baxter Healthcare, Deerfield, IL, USA). Gentamicin 20 mg/L (intermittent dose) alone or admixed with vancomycin 1000 mg/L (intermittent dose) or with cefazolin 500 mg/L [loading dose (LD)/intermittent dose] retained >90% of their respective initial concentrations when stored at 37°C for 14 days, 4 days and 1 day, respectively; and at 4°C or 25°C for 14 days for all studied antibiotic regimens [1, 2].

## CEPHALOSPORINS

Cephalosporins, such as cefazolin and ceftazidime, are used intraperitoneally for first-line empirical treatment of PD-related peritonitis prior to identification of the responsible organism from PD effluent cultures.

### Cefazolin

Cefazolin is commonly used for Gram-positive empirical coverage and known pathogens such as coagulase-negative staphylococci. Deslandes *et al.* [3] showed that cefazolin MD retained 99 and 92% of its initial concentration in pH-neutral PD solution (Physioneal, Baxter Healthcare) 1.36 and 3.86%, respectively, at 37°C after 1 day.

Cefazolin is commonly used with gentamicin or ceftazidime for empirical treatment. A study by Ranganathan *et al.* [2] investigated the stability of these antibiotic combinations. Cefazolin 500 mg/L (LD/intermittent dose) alone or admixed with gentamicin 20 mg/L (intermittent dose) or admixed with ceftazidime 500 mg/L (LD/intermittent dose) retained >90% of their respective initial concentrations when stored at 4°C for 14 days in Extraneal for the studied regimens. At 25°C, stability was reduced to only 7 days for cefazolin alone, 4 days when combined with gentamicin and 2 days when combined with ceftazidime. At 37°C, cefazolin could only be stored for 1 day, either alone or in combination with any of the two other antibiotics [2].

### Ceftazidime

Ceftazidime is commonly used for Gram-negative empirical coverage and is also used for directed treatment of PD-related peritonitis known to be caused by *Pseudomonas* species. Previous studies demonstrated the stability of ceftazidime in dextrose-based PD solutions but the dose (100 mg/L) was different from those suggested by the ISPD guidelines 2016 update [1, 4]. Nguyen *et al* [5]. compared the stability of ceftazidime at concentrations recommended in the ISPD guidelines 2016 update in dextrose-based (Dianeal, Baxter Healthcare) and pH-neutral (Physioneal) PD solutions at 37°C. Ceftazidime 500 mg/L (LD/intermittent dose) and 125 mg/L [maintenance dose (MD)] retained >90% of their initial concentrations after 10 hours in Dianeal 1.5, 2.5 and 4.25% bags. Ceftazidime LD/intermittent dose was stable for 8, 6 and 2 hours in Physioneal 1.36, 2.27 and 3.86%, respectively. Ceftazidime MD was stable for 10 hours, 8 hours and 6 hours in Physioneal 1.36, 2.27 and 3.86%, respectively. The study showed that ceftazidime degraded faster at higher concentrations of ceftazidime and at higher concentrations of dextrose in both Dianeal and Physioneal. Ceftazidime was more stable in Dianeal than in Physioneal [1, 5, 6].

Deslandes *et al.* [3] also showed reduced stability with an increased concentration of dextrose in Physioneal. Ceftazidime MD was reduced from 100 to 90% at 37°C after 12.8 and 6 hours, respectively, in 1.36 and 3.86% Physioneal 40. Kandel *et al.* [7] carried out a study with the same ceftazidime MD admixed with heparin 500 IU/L at 37°C in a different pH-neutral PD solution (Balance, Fresenius Medical Care, Bad Homburg, Germany). Ceftazidime MD was reduced from 96.4 to 94.2% in 12 hours in Balance 2.3%. Although Balance and Physioneal 40 are both pH-neutral PD solutions, the injection port for admixing antibiotic connects to different compartments (the bicarbonate compartment for Balance or the glucose compartment for Physioneal). The effect of this on the degradation rate of ceftazidime will require further investigation.

Ranganathan *et al.* [2] looked into the stability of ceftazidime in icodextrin-based PD solution (Extraneal). It was demonstrated that ceftazidime LD/intermittent doses were stable at 4°C for 14 days, at 25°C for 2 days and 37°C for 6 hours in Extraneal. Ceftazidime MD and vancomycin 30 mg/L (MD) admixed in Extraneal were stable for 12 hours at 22 ± 2°C, followed by 12 hours at 37°C [3].

Ceftazidime 125 mg/L (MD) and heparin 500 IU/L both retained >95% of their initial concentrations at 4°C for 5 days in Dianeal 2.5 and 4.25%, Extraneal and the bicarbonate compartment of 2 L Balance (ceftazidime 250 mg and heparin 1000 IU in the 1 L bicarbonate compartment). Ceftazidime and heparin retained 95% of their initial concentrations after they were placed at 25°C for another 6 hours for all studied regimens [7].

Apart from the loss of ceftazidime over time in PD solutions, the other important consideration is hydrolytic degradation of ceftazidime into the metabolite, pyridine, which can have toxic effects on the brain, liver and kidney [8]. Pyridine production is accelerated at higher temperatures, which can be problematic for PD. The ISPD guidelines 2016 update recommends that intermittently dosed antibiotics be dwelled in the peritoneal cavity for at least 6 hours, but for ceftazidime doses of 1000–1500 mg (LD/intermittent dose) dwelled in Extraneal, Dianeal or Physioneal at 37°C for 6 hours, measured pyridine levels could exceed the maximum recommended daily exposure of 2 mg [5, 6, 9]. Ceftazidime MD was shown to be relatively safer, with pyridine levels less than the daily limit when used for four 6-hour exchanges per day; and ceftazidime retained >94% of its initial concentration at 37°C after 10 hours in Dianeal 1.5, 2.5 and 4.25%. Moreover, ceftazidime MD was shown to degrade faster in Physioneal than in Dianeal. Therefore the study encourages the use of continuous dosing for ceftazidime in Dianeal but not Physioneal [5]. Further studies may be required to evaluate the clinical outcome and impact of elevated pyridine levels in PD solutions.

### Cefepime

Cefepime is used for treatment of PD-related peritonitis caused by known pathogens such as *Pseudomonas* species. It is not as commonly used as the other cephalosporins for PD-related peritonitis and it also has less stability data on IP administration. Cefepime 312.5 mg in a 1.25 L bicarbonate compartment

of pH-neutral PD solution (Balance) (i.e. final concentration 125 mg/L), retained >90% of the initial concentration at 4°C for up to 7 days, at 25°C for 4 days, and after mixing the dual compartments, at 37°C for 12 hours [1, 10]. Cefepime 125 mg/L lost 10% of the initial concentration at 37°C after 10 hours and 5 hours, respectively, in pH-neutral PD solution (Physioneal 1.36 and 3.86%) [3].

## PENICILLINS

### Ampicillin and amoxicillin

Ampicillin and amoxicillin are aminopenicillins that show activity against susceptible strains of streptococci and enterococci. These antibiotics are used intraperitoneally for known pathogen treatment of PD-related peritonitis caused by *Streptococcus* and *Enterococcus*. Patel *et al.* [11] demonstrated that ampicillin 125 mg/L (MD) and amoxicillin 125 mg/L retained >90% of their initial concentrations in dextrose-based PD solution (Dianeal PD-4) for 14 days at 4°C, 3 days at 25°C and 1 day at 37°C. However, the dextrose concentration of these tested PD solutions was not specified. Both antibiotics also retained >90% of their initial concentrations in icodextrin-based PD solution (Extraneal) for 14 days at 4°C, 2 days at 25°C and 1 day at 37°C, and in pH-neutral PD solutions (Balance) for 14 days at 4°C and 12 hours at both 25°C and 37°C. These emerging data on ampicillin supplement those of a review that showed a lower concentration (50 mg/L) was stable in Dianeal for 2 days at 25°C [4]. There are two important points to note when considering the new stability data. First, the tested amoxicillin concentration of 125 mg/L is slightly lower than the guideline recommended MD, i.e. 150 mg/L. Second, the methodology regarding the sequence of antibiotic injection in the compartments and mixing of compartment solutions was not provided.

### Piperacillin/tazobactam

Piperacillin/tazobactam (PIP/TZB) is a combination of antipseudomonal penicillin and beta-lactamase inhibitor. In the management of PD-related peritonitis, it is often used for treatment of *Pseudomonas* peritonitis. Mendes *et al.* [12] investigated the stability of PIP/TZB admixed with heparin in dextrose-based (Dianeal 1.5, 2.5 and 4.25%), icodextrin-based (Extraneal) and pH-neutral PD solutions (Balance 2.3%, and Physioneal 1.36, 2.27 and 3.86%). The solutions were first stored at 4°C for 7 days, followed by 25°C for 3 hours and finally 37°C for 10 hours. Both PIP/TZB 500/62.5 mg/L (MD in 2 L bags) and heparin 500 IU/L retained at least 97% of their initial concentrations in Dianeal and Extraneal when stored at 4, 25 and 37°C throughout the study period. For tests in Balance PD solution, PIP/TZB 1000/125 mg and heparin 1000 IU were added to the 1 L bicarbonate compartment. Both agents retained >98% of their initial concentrations after storage at 4°C for 7 days, then at 25°C for 3 hours and finally at 37°C for 10 hours. Similarly, PIP/TZB 1000/125 mg and heparin 1000 IU in a 725 mL dextrose compartment of Physioneal retained at least 98% of their initial concentrations after storing under the same conditions, where temperatures changed sequentially, as above.

## CARBAPENEMS

The carbapenem antibiotics have a broad spectrum of coverage for both Gram-positive and Gram-negative bacteria. They are used intraperitoneally for empirical and known pathogen treatment of PD-related peritonitis caused by *Pseudomonas* species that are resistant to ceftazidime and extended-spectrum beta-lactamase (ESBL)-producing bacteria. Data available on the stability and compatibility of carbapenem antibiotics in PD solutions are scarce.

### Meropenem

Mendes *et al.* [12] investigated the stability of meropenem in combination with heparin in different PD solutions. Meropenem 500 mg/L (intermittent dose) and heparin 500 IU/L retained >90% of their initial concentrations when stored at 4°C for 7 days in dextrose-based (Dianeal 1.5, 2.5, 4.25%) and icodextrin-based (Extraneal) PD solutions, followed by storage at 25°C for 3 hours and sequentially at 37°C for 10 hours. In addition, meropenem when admixed with heparin retained >98% of its initial concentration in Dianeal 1.5, 2.5, 4.25% and Extraneal when stored sequentially at 4, 25 and 37°C throughout the study period. However, meropenem lost >25% of its initial concentration in the pH-neutral PD solution (Balance 2.3%) when stored at 4°C for 36 hours, followed by 3 hours at 25°C and 4 hours at 37°C. When meropenem was added to heparinized Balance 2.3% PD solution directly at 37°C, the initial concentration of meropenem decreased by >15% upon storage for up to 10 hours.

### Imipenem

Deslandes *et al.* [3] evaluated the stability of some antibiotics in three different PD solutions (Physioneal 40 1.36 and 3.86% and Extraneal) [3]. Imipenem was the only carbapenem antibiotic evaluated in the study and was admixed in three different 2.5 L PD solutions. Imipenem 200 mg/L and 50 mg/L reached a drug degradation of up to 10% in 6 hours at 22 ± 2°C in Extraneal and 2 hours at 37°C in Physioneal 40. In the study, imipenem solutions showed a yellow coloration that increased over time, which highlighted its instability in various PD solutions.

## CIPROFLOXACIN

Ciprofloxacin is a fluoroquinolone antibiotic that has the greatest potency against aerobic Gram-negative bacilli. In the management of PD-related peritonitis, ciprofloxacin is often used in known pathogen treatment of peritonitis caused by *Pseudomonas*. Kussmann *et al.* [13] conducted a stability study with ciprofloxacin at a concentration consistent with the guideline-recommended MD, i.e. 50 mg/L. Ciprofloxacin MD was found to be stable in icodextrin-based PD solution (Extraneal) for 14 days at 6°C, 7 days at 25°C and at least 1 day at 37°C. In pH-neutral PD solutions (Physioneal 40 1.36, 2.27 and 3.86%), it retained at least 97% of the initial concentration for 14 days at 6°C and for 1 day at 37°C. Ciprofloxacin MD was stable in Physioneal 40 2.27 and 3.86% for 2 days at 25°C. Nonetheless, its stability in Physioneal 40 1.36% was inconclusive because the early significant drop in drug potency after 6 hours was presumably due to drug adsorption to the PD bag material. Another thing to note is that stability in pH-neutral PD solutions was investigated by adding ciprofloxacin to the dextrose compartment followed by immediate mixing of the compartment solutions. Even though data from Physioneal suggest ciprofloxacin is stable for >1 day at certain temperatures, the interpretation of its stability should be limited to within the expiry of 24 hours of mixing the components for Physioneal.

## VANCOMYCIN

Vancomycin is a glycopeptide antibiotic that is used intraperitoneally for empirical treatment and targeted treatment of PD-related peritonitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative *Staphylococcus* species, *Corynebacterium* species and susceptible strains of *Enterococcus* species [1]. Ranganathan *et al.* [2] showed that vancomycin 1000 mg/L (LD/intermittent dose) retained >94% of the initial concentration in icodextrin-based PD solution (Extraneal) for 14 days at 4°C and 25°C. The antibiotic was also stable in Extraneal for 4 days at 37°C. These recent data are most relevant to the intermittent dose or LD at 30 mg/kg/bag for patients weighing between 60 and 70 kg, as per the dosage recommendation of the ISPD guidelines. These data extend the findings by Nornoo *et al.* [14] in 2006 that concluded the vancomycin LD/intermittent dose was stable in Extraneal for 7 days at 4°C and 24°C, and for 1 day at 37°C.

## CONCLUSION

Antibiotic stability in PD solutions can be affected by a range of factors, including temperature, antibiotic concentration, PD solution type, dextrose concentration of the PD solution and the presence of co-administered agents (such as other antimicrobial agents and heparin). This article provides a comprehensive review of recent stability and compatibility studies on antibiotic activity when admixed in various PD solutions. These studies offer an extended scope of antibiotic stability data for certain antibiotic groups including aminoglycosides, cephalosporins and penicillins. The antibiotic activity was also investigated in most types of commercially available PD solutions, including dextrose-based, pH-neutral and icodextrin-based solutions under the mimic end-user conditions. The antibiotics most commonly used for IP treatment in PD-related peritonitis (e.g. cephalosporins, vancomycin, aminoglycosides) remain sufficiently stable to be safely stored in most types of PD solutions. However, knowledge gaps still exist regarding the impact of administration of antibiotics in different compartments of dual-chamber bags and the stability and compatibility data of antifungal agents and narrow-spectrum antibiotics targeting specific species. Future research is required in this area to ensure optimal peritonitis treatment and outcomes in people receiving PD.

## CONFLICT OF INTEREST STATEMENT

D.W.J. received consulting fees from Baxter Healthcare, Fresenius Medical Care, AstraZeneca, Bayer and AWAK; speaker honoraria from Baxter Healthcare, Fresenius Medical Care, Ono Pharmaceutical and Boehringer Ingelheim & Lilly and travel sponsorship from Ono Pharmaceutical and Amgen. P.K.L. received speaker honoraria from FibroGen, AstraZeneca and Baxter Healthcare. All others have no conflicts to declare.

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