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Newer Antibiotics for the Treatment of Peritonitis Caused by Resistance Bacteria in Patients with End Stage Kidney Disease and Using Peritoneal Dialysis

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Abstract

End-stage kidney disease (ESKD) is a serious condition that has a significant impact on patients' lives. The most preferred treatment is to get a kidney transplant, or the patient is shifted to dialysis options including haemodialysis (HD) and peritoneal dialysis (PD). Peritoneal dialysis is one of the effective modalities for the treatment of end-stage kidney disease (ESKD), but it was found to be associated with a serious complication called peritoneal dialysis- associated peritonitis (PDAP). The consequences of PDAP have been found to include removal of the catheter, relapse, transfer to haemodialysis, and death. Thus, it is usually treated using the appropriate antibiotic, which is based on the results of the culture. However, most of the conventional antibiotics used for the treatment of PDAP are not currently showing effectiveness, which is due to the growing resistance worldwide among the causative micro-organisms including Gram-positive and Gram-negative bacteria. Therefore, newer antibiotics that can eradicate these high-resistance microorganisms are required. This article reviews the available examples of novel antibiotics that can be used for peritonitis caused by strains that are showing resistance against conventional antibiotics. Examples include antibiotics like oxazolidinone, lipoglycopeptide, glycylcycline, moxifloxacin and cephalosporins.

Keywords: Resistance Bacteria- End Stage Kidney Disease- Peritoneal Dialysis.

INTRODUCTION

End-stage kidney disease (ESKD) is a serious condition that has a significant impact on patients' lives. The most preferred treatment is to get a kidney transplant where the patient is put on a list to receive a healthy functional donor kidney, but the waiting time is considered long. Therefore, Patients are shifted to dialysis options including hemodialysis (HD) and peritoneal dialysis (PD). HD is an efficient modality, but it requires the presence of the patient at the hospital multiple times per week, while peritoneal dialysis is more convenient as it is a home-based method. However, PD was found to be associated with a serious complication called peritoneal dialysis-associated peritonitis (PDAP). The consequences of PDAP have been found to include removal of the catheter, relapse, transfer to hemodialysis, and death. Thus, it is usually treated using empirical antibiotics, and then the treatment plan is narrowed to more specific antibiotics based on the results of the culture. However, most of the conventional antibiotics used for the treatment of PDAP are not currently showing effectiveness, and this is due to the growing resistance worldwide among the causative micro- organisms including Gram-positive and Gram- negative bacteria. Therefore, newer antibiotics that can eradicate these high-resistance microorganisms are required. The novel antibiotics could be the first-line option in future for the treatment of peritonitis when the conventional antibiotics are not working anymore due to bacterial resistance. In this study, the available examples of novel antibiotics that can be used for peritonitis caused by strains that are showing resistance against conventional antibiotics will be reviewed and discussed. Moreover, the types of antibiotics used in Prince Sultan Centre for dialysis in Hafer Albatin will be checked and their doses and duration of use for patients on dialysis will be checked as well.

METHODOLOGY

This study aims to evaluate the treatment options for the patient using PD modality and

developing PDAP that is caused by resistant bacteria. Examples include novel antibiotics from different classes and approved for the treatment of different infections with prior activity against highly resistant bacteria in comparison to conventional antibiotics. Different databases including web of science, PubMed and google scholar were used to search for novel antibiotics that are effective against resistant bacteria.

Patients' files from Prince Sultan Centre for Dialysis will be evaluated to check the type of antibiotics used by the patients. Moreover, the culture results, doses, duration of use and response to the treatment will be evaluated, and patients' data will be compared at the end.

1. End Stage Kidney Disease

End-stage kidney disease (ESKD) is a condition in which the kidneys lose their ability to function, leading to fluids and wastes building up in the body [1]. It is associated with a reduction in the glomerular filtration rate (GFR) of the kidney to 15 or less as shown in table 1 in which the stages of kidney failure are classified based on GFR [1, 2]. Patients with ESKD could experience symptoms such as fatigue, headaches, nausea, vomiting and problems with urination. In addition, there is a negative impact on the patient's quality of life and social, financial and mental wellness [3]. Patients with ESKD should use renal replacement therapy (RRT) to replace the advanced loss in function and sustain life [1, 2].

Unfortunately, the incidence of ESKD is increasing worldwide leading to major health consequences and high rates of mortality and morbidity [4]. In the USA, for example, the number of patients with ESKD has increased from 209 000 in 1991 to 472 000 in 2004 [5]. In addition, the number of people on RRT is found to be about 2·618 million in 2010, and it is expected to increase by more than double to 5·439 million by 2030 [6]. The levels of ESKD are shown to be sharply increased worldwide so it is important to make sure all patients are being treated with the most effective and safe treatment modality.

Table 1: Stages of kidney failure based on GFR

Stage	GFR (ml/min/1.73 m^2)	Health of kidneys
1	≥90	Normal renal function- First signs appear
2	60-89	Slightly reduced renal function
3A/3B	45-59 (3A) and 30-44 (3B)	Noticeably reduced renal function
4	15-29	Extremely reduced renal function
5	<15	Lost renal function (ESKD)

2. Management of ESKD

The treatment options for ESKD include kidney transplant, haemodialysis and peritoneal dialysis.

2.1. Kidney Transplantation

A kidney transplant is a surgical procedure where the non-functional kidney is replaced with a functioning donated kidney. In 2003, about 17,600 kidney transplants were performed in the USA. Kidney transplantation is found to be superior to dialysis methods due to some reasons. It helps to replace up to half of the total function of a normal kidney, while dialysis helps to replace only some of the function. Survival rates could reach up to 90% for recipients of kidney transplants [7], and mortality was noticed to be lower by 68% for kidney recipients in comparison to patients on a waiting list [8]. In addition, kidney transplantation is related to terms of improved quality of life and lower costs [9-11]. However, the applicability of kidney transplantation has been limited by the shortage of kidneys and the long waiting time until a kidney is found. The mean waiting time is shown to be steadily increasing worldwide [12]. Moreover, in the case of kidney transplantation, there is a chance of immunological rejection after transplantation and the adverse effects of immunosuppressive medications are unfavourable [8]. As a result, patients could start to use haemodialysis or peritoneal dialysis to replace the renal function.

2.2. Haemodialysis

Haemodialysis is an RRT where a machine (dialyser) is used for the filtration of blood from waste products [14]. For this purpose, access should be made to remove the blood from the body and it is usually made using a fistula, graft or catheter [15, 16]. The blood passes through tubes to the machine where it is filtered and returned to the body through different tubes [14].

Haemodialysis is the most popular dialysis method as it is preferred by many patients. In 2013, about 88.2% of cases started RRT with haemodialysis, while the cases that started PD and kidney transplantations were 9 % and 2.6%, respectively [17]. Studies revealed that haemodialysis is associated with higher survival rates and less mortality in comparison with peritoneal dialysis [18]. However, the quality of life for patients suffering from chronic conditions such as ESKD has also become a great concern. Haemodialysis is usually performed at a dialysis centre two to three times per week and each session could take 4-5 hours. This could affect the personal and professional life of patients. On the other hand, peritoneal dialysis offers a more convenient method that could fit the patient lifestyle [19].

2.3. Peritoneal Dialysis

Peritoneal dialysis is a home-based method that can be done independently or with the assistance of a caregiver. The idea of PD is to place a PD solution into the peritoneal cavity using a catheter that is previously inserted into the abdomen [20]. In PD, the peritoneal membrane of the patient is the filter, and the waste products pass through it into the peritoneal dialysis solution. After that, the solution containing the waste products will be removed from the abdomen [20, 21]. As shown in, the PD solution flows through a catheter to the abdominal cavity where the waste products are filtered and after that, the waste products are removed to the waste bag. PD can be performed manually multiple times during the day which is called continuous ambulatory peritoneal dialysis CAPD, or while sleeping at night which is called automated peritoneal dialysis (APD) [20, 21]. About 22% of the dialysis population in Australia is using PD with 12% on CAPD and 10% using APD [22].

PD has become a replacement for haemodialysis as it could fit the lifestyle of the patient without affecting their daily activities. The number of patients with PD has grown by 24.9 patients per million population in developing countries and by 21.8 per million population in developed countries [23]. However, although PD has the benefit of being a simple and convenient method, it is associated with some complications such as peritoneal dialysis-related peritonitis PDAP.

3. Peritoneal Dialysis-Associated Peritonitis

PDAP is a serious and frequent complication of using CAPD [24]. It could be a consequence of the entrance of skin bacteria into the abdominal cavity, poor catheter technique or organisms from the bowel lumen [25, 26]. The presence of bacteria inside the peritoneal cavity leads to an inflammatory response, and the patient could present with symptoms and signs such as cloudy effluent and abdominal pain [27]. PDAP is associated with high mortality and morbidity rates [28, 29]. In addition, it is responsible for technique failure, termination of CAPD and the switch to haemodialysis [27, 30, 31].

4. Management of PDAP

PDAP should be managed to avoid the complications of peritonitis including removal of the catheter, relapse, transfer to hemodialysis, and death [34]. Empirical antibiotic treatment is recommended to be started immediately for the preservation of the peritoneal membrane function. It should cover mostly offending microorganisms including Gram- positive and Gram-negative bacteria [35]. For the Gram-positive organism, vancomycin or a cephalosporin can be used while the gram-negative organisms can be covered by a third-generation cephalosporin or aminoglycoside. After that, the PD effluent should be cultured, and when the culture study results are obtained, more targeted therapy is started to eradicate the causative bacteria and effectively treat the infection [35, 36].

5. Causative Micro-Organisms

Gram-positive bacteria, including coagulase-negative *staphylococci* (*Staphylococcus epidermidis* and *Staphylococcus Aureus),* are found to be responsible for the majority of PDAP cases (about 45–65%), while 15–35% of the cases were found to be caused by gram-negative bacteria such as *Klebsiella, Escherichia coli, and Pseudomonas aeruginosa* (*P. aeruginosa)* [33, 37-40]. Even though the incidence of peritonitis caused by Gram-positive bacteria is higher, Gram-negative bacteria peritonitis is shown to be increasing [41] and is associated with higher mortality, hospitalization, catheter removal, and PD discontinuation rates [33, 37].

Regardless of the causative micro-organism, peritonitis statistics revealed that the cure rates have failed to show improvement and increasing recurrence and replacement rates have been noticed with conventional antibiotics. One explanation for the treatment failure is the developed resistance among the causative bacteria.

6. Bacterial Resistance

The resistance of bacteria (Gram-positive and Gram-negative) against conventional antibiotics has become a global concern as the resistance rates have increased over the years [42]. Different gram-positive bacteria with multi-drug resistance have been reported, such as methicillin-resistant *Staphylococcus aureus,* penicillin-resistant *Streptococcus pneumoniae* and *coagulase-negative Staphylococci* [42, 43]. In the USA, about 60% of *Staphylococcus* infections are caused by the methicillin-resistant Staphylococcus aureus (MRSA) strain, which is a type of *Staphylococcus aureus* that shows resistance to conventional antibiotics [44, 45]. Moreover, recent studies reported *Staphylococcus aureus* strains called vancomycin-intermediate *S. aureus* with a higher minimum inhibitory concentration for vancomycin which is usually a good choice for drug-resistant *Staphylococcus aureus* [46, 47]. Another study revealed that clones of multidrug- resistant, oxacillin-resistant *S. aureus* have been developed, which increased the concern about *S. aureus* infections that cannot be treated with available antibiotics [48, 49]. These organisms can resist the activity of antibiotics by multiple mechanisms [43].

On the other hand, resistance was seen with Gram-negative bacteria; especially *Pseudomonas aeruginosa* (*P. aeruginosa)* is considered the most common highly resistant gram-negative bacteria causing PDAP. The challenge associated with the treatment of *Pseudomonas* peritonitis is attributed to the invasive nature of this micro-organism [50] and its inherent propensity to develop resistance. There are different mechanisms by which *P. aeruginosa* can

develop resistance to antibiotics, including altering the anti-microbial targets, decreasing the expression of porins or developing multiple efflux pumps. As a result, the efficacy of available anti-*pseudomonas* agents such as beta-lactams, aminoglycosides and cephalosporin has been decreased. For example, Wanhong Lu *et al*., compared the resistance rates of *P. aeruginosa* between the periods of 1999 and 2015 and found to increase from 4% to 20% against ceftazidime (cephalosporin) and from 9% to 10% against gentamicin (aminoglycoside) [51]. Krothapalli R. *et al.,* have found that aminoglycosides failed to eradicate *P. aeruginosa* in all P. peritonitis cases under treatment [52]. Similar outcomes were found by Juergensen PH *et al.,* where none of the *Pseudomonas* peritonitis cases responded to the antibiotic therapy and catheter removal was required to achieve resolution. Therefore, new potent antibiotics to which causative micro- organisms show sensitivities have been developed, such as the combination of ceftolozane/tazobactam which has shown potent activity against many strains of *P. aeruginosa.*

Thus, newer antibiotics are required to address these concerns. There are different examples of novel antibiotics that can be considered in future for the treatment of peritonitis caused by resistant bacteria.

7. Oxazolidinone

7.1. Linezolid

Linezolid is the first approved oxazolidinone by the Food and Drug Administration (FDA) in 2000. Its mechanism of action involves binding to the ribosomal peptidyl transferase centre and inhibiting protein synthesis, which eventually stops bacterial growth. Linezolid was found to be effective against highly resistant Gram-positive bacteria, including vancomycin-intermediate *S. aureus* (VISA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), MRSA and vancomycin-resistant *S. aureus* (VRSA) [53]. It was found that the resistance rates against linezolid remained low in comparison to other conventional antibiotics [54, 55].

8. Glycylcycline

8.1. Tigecycline

Tigecycline is a novel glycylcycline that got FDA approval in 2005 for the treatment of complicated intra- abdominal infections (cIAIs) caused by various Gram-positive, Gram-negative and anaerobic bacteria. It works by binding to bacterial 30S ribosome, blocking the entry of transfer RNA and preventing protein synthesis. Tigecycline is considered bacteriostatic, but in some cases, it was found to be bactericidal against *S. pneumoniae* and *Legionella pneumophila* [56]. *In vitro* Studies revealed that it is effective against resistant strains like MRSE and ESBL-*E. coli*, meropenem-resistant *Klebsiella*, ceftazidime-resistant *Enterobacter* and meropenem-resistant *Acinetobacter* [57]. In one study, IV tigecycline was used in PD patients for the treatment of peritonitis caused by MRSA, and it was successful [58].

9. Lipoglycopeptides

9.1. Telavancin

Telavancin is a semi-synthetic glycopeptide with bactericidal activity against Gram-positive bacteria. The activity of telavancin is exhibited by multiple mechanisms of action. It can disturb the integrity of bacterial cell membranes and inhibit cell wall synthesis [59, 60]. It is shown to be more potent against Gram-positive bacteria than standard antibiotics [61]. For example, studies revealed that it is highly effective against strains including MRSA, vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA) [62, 63]. Another study reported serum bactericidal titers of telavancin persisting for 24 hours against penicillin-resistant *S. pneumonia* and MRSA strains [64]. This indicates the effectiveness of telavancin against the high-resistance strains of gram-positive bacteria. Therefore, telavancin can be used through the intra-peritoneal IP route with the PD solution for the treatment of PDRP caused by Gram-positive bacteria.

10. β-Lactams

10.1. Ceftolozane /Tazobactam

Ceftolozane is a novel cephalosporin with a more potent anti-psoudomnal activity and a broader bacterial spectrum compared to the rest of cephalosporins [65]. Tazobactam is a beta-lactamase inhibitor that is usually combined with other antibiotics to offer a broader spectrum and more resistance against beta-lactamases [66]. The higher potency of the combined antibiotic ceftolozane/tazobactam is related to the chemical structure of ceftolozane and the addition of the tazobactam.

The chemical structure of cephalosporins consists of a four-membered ring (beta-lactam ring) fused to a six- membered dihydrothiazine ring, which has a carboxyl group located in the 4-position. The variations in cephalosporins are related to the difference in the groups substituted at the 3rd and 7th positions. Ceftolozane, similarly to ceftizedime, has an aminothiadiazole ring at the 7th position in the side chain which is responsible for the enhanced antigram-negative bacteria activity. The dimethylacetic acid moiety is responsible for the enhanced activity against *P. aeruginosa* species while stability against beta-lactamases is conferred by the oxime moiety [65]. However, ceftolozane has a heavier group substituted at the 3-position pyrazole which grants greater stability and resistance against beta-lactmases producing P. aeruginosa by conferring a hindrance at the beta-lactamases active site, while ceftazidime has a lighter pyridinium substituted at the 3-position.

Tazobactam is a penicillanic acid derivative that acts as a beta-lactamase inhibitor. It has a lactam ring with a sulfone group situated at position 1, which facilitates the irreversible inhibition of the enzyme. The triazole ring is responsible for improving the 50% inhibitory concentration IC_{50} against beta-lactmases [66]. Thus, adding tazobactam has extended the spectrum of ceftolozane by providing irreversible beta-lactamase activity.

11. Flouroquinolone

11.1. Moxifloxacin

Moxifloxacin was approved to be used via the IV route in 1999 for IV use, while oral use was approved in 2001 for respiratory infections [67]. It has a bactericidal activity that inhibits bacterial DNA replication, transcription, repair, and recombination. This is achieved by its ability to inhibit the topoisomerase II (DNA gyrase) and topoisomerase. In comparison to vancomycin, moxifloxacin has superior activity against MRSE and MRSA [68]. However, it has little activity against *P. aeruginosa*, and thus ciprofloxacin is used in the case of *Pseudomonas* peritonitis. For PD patients, there is no need to adjust the dose as the drug is not excreted renally [69].

12. CONCLUSION

Treatment of peritonitis caused by resistant bacteria is challenging. The growing resistance is associated with the use of newer, more potent antibiotics. In comparison to conventional antibiotics, Studies revealed that some of the novel antibiotics are showing greater bactericidal and bacteriostatic activities against resistant bacteria like MRSA, vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA), ESBL-*E. coli*, meropenem-resistant *Klebsiella*, ceftazidime-resistant *Enterobacter*, and meropenem-resistant *Acinetobacter* This indicates that some of them can be used as a replacement in case the first-line antibiotics are not effective due to resistance. However, these drugs need to be examined for PD patients to obtain their pharmacokinetic data and evaluate their efficacy and safety.

AUTHORS CONTRIBUTIONS

This work was carried out in collaboration among all authors. All read and approved the final manuscript.

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