

Successful salvage of peritoneal catheter in unresolved methicillin-resistant

*Staphylococcus aureus* peritonitis by combination treatment with daptomycin and rifampin

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**Running head:** Daptomycin and rifampin in MRSA peritonitis

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## **Abstract**

Peritoneal dialysis patients are at increasing risk of gram-positive organism infections because of disrupted skin barrier function, presence of a peritoneal catheter, and a deficient immunological system. In particular, the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections is clinically challenging. Herein, we present a case of MRSA peritonitis that showed no response to a 14-day treatment with intraperitoneal (IP) vancomycin. To overcome unresponsiveness to vancomycin, we shifted the regimen to IP daptomycin (given every 6 hours through manual peritoneal dialysate exchanges) and oral rifampin (300 mg twice daily).

The peritonitis resolved without sequelae or relapse. We suggest daptomycin and rifampin as an alternative combination therapy for MRSA infections that may otherwise remain unresolved.

## **Introduction**

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a pathogen that spreads rapidly from hospitals to the community and causes greater morbidity, increased length of hospitalization, and higher treatment costs than methicillin-susceptible *S. aureus* (MSSA) [1, 2]. Treatment of MRSA remains a clinical challenge, especially in peritoneal dialysis (PD)-associated peritonitis. Vancomycin is the drug of choice for treating MRSA peritonitis. However, some MRSA infections are unresponsive to vancomycin. Here, we describe a case of unresolved MRSA peritonitis that had been treated with an intermittent dosing of intraperitoneal (IP) vancomycin every 3–5 days. Shift of the treatment to IP daptomycin and oral rifampin resulted in successful salvage of the PD catheter.

## **Case report**

A 51-year-old woman with end-stage renal disease and undergoing continuous ambulatory peritoneal dialysis (CAPD) for 5 years presented with turbid dialysate at the emergency department.

On presentation, she was afebrile, blood pressure was around 110/72 mm Hg, and pulse rate was 76/minute. Abdominal examinations revealed a soft abdomen without obvious signs of tenderness. There was no pus or erythematous changes around the catheter exit site. Abdominal film revealed a well-positioned catheter with the tip in

the pelvis. Initial dialysate leukocyte count was 859 cells/ $\mu$ L (85% polymorphonuclear leukocytes [PMN]) (Table 1). Her body weight was 50 kg, and the daily urine amount was less than 100 mL. According to guidelines, empirical treatment was started with intermittent dosing of IP vancomycin (1 g every 5 days) and IP cefazolin (750 mg) [3]. Dialysate cultures grew MRSA on admission day 3 with a minimal inhibitory concentration of vancomycin of 1  $\mu$ g/mL. However, the patient refused any further blood aspiration, even trough levels of vancomycin. The dialysate remained turbid with high leukocyte counts of 1720 cells/ $\mu$ L (93% PMN). Therefore, we increased the dose of vancomycin and shortened the dosing intervals. The second dose of IP vancomycin (1.5 g) was given on day 5, the third dose (1.5 g) on day 8, and the fourth dose (1.5 g) on day 11. On day 14, the dialysate leukocyte count was 1260 cells/ $\mu$ L (61% PMN). Further dialysate cultures for bacterial and fungus revealed no growth during vancomycin therapy. On day 15, IP daptomycin was given in the first dialysate bag at 100 mg/L for a 12-hour dwell. The IP daptomycin dose was decreased in the second dialysate bag to 20 mg/L every 4 hours through manual 2.5-L peritoneal dialysate exchanges during the day and a 12-hour dwell with 2-L icodextrin dialysate exchange during the night. On the third day of daptomycin treatment, the dialysate was still turbid. Therefore, we added oral rifampin (300 mg twice daily) to the treatment regimen. On the third day of

daptomycin/rifampin combination therapy, the dialysate started becoming clear, with dialysate leukocyte counts of 22 cells/ $\mu$ L. In total, the patient received 21 days of IP daptomycin and 18 days of oral rifampin. During the post-treatment follow-up, the dialysate culture remained clear. The patient is clinically well and undergoing CAPD without peritonitis relapse.

## **Discussion**

In recent years, MRSA strains have become serious and prevalent pathogens not only in hospitals but also in the community [4]. Vancomycin is considered the first-line therapy in populations with high risk of gram-positive bacteria infections, including PD-related peritonitis [5]; however, its frequent use may lead to development of full resistance, intermediate resistance, or tolerance by methicillin-resistant strains of staphylococci [6, 7].

In this study, the dialysate cultures grew vancomycin-sensitive MRSA. However, this finding was not consistent with the clinical course of the patient: the peritonitis persisted despite administration of intermittent IP vancomycin (1.5 g every 3 days).

Unfortunately, the serum vancomycin trough levels were not determined. According to Blunden et al., the proportion of anuric CAPD patients with low vancomycin levels at day 5 (<12 mg/l) is 9.2% and that at day 10, after increasing the dose of vancomycin by 500 mg, is 0% [8]. Thus, the serum vancomycin trough levels of our

patients might not be inadequate. Therefore, we suspect that persistence of unresolved peritonitis in our patient might have resulted from phenotypic tolerance, paradoxical effects, *S. aureus* biofilm formation, fungal infections, or atypical infections [9]. The subsequent dialysate culture and the later clinical course excluded the possibility of other pathogen infections.

In recent years, numerous clinical studies have investigated the possible use of linezolid, tigecycline, or daptomycin in difficult-to-treat MRSA infections [9–11]. Daptomycin—a novel lipopeptide antibiotic approved in the USA in 2003—shows rapid bactericidal activity against gram-positive bacteria via a calcium-dependent mechanism. Daptomycin has demonstrated clinical efficacy in *Staphylococcus* endocarditis and infections of soft tissue, bones, and joints [12, 13]. In an in vitro peritoneal dialysate model of peritonitis, daptomycin exhibited greater bactericidal activity than vancomycin against MRSA and MSSA [14]. Despite the anticipated benefit of daptomycin in treating gram-positive bacterial peritonitis, information regarding the pharmacokinetics of IP daptomycin and the best dose for different concentrations of dextrose dialysates is limited. Bahte et al. have reported the therapeutic plasma concentration of daptomycin after single IP daptomycin administration in a peritonitis patient [15]. Huen et al. and Hassoun et al. have successfully used IP daptomycin to treat cases of vancomycin-resistant enterococci

(VRE) peritonitis [16, 17]. In our case, IP daptomycin at 20 mg/L in 2.5% dextrose low calcium (2.5 mEq/L) dialysate every 4 hours and 7.5% icodextrin dialysate every 12 hours exerted the same therapeutic effects as reported by Huen et al. [16].

The successful use of daptomycin in PD-related peritonitis has been previously reported [15–17]. Here, we further show that daptomycin eradicates biofilm-associated foreign body infections and that it exerts synergistic effects with rifampin. Thus, daptomycin offers a therapeutic alternative for vancomycin-unresponsive MRSA peritonitis, while avoiding removal of the catheter.

Previously, Bahte et al. had already suggested the use of IP daptomycin in *S. aureus* peritonitis. However, in that study, IP daptomycin was administered immediately after diagnosis; this might have masked the effects of daptomycin in eradicating previously formed *S. aureus* biofilms and preserving the catheter [15]. The glucose-based dialysate may harbor multicellular bacterial aggregates that easily grow into biofilms on the PD catheter, ultimately causing antibiotic resistance [18, 19]. To circumvent this problem, Stewart et al. have suggested the use of antibiotics that can disrupt layers of multicellular aggregates [20]. Interestingly, fluorescence-labeled daptomycin rapidly penetrates *Staphylococcus epidermidis* biofilms [20]. In addition, daptomycin efficiently inhibits staphylococci adherence and biofilms on biomedical devices, as demonstrated in in vitro and clinical studies [21–23]. In agreement, we show that IP



daptomycin might be effective in eradicating persistent MRSA peritonitis and preserving the PD catheter.

On the other hand, daptomycin seems to exert synergistic effects when administered with rifampin. In fact, daptomycin is known to synergize *in vitro* with rifampin or  $\beta$ -lactams against VRE, and with gentamicin or  $\beta$ -lactams against MRSA [24–26].

While investigating the combinatory effect of daptomycin and rifampin against *S. aureus*, Credito et al. found that the synergistic effects were only revealed against 1 particular vancomycin-intermediate *S. aureus* strain but not against MSSA, MRSA, or vancomycin-resistant *S. aureus*. The clinical course of our patient might disclose the possible synergistic effect of rifampin and daptomycin *in vivo*. The dialysate effluents became clear 3 days after oral rifampicin was used. Although rifampin exerts bactericidal effects against MRSA, the rapid selective ability of resistant mutants limits its use alone [27]. More clinical trials are required to prove the synergistic effects of daptomycin and rifampin against MRSA.

Nonetheless, we show that IP daptomycin might synergistically act with rifampin in treating vancomycin-unresponsive MRSA peritonitis. Further pharmacokinetic and experimental studies are required to establish the appropriate dose of IP daptomycin and to ensure catheter salvage by IP daptomycin in MRSA peritonitis.

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## Tables

Table 1. Serial leukocyte counts of dialysate drainage during vancomycin therapy.

WBC, white blood cells; PMN, polymorphonuclear cells

Admission day	1	3	9	10	12	13	14	17	19	28	35
WBC (cell/uL)	859	1720	945	1679	961	1113	1260	345	22	31	3
PMN (%)	85	93	81	70	64	68	61	72	52	89	
Mononuclear cells (%)	15	7	19	30	36	32	39	28	48	11	