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Successful Treatment of Extensively Drug-Resistant *Acinetobacter baumannii* Peritoneal Dialysis Peritonitis with Intraperitoneal Polymyxin B and Ampicillin-Sulbactam

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Abstract

OBJECTIVE: To describe a case of extensively drug-resistant (XDR) *Acinetobacter baumannii* peritoneal dialysis (PD)–associated peritonitis successfully treated with combination antibiotics, including intraperitoneal polymyxin B, with retention of the catheter.

CASE SUMMARY: A 54-year-old woman with end-stage renal disease receiving chronic PD and recent antibiotic and hospital exposure presented with abdominal pain, nausea, and vomiting. She was found to have XDR *A. baumannii* PD peritonitis. Treatment was initiated with intravenous and intraperitoneal ampicillinsulbactam, followed by the addition of intraperitoneal polymyxin B based on susceptibilities. The patient recovered without the need for catheter removal or switch to hemodialysis.

DISCUSSION: The frequency of XDR *A. baumannii* as a nosocomial pathogen is increasing, and polymyxins are being used more often as part of combination therapy for infections caused by this organism. Neither XDR *A. baumannii* PD peritonitis nor the use of intraperitoneal polymyxin B has been well described. In our patient, intraperitoneal dosing of polymyxin B was determined based on limited published pharmacokinetic and pharmacodynamic data.

CONCLUSIONS: A case of XDR *A. baumannii* PD peritonitis was successfully treated with combination antibiotic therapy, including intraperitoneal polymyxin B, without major complications.

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Keywords

Acinetobacter baumannii ; dialysis; intraperitoneal; polymyxin B

Peritonitis is a serious complication of peritoneal dialysis (PD). The mortality rate associated with PD peritonitis is estimated to be 4%, and this complication is identified as a contributing factor in 16% of peritoneal dialysis–related deaths.[1] Rates of PD peritonitis have been decreasing since the early 1990s; however, the relative proportion of peritonitis episodes caused by gram-negative bacteria is increasing.[2,3] Gram-negative PD peritonitis is associated with increased rates of catheter loss, hospitalization, switch to hemodialysis, and mortality.[3–5] Although *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella* spp. are the most common causes of gram-negative PD peritonitis, *Acinetobacter* spp. are also frequently isolated pathogens.[2–4] In a review of PD peritonitis from Singapore, *Acinetobacter* spp. was the most commonly isolated gram-negative bacteria; however, this was a single-center experience and the microbiologic trend may not be applicable to other centers.[5]

Acinetobacter baumannii is recognized as an important and increasingly drug-resistant nosocomial pathogen.[6] As a result of this species' ability to resist desiccation and disinfectants, colonize the skin, and form biofilms, *A. baumannii* is particularly well adapted to infect foreign material.[7] Multidrug-resistant (MDR) strains, commonly defined as resistant to at least 3 classes of antibiotics, and extensively drug-resistant (XDR) strains, defined as susceptible only to the polymyxins, have been implicated primarily in health care–associated infections and nosocomial epidemics.[7] To date, there are no published reports of successful treatment of nosocomial MDR or XDR *Acinetobacter* PD peritonitis. We present a case of XDR *A. baumannii* PD peritonitis successfully treated with a combination of intraperitoneal polymyxin B and ampicillin-sulbactam.

Case Report

A 54-year-old woman with end-stage renal disease, receiving continuous ambulatory peritoneal dialysis (CAPD) for the past 15 months, was admitted to our large, urban, tertiary medical center with acute onset of severe epigastric abdominal pain, nausea, vomiting, and diarrhea for 12 hours. She reported new-onset cloudy peritoneal dialysate fluid but denied any fever or chills, bloody stools, or abnormal dietary intake. The patient had no prior episodes of peritonitis, catheter removal, or other complications related to CAPD. Her PD regimen involved 4 cycles per day with 2 L of dialysate for each cycle, alternating between 1.5% and 2.5% glucose concentrations.

During the month before this hospitalization, the patient had been hospitalized 21 days for an elective iliac artery to popliteal artery bypass graft for severe peripheral vascular disease. Her hospital course was complicated by a polymicrobial postsurgical deep-wound infection in her groin. The patient's home medications included oral ciprofloxacin, oral metronidazole, and intravenous vancomycin as treatment for this infection. The patient also had a history of well-controlled type 2 diabetes mellitus, congestive heart failure, and coronary artery disease.

On examination, vital signs were temperature 38 °C, blood pressure 127/66 mm Hg, and pulse 106 beats/min.She had diffuse abdominal tenderness to deep palpation, most pronounced in the epigastric region, without rebound tenderness or guarding. Her PD catheter was in place in the right lower abdominal quadrant with no erythema, tenderness, or drainage around the exit site. She had a large left-sided inguinal wound with healthy pink granulation tissue at the base and minimal serosanguinous discharge. Initial laboratory test results were notable for serum creatinine 4.11 mg/dL, blood urea nitrogen 25 mg/dL, and glucose 284 mg/dL. Liver function test results and peripheral white blood cell (WBC) count were within normal limits. Peritoneal fluid analysis and culture results are listed in Table 1. A series of acute abdominal X-rays did not show any signs of intestinal perforation or bowel obstruction.

The patient was initially continued on intravenous vancomycin. Metronidazole was changed from oral to intravenous administration, given her vomiting. Ciprofloxacin was stopped and intravenous ceftazidime was started. On the third day of hospitalization, peritoneal fluid culture results showed few *A. baumannii*. Susceptibility testing is reported in Table 2 and was performed via Vitek 2 (BioMerieux), Kirby-Bauer (KB) disk diffusion method, and Etest (BioMerieux). Based on initial susceptibilities, ceftazidime and metronidazole were stopped and the patient was started on intravenous ampicillin-sulbactam 1.5 g every 12 hours and intraperitoneal ampicillin-sulbactam 200 mg per 2-L bag, which dwelled for the entire 6 hours of every peritoneal dialysate exchange.

On the fourth day of hospitalization, the patient continued to have abdominal tenderness and nausea. Additional susceptibility testing of the initial *A. baumannii* isolate demonstrated a minimum inhibitory concentration (MIC) of 4 μg/mL to tigecycline (no Clinical and Laboratory Standards Institute [CLSI] susceptibility criteria established) and susceptibility to colistin with an MIC of 0.5 μg/mL. Intraperitoneal polymyxin B 300,000 IU (30 mg) per 2-L bag was initiated and dwelled for the entire 6 hours of every peritoneal dialysate exchange. In addition, the intravenous dose of ampicillin-sulbactam was increased to 3 g every 12 hours. Subsequent KB disk diffusion testing of polymyxin B revealed a zone of inhibition of 14 mm (no CLSI susceptibility criteria established).

By the sixth day of hospitalization, the patient had clinically improved with resolution of abdominal pain, vomiting, and diarrhea. Her peritoneal WBC count had decreased with a concomitant decrease in the percentage of polymorphonuclear cells (Table 1). Given the improvement in the peritoneal fluid cell count, we did not remove the catheter, per 2010 International Society of Peritoneal Dialysis guidelines regarding the management of peritoneal dialysis–associated infections.[1] She was eventually discharged on ampicillin-sulbactam 200 mg and polymyxin B 300,000 IU (30 mg) per 2-L bag allowed to dwell with every peritoneal dialysate exchange and intravenous ampicillin-sulbactam 3 g every 12 hours. Intravenous vancomycin was also continued to complete treatment for her prior surgical site infection. The patient completed a total of 16 days of intraperitoneal and intravenous ampicillin-sulbactam and 15 days of intraperitoneal polymyxin B.

One day after completing her intraperitoneal and intravenous antibiotics at home, the patient was readmitted with nausea and diarrhea. Peritoneal fluid analysis demonstrated

87 white blood cells; fluid culture was negative. She was treated with intravenous fluids and empiric oral metronidazole. Although a *Clostridium difficile* toxin assay was negative, her diarrhea improved dramatically with treatment. Subsequently, she developed worsening nausea and metronidazole was switched to oral vancomycin. Her nausea and diarrhea resolved completely and she was discharged home to complete 14 days of empiric oral vancomycin for possible *C. difficile* colitis. At 2 months after discharge, she had not had any further episodes of PD peritonitis.

Discussion

MDR *Acinetobacter* spp. are now a commonly identified cause of serious infections in critically ill, hospitalized patients. Rates of *Acinetobacter* spp. as a cause of gram-negative PD peritonitis vary. A large review of PD centers in Australia found *Acinetobacter* spp. to be a cause of PD peritonitis in 1.8% of episodes,[3] and a smaller, single-center review from Toronto found them to account for 2% of episodes.[4] However, in a single-center study from Singapore, Lye et al. reviewed 200 patients with PD peritonitis and reported *Acinetobacter* spp. as the most common gram-negative organism, accounting for 10.7% of all episodes.[5]

In previously published case series and case reports, the majority of cases of *Acinetobacter*-related PD peritonitis were community acquired and all isolates retained susceptibility to multiple classes of antibiotics. A search of the English language literature in MEDLINE, from January 1980, yielded 5 case series (1 of which was an expansion from a published case series from Singapore) and 4 case reports discussing *Acinetobacter* spp. PD peritonitis treated with intraperitoneal antibiotics.[5,8–14] With the exception of 1 case report, published in 2009, these were all published in the 1980s or early 1990s. As a result, none of the patients described in these reports had XDR *Acinetobacter*. The majority of patients were successfully treated with intraperitoneal aminoglycoside monotherapy, although some received intraperitoneal β-lactam monotherapy or a combination of an intraperitoneal aminoglycoside, intraperitoneal ß-lactam, and oral fluoroquinolone.

As gram-negative bacteria increasingly acquire resistance to many frequently used antibiotics, cases of XDR *Acinetobacter* PD peritonitis are likely to increase. Patients who are immunosuppressed, have multiple comorbidities, have been recently hospitalized, and/or have recently been treated with antibiotics are at particular risk of acquiring MDR pathogens. As illustrated by the case reported here, nosocomial XDR *Acinetobacter* spp. PD peritonitis presents far greater treatment challenges than infections with more sensitive strains. Successful intraperitoneal antibiotic therapy for XDR *Acinetobacter* spp. PD peritonitis that achieves high concentrations locally, within the peritoneal cavity, may result in decreased rates of catheter removal or switching to hemodialysis.

Polymyxins, which were studied extensively in the 1960s, have emerged as crucial antibiotics in the era of MDR and XDR gram-negative nosocomial infections. Polymyxins may be the only remaining therapeutic option for infections caused by XDR gram-negative bacteria. Polymyxin B and polymyxin E (colistin) are the 2 clinically available polymyxin antibiotics. In the past few years, more data have accumulated regarding pharmacokinetic and pharmacodynamic properties, clinical efficacy, and toxicity profiles of polymyxins.[15]

Parchuri et al. reported a case of extended spectrum β-lactamase *Klebsiella pneumoniae* CAPD peritonitis unresponsive to intravenous meropenem and intravenous amikacin that was successfully treated with catheter removal and intravenous polymyxin B.[16] However, there is a paucity of published data on the pharmacology and clinical outcomes of intraperitoneal polymyxin B.

Greenberg and Sanford reported a study of uninfected patients undergoing peritoneal dialysis who were given colistimethate (polymyxin E) 300 mg by the intramuscular route (n = 5) or 5 mg/kg by the intraperitoneal route (n = 2) in 2 L of dialysate fluid.[17] Dialysate was allowed to dwell for 30–60 minutes and then removed. The authors found that serum concentrations of colistimethate in patients receiving intraperitoneal administration reached a level that was approximately 30% of that in patients who received intramuscular administration, suggesting limited peritoneal absorption over the dwell time used. Interpretation of these data is difficult, however, as the study was small and colistimethate is a prodrug of the active drug colistin. Colistin levels were not assayed in this study, and conversion of colistimethate to colistin may be variable based on differing formulations and patient pharmacokinetics.

Buck and Cohen conducted a study evaluating the peritoneal absorption of polymyxin B.[18] Polymyxin B was instilled in 2 L of dialysate and allowed to dwell intraperitoneally for 45 minutes before removal. Mean dialysate concentrations prior to administration and after removal were 16.5 μg/mL and 11.8 μg/mL, respectively. The authors noted that decreases in drug concentration could be partially due to a dilution effect as a greater volume of dialysate was removed than instilled; however, they estimated peritoneal absorption of polymyxin B to be a mean of 30%. While we could find no other studies evaluating intraperitoneal polymyxin B absorption specifically, these data do agree with the Greenberg and Sanford study of intraperitoneal polymyxin E absorption.

We chose to use intraperitoneal polymyxin B in combination with intraperitoneal and intravenous ampicillin-sulbactam based on a number of factors. First, we wanted to avoid polymyxin monotherapy. Polymyxins are considered cidal agents for gram-negative organisms; however, heteroresistance of *A. baumannii* to colistin has been demonstrated in vitro, suggesting that combination therapy may be advisable to prevent the emergence of resistance during therapy with polymyxins.[19] Second, we decided to use polymyxin B rather than polymyxin E because relatively little is known about peritoneal conversion and absorption of the latter's active component (colistin). Although we did not have a definitive susceptibility test for polymyxin B against the infecting organism, we felt comfortable with its activity knowing the colistin MIC was 0.5 μg/mL.[20] Third, we selected ampicillin-sulbactam as a second agent because it is the only other drug shown to have activity against this organism, has an excellent safety profile, and has been studied previously with intraperitoneal dosing.[21] Finally, we confirmed that polymyxin B and ampicillin-sulbactam are compatible in normal saline at the selected doses.[22] The dialysis fluid containing both drugs appeared clear, as observed by a pharmacist, and was without evidence of visual incompatibility.

In designing the specific dosing regimen, the following was taken into consideration. Polymyxin B was expected to undergo 30% peritoneal absorption[18]; therefore, 30 mg was put into each 2- L bag of dialysate. This dose was chosen on the assumption that intraperitoneal concentrations would be maintained at 10 μg/mL for the duration of each dialysate dwell time, which would be well above the MIC of the organism, while sparing the patient significant systemic drug exposure. Intraperitoneal ampicillin-sulbactam dose was determined with similar considerations. Based on an MIC of 16 μg/mL, ampicillin-sulbactam 200 mg was put into each 2-L bag of dialysis fluid. Assuming 60–75% peritoneal absorption, as previously identified,[18,21] a systemic intravenous dose of ampicillin-sulbactam 3 g every 12 hours was also administered to achieve an expected peak serum concentration of 109–170 μg/mL in an effort to create equilibrium at a higher concentration across the peritoneal cavity and minimize absorption of drug from the intraperitoneal space.

In the case reported here, intraperitoneal polymyxin B in combination with intraperitoneal ampicillin-sulbactam and intravenous ampicillin-sulbactam resulted in both clinical and microbiologic cure without significant acute complications or adverse effects.

To our knowledge, this is the first report of successful treatment of XDR *A. baumannii* PD peritonitis using intraperitoneal administration of polymyxin B and ampicillin-sulbactam. As the frequency of PD peritonitis secondary to MDR and XDR organisms rises, more data are needed regarding the intraperitoneal dosing of less frequently used drugs, such as polymyxin B.

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Table 1.

Peritoneal Fluid Analysis Results

Hospital Day	White Blood Cell Count (PMN %)	Culture Results
1	6150 cells/μL (95)	Few *Acinetobacter baumannii*
3[a]	9100 cells/μL (95)	Rare *A. baumannii*
6	320 cells/μL (73)	Negative
10	23 cells/μL (3)	Negative

PMN = polymorphonuclear.

[a]Intraperitoneal polymyxin B initiated on hospital day 4.

Table 2.

Susceptibility Results for *Acinetobacter baumannii* Isolate

Testing Method	Antibiotic	MIC (μg/mL)	Interpretation
Vitek 2	Ampicillin-sulbactam	16	Intermediate
Vitek 2	Cefepime	≥64	Resistant
Vitek 2	Ceftriaxone	≥64	Resistant
Vitek 2	Ciprofloxacin	≥4	Resistant
Vitek 2	Gentamicin	≥16	Resistant
Vitek 2	Imipenem	≥16	Resistant
Vitek 2	Tobramycin	≥16	Resistant
Vitek 2	TMP/SMX	≥16/304	Resistant
Kirby-Bauer	Amikacin		Resistant
Kirby-Bauer	Meropenem		Resistant
Kirby-Bauer	Doxycycline		Resistant
Kirby-Bauer	Minocycline		Resistant
Kirby-Bauer	Tetracycline		Resistant
Kirby-Bauer	Piperacillin/tazobactam		Resistant
Etest	Tigecycline	4	No CLSI guidelines
Etest	Colistin	0.5	Susceptible
Kirby-Bauer	Polymyxin B	(14-mm zone)	No CLSI guidelines

CLSI = Clinical and Laboratory Standards Institute; Etest = epsilometer test; MIC = minimum inhibitory concentration; TMP/SMX = trimethoprim/sulfamethoxazole.