Combination Treatment of Piperacillin/Tazobactam, Amikacin and Fosfomycin for Probable Multidrug-Resistant *Pseudomonas aeruginosa* Infection: A Case Report

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**ABSTRACT**

This is a probable case of 50-year-old man with necrotizing fasciitis caused by multidrug-resistant (MDR) *Pseudomonas aeruginosa*. He was successfully treated with surgical debridement and a combination of piperacillin/tazobactam, amikacin and fosfomycin for 21 days. Many studies showed that fosfomycin has a synergistic effect with antipseudomonal betalactam. In addition, aminoglycoside can enhance the bactericidal effect of fosfomycin and antipseudomonal betalactam in the treatment of *P. aeruginosa* infections. Antipseudomonal betalactam, aminoglycoside and fosfomycin may be an alternative regimen for the treatment of MDR *P. aeruginosa* infections. (*J Infect Dis Antimicrob Agents* 2004;21:89-91.)

**INTRODUCTION**

*Pseudomonas aeruginosa* is an important pathogen of hospital-acquired infections. The emergence of multidrug-resistant (MDR) *P. aeruginosa* has recently become a major concern worldwide. Outbreaks of MDR *P. aeruginosa* infections in many hospitals have been reported. Evelina and colleagues reported the mortality rate of patients with *P. aeruginosa* infections was 31 percent. The rate was higher among patients with higher APACHE III score (39%) and with MDR *P. aeruginosa* infections (67%). Combination antimicrobial therapy in *P. aeruginosa* bacteremia is associated with four-fold reduction in mortality rate, compared with monotherapy. Antipseudomonal betalactam and aminoglycoside are generally suggested in patients with *P. aeruginosa* infections. Aztreonam can be used as an alternative agent of aminoglycoside in combination with antipseudomonas betalactam in patients with renal failure or contraindication to aminoglycoside. Several studies reveals that fosfomycin has a synergistic effect with antipseudomonal betalactam and aminoglycoside. In addition, aminoglycoside can enhance the bactericidal effect of fosfomycin and antipseudomonal beta-lactam in the treatment of *P. aeruginosa* infections. We present a successful treatment of a probable case of MDR *P. aeruginosa* necrotizing fasciitis...
with a combination of piperacillin/tazobactam, amikacin and fosfomycin.

**CASE REPORT**

A 50-year-old Thai man was admitted to Chonburi Hospital, Chonburi, Thailand due to severe necrotizing fasciitis of his right leg. Three weeks prior to admission, he had a puncture wound at right pretibial area from a fish-tail injury. Two days later, he developed an inflammation with bruising over the injured area, high-grade fever and altered consciousness. He had diabetes mellitus and a history of taking herbal medicine for many years. He was hospitalized at a private hospital in Bangkok. The first diagnosis was cellulitis, septic shock with multiple-organ failure and adrenal insufficiency. Cultures of blood and pus from the wound grew *Aeromonas* spp. The patient received several regimens of antibiotics and surgical debridement for 3 times. After hospitalization for 2 weeks, his clinical condition gradually improved, and was transferred to Chonburi Hospital due to financial problem.

On admission, he had fever and pain at his wound. Physical examination revealed the body temperature of 38.9°C and the infected wound at the right leg. It extended to the muscular layer, and had pululent discharge and necrotic tissue. Complete blood count showed a hematocrit of 30 percent, white blood cell count of 6,950 cells/mm³ (PMN 69%, L 20% and M 9%) and platelet count of 251,000 cells/mm³. Blood and pus cultures were taken. He was empirically treated as necrotizing fasciitis with oral amoxicillin/clavulanate (625 mg 3 times daily). Two days after hospitalization, a surgical debridement with tissue culture was performed, and oral amoxicillin/clavulanate was changed to intravenous amoxicillin/clavulanate (1.2 g every 8 hours) for one day without clinical improvement. The antibiotic was then changed to a combination therapy of intravenous ceftazidime (1 g every 8 hours), amikacin (750 mg once daily). Three days after hospitalization, the pus culture grew *P. aeruginosa* which was resistant to ceftazidime, imipenem/cilastatin, meropenem, amikacin and ciprofloxacin.

The antibiotics were changed to piperacillin/tazobactam (4.5 g every 8 hours), amikacin (750 mg once daily) and fosfomycin (2 g every 12 hours). The pus culture was repeated about one week after hospitalization and still grew MDR *P. aeruginosa*. Surgical debridement was performed for several times. The patient gradually improved after three weeks of treatment when antibiotics were discontinued. He was hospitalized for two months, and discharged after the skin graft was performed. He was seen for the last time two weeks after discharge without clinical relapse.

**DISCUSSION**

This is a probable case of severe necrotizing fasciitis caused by MDR *P. aeruginosa*. The infection is probably nosocomial, and a successful outcome may be due to extensive debridement. MDR *P. aeruginosa* may be a colonizer, even though it was isolated from the wound for two times. Unfortunately, the blood cultures were negative.

Fosfomycin is an antibiotic which has a bactericidal activity through the first-step of cell-wall synthesis inhibition. This unique mechanism of action may provide a synergistic effect to other classes of antibiotics including betalactams, aminoglycosides and fluoroquinolones. A study in mice showed that aminoglycoside can enhance the bactericidal effect of fosfomycin and carbenicillin in the treatment of *P. aeruginosa* infections. Okazaki and colleagues demonstrated the efficacy of fosfomycin when used in combination with other antibiotics for the treatment of MDR *P. aeruginosa* infections by measuring the efficacy time index (ETI). They showed that fosfomycin can improve the therapeutic effect when used with ceftazidime (70%), cefepime (76.7%), meropenem (70.7%), imipenem/cilastatin (73.3%), gentamicin (70%) and levofloxacin (66.7%). Furthermore, an additive effect was observed with a combination treatment of fosfomycin and low-dose aminoglycoside
in a rat model.\textsuperscript{13}

The animal studies showed that fosfomycin has a protective effect against nephrotoxicity of aminoglycoside by inhibiting aminoglycoside-induced histamine release from a mast-cell destruction.\textsuperscript{14} Fosfomycin also increases the oxygen levels in the mitochondria and cyclic-AMP in the mast cells.\textsuperscript{15}

Fosfomycin thus may be another choice for the treatment of MDR \textit{P. aeruginosa} infections especially in combination with other antibiotics due to its unique mechanism of action, and a protective effect against nephrotoxicity induced by aminoglycoside. Randomized clinical studies are needed to evaluate the efficacy of fosfomycin-containing regimens for the treatment of MDR \textit{P. aeruginosa} infections.

\textbf{CONCLUSION}

We present a probable case of necrotizing fasciitis caused by MDR \textit{P. aeruginosa}. The patient was successfully treated with surgical debridement and a combination of piperacillin/tazobactam, amikacin and fosfomycin.

\section*{References}