Case Report

Successful Management of Methicillin-Resistant *Staphylococcus aureus* Bacteremia Unresponsive to Vancomycin by Adding Fosfomycin: A Case Report

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Background: *Vancomycin is the drug of choice for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) bacteremia. However, vancomycin treatment failures are occasionally observed with some strains that are considered susceptible to vancomycin according to Clinical and Laboratory Standards Institute breakpoints (vancomycin minimum inhibitory concentration [MIC] ≤ 2 μg/mL). Although fosfomycin has in vitro activity against MRSA, clinical data regarding the use of fosfomycin either alone or in combination for the management of MRSA bacteremia is limited.*

Case Report: *A 57-year-old woman who was on regular hemodialysis for chronic kidney disease presented with sepsis associated with possible infection of arteriovenous fistula. Blood culture grew MRSA with vancomycin MIC of 1.5 μg/mL. Despite placement of a double-lumen catheter for hemodialysis and treatment with vancomycin and serum concentrations monitoring to keep trough levels of 15 to 20 μg/mL, her blood cultures still continued to grow MRSA for over 10 days. Later, intravenous fosfomycin was added to the regimen along with vancomycin. After three days of this combination, suppression of bacteremia was achieved.*

Conclusion: *Combination of fosfomycin and vancomycin might be another option for the treatment of bacteremia due to MRSA with vancomycin MIC of 1.5 μg/mL that is not responsive to vancomycin alone.*

Keywords: *MRSA, Fosfomycin, Vancomycin, Combination therapy*

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For decades, vancomycin has been the mainstay in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection and bacteremia. According to breakpoints published by Clinical and Laboratory Standards Institute (CLSI), *Staphylococcus aureus* isolates with vancomycin minimum inhibitory concentration (MIC) values of ≤ 2 μg/mL are considered susceptible to vancomycin[1]. However, vancomycin treatment failures have been occasionally observed among patients infected with vancomycin-susceptible strains[2-4] especially when MRSA having vancomycin MICs of ≥ 1.5 to 2 μg/mL[4]. Although fosfomycin has *in vitro* activity against MRSA[5-7], clinical data regarding the use of fosfomycin either alone or in combination for the management of MRSA bacteremia is very limited. The author hereby reported the use of fosfomycin in combination with vancomycin for the treatment of persistent bacteremia due to MRSA having vancomycin MIC of 1.5 μg/mL that was not responsive to an adequate dose of vancomycin. Written informed consent to report this case was already obtained from the patient.

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Case Report

In August 2010, a 57-year-old woman who had been receiving regular hemodialysis three times per week for chronic kidney disease via arteriovenous fistula in her left arm presented to HRH Princess Maha Chakri Sirindhorn Medical Center with fever after a hemodialysis session. On admission, physical examination revealed a temperature of 38.5°C, pulse rate of 100/minute, respiratory rate of 20/minute, and a blood pressure of 100/70 mmHg, with erythema, and tenderness along the arteriovenous fistula without local abscess formation. The leukocyte count was 10.8 x 10^9/L (89% neutrophils), hematocrit 28%,

platelet count 217 x 10^9/L. Infection of arteriovenous fistula was diagnosed and empirical vancomycin was given. The vancomycin dosage was guided by serum concentrations monitoring to achieve trough levels of 15 to 20 μg/mL.

The blood culture subsequently grew MRSA with vancomycin MIC of 1.5 μg/mL as determined by E-test strip. The ultrasonography of her left arm revealed no thrombosis in the arteriovenous fistula and no fluid collection was found in the surrounding soft tissue. No definite vegetation was identified by transesophageal echocardiography. Despite placement of a double-lumen catheter for hemodialysis and treatment with adequate dose of vancomycin, the patient still had fever and her blood cultures continued to grow MRSA repeatedly for over 10 days.

Since the isolate appeared to be susceptible to fosfomycin as determined by disc diffusion method (with zone diameter interpretation provided by Thai Meiji Pharmaceutical Co., Ltd.), intravenous fosfomycin (at a dose of 2 grams every 12 hours for two doses and then tapered to 1 gram every 8 hours) was added to the regimen along with vancomycin. After three days of this combination, suppression of bacteremia was achieved as MRSA was not isolated from blood cultures anymore along with resolution of fever. However, further investigation revealed abdominal aortitis with mycotic aneurysm that was finally managed by surgical intervention. Combination of intravenous fosfomycin and vancomycin was given for six weeks before the surgical placement of an aortic graft was performed. No organism was identified by Gram stain and culture of aortic tissue. The patient tolerated this combination regimen well and no side effects were observed. After the operation, this combination was continued for another week. Fosfomycin dosage was further tapered to 1 gram every 12 hours and vancomycin was later discontinued with the addition of oral rifampicin. The patient received this regimen for six weeks and finally switched to combination of oral fusidic acid and rifampicin for another six months.

Discussion

The author reported a case of vancomycin treatment failure in a hemodialysis-dependent patient who had persistent bacteremia due to an MRSA strain that was considered to be vancomycin-susceptible.

According to the current guideline by the Infectious Disease Society of America (IDSA), an alternative to vancomycin should be used when encountering infections due to MRSA isolates with vancomycin MICs of > 2 μg/mL or treatment failures regardless of MICs[1]. One study even recommended using an alternative to vancomycin for the treatment of bacteremia due to MRSA with vancomycin MICs of ≥ 1.5 μg/mL[4].

In the presented patient, bacteremia due to MRSA with vancomycin MIC of 1.5 μg/mL was unable to be controlled with an adequate dose of vancomycin as determined by serum trough concentrations monitoring for more than 10 days. Although suppression of bacteremia may be achieved with continued vancomycin treatment in some clinically responsive patients infected with MRSA strains having vancomycin MIC < 2 ug/mL[1], persistent MRSA bacteremia at or around day 7 of vancomycin therapy should generally prompt an evaluation for treatment modification[1]. In addition, persistent bacteremia for more than 10 days was defined as vancomycin treatment failure in one study[4]. Therefore, a change in therapy for the presented patient was indicated. The most appropriate choices for this setting would be daptomycin or linezolid[1], however, these agents were unfortunately not readily available at that time. According to the susceptibility result, fosfomycin was considered.

Fosfomycin has *in vitro* activity against MRSA[5-7]; nevertheless, clinical data regarding its use in the treatment of MRSA bacteremia is very limited and it has not been recommended by the current IDSA guideline. Since there was not enough clinical data to support the use of fosfomycin as a single agent, combination with rifampicin was initially considered as suggested by evidence from *in vitro* study[6]. However, intravenous rifampicin was not available and the oral administration was not feasible as the patient was kept nil per os (NPO) at that time due to unstable condition.

Although data from earlier *in vitro* studies suggested that the combinations of fosfomycin and vancomycin for MRSA exhibited mostly indifference and some evidence of antagonism[5,6], a more recent study using MRSA strains with relatively high vancomycin MICs demonstrated that the combinations exhibited synergistic activities with no antagonism[7]. Therefore, a combination of fosfomycin and vancomycin was eventually chosen.

In Thailand, the usual dosage of intravenous fosfomycin recommended for the patients receiving hemodialysis is 500 mg every 12 hours with an additional dose of 1 to 2 grams given after each hemodialysis session since fosfomycin is largely

dialyzed[8,9], while the usual dosage for patients with normal renal function is 2 grams every 12 hours (4 grams per day). However, the dosage can be as high as 16 to 24 grams per day for patients with normal renal function[10]. One study recommended that fosfomycin dosage should not be altered in patients subjected to periodic hemodialysis[9]. To simplify the dosage schedule, the presented patient was given fosfomycin at a dose of 1 gram every 8 hours (after a dose of 2 grams every 12 hours for two doses) without giving additional doses (but deferring some doses to be given after hemodialysis sessions) while receiving hemodialysis three times per week. The patient tolerated well on this dosage schedule of fosfomycin.

In the presented case, suppression of bacteremia was rapidly achieved after the addition of fosfomycin to vancomycin as a combination therapy. Although this might result from delayed effect of vancomycin monotherapy as bacteremia may be eventually suppressed with continued vancomycin therapy in some patients as discussed above, it was not appropriate to continue vancomycin alone to prove this assumption as modification of treatment was indicated. Given the fact that this MRSA isolate was susceptible to fosfomycin, and the dosage schedule was higher than the usual recommendation, the treatment effect observed in the presented case may not have resulted from this combination therapy, but possibly from fosfomycin alone. Nevertheless, as there was not enough clinical data regarding the use of fosfomycin monotherapy for MRSA bacteremia, the author decided to continue vancomycin along with fosfomycin with hope of synergism[7]; however, a synergy test was not performed on this isolate.

Although suppression of bacteremia was achieved, this may not be perceived as successful treatment since aortitis and mycotic aneurysm could not be prevented or treated with this antibiotic combination without surgical intervention. However, there seemed to be microbiological success since the Gram stain and culture of aortic tissue were negative; moreover, there was a delay in the addition of fosfomycin. It was not known whether these complications from MRSA bacteremia could have been prevented or treated more successfully if fosfomycin was initiated earlier in the course of treatment.

Conclusion

The addition of fosfomycin to vancomycin as a combination therapy is safe and well tolerated. This combination could be another option for the treatment of bacteremia due to MRSA with vancomycin MICs of 1.5 μg/mL, and possibly > 1.5 to 2 μg/mL, that is not responsive to vancomycin, especially when other agents such as daptomycin or linezolid are not readily available or not affordable. However, more research should be conducted regarding the use of fosfomycin either alone or in combination with vancomycin for the management of vancomycin treatment failure.

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Potential conflicts of interest

None.

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รายงานผู้ป่วย: การรักษาการติดเชื้อ methicillin-resistant Staphylococcus aureus ในกระแสเลือด ซึ่งไม่ตอบสนองต่อยา vancomycin ประสบผลสำเร็จได้โดยการเพิ่มยา fosfomycin

พัชรสาร ลีนะสมิต

ภูมิหลัง: *ยา vancomycin เป็นยาหลักที่ใช้สำหรับการรักษาการติดเชื้อ methicillin-resistant Staphylococcus aureus (MRSA) อย่างไรก็ตาม การรักษาล้มเหลวสามารถเกิดขึ้นได้ในบางครั้ง แม้ว่าจะเป็นการติดเชื้อ MRSA สายพันธุ์ที่ได้ทดสอบแล้วว่าไวต่อยา vancomycin (ค่า minimum inhibitory concentration [MIC] สำหรับ vancomycin น้อยกว่าหรือเท่ากับ 2 ไมโครกรัมต่อมิลลิลิตร) แม้ว่ายา fosfomycin จะมีฤทธิ์ต่อเชื้อ MRSA ทว่าข้อมูลทางคลินิกเกี่ยวกับการใช้ยานี้เพื่อรักษาการติดเชื้อ MRSA ในกระแสเลือดยังมีอยู่อย่างจำกัด*

รายงานผู้ป่วย: *หญิงอายุ 57 ปี ซึ่งป่วยเป็นโรคไตวายเรื้อรังและต้องทำการฟอกเลือดด้วยเครื่องไตเทียมเป็นประจำ เข้ารับการรักษาในโรงพยาบาลเนื่องจากการติดเชื้อในกระแสเลือดสัมพันธ์กับการติดเชื้อของหลอดเลือดที่ไว้สำหรับการฟอกเลือด ผลการเพาะเชื้อในเลือดพบเชื้อ MRSA ซึ่งมีค่า MIC สำหรับ vancomycin เท่ากับ 1.5 ไมโครกรัมต่อมิลลิลิตร แม้ว่าผู้ป่วยจะทำการฟอกเลือดผ่านสายเส้นใหม่ และได้รับการรักษาด้วยยา vancomycin เป็นเวลานานกว่า 10 วัน โดยมีการปรับระดับยาในเลือดให้ได้ค่าต่ำสุดอยู่ในช่วง 15-20 ไมโครกรัมต่อมิลลิลิตร แล้วก็ตาม เชื้อ MRSA ก็ยังคงเพาะขึ้นได้จากเลือดของผู้ป่วยอยู่ หลังจากนั้นจึงได้มีการเพิ่มยา fosfomycin โดยให้ร่วมไปกับยา vancomycin ซึ่งหลังจากนั้นเพียง 3 วัน เชื้อ MRSA ก็เพาะไม่ขึ้นจากเลือดของผู้ป่วยอีก*

สรุป: *การให้ยา fosfomycin ร่วมกับยา vancomycin อาจใช้เป็นอีกทางเลือกหนึ่ง เพื่อจัดการกับการติดเชื้อ MRSA ในกระแสเลือดซึ่งไม่ตอบสนองต่อการรักษาด้วยการให้ยา vancomycin เพียงขนานเดียว เมื่อ MRSA นั้นมีค่า MIC สำหรับ vancomycin เท่ากับ 1.5 ไมโครกรัมต่อมิลลิลิตร*