EFFICACY OF FUSIDIC ACID ALONE AND IN COMBINATION WITH OTHER ORAL ANTIMICROBIAL AGENTS AGAINST CLINICAL METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* ISOLATES *IN VITRO*

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Abstract. Fusidic acid (FA), an anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotic is recommended for use in combination with other antibiotics to prevent antimicrobial resistance development. However, optimal choice of the partner agent has been poorly studied. The study assessed in vitro activity of FA alone or combined with doxycycline (DOX), ciprofloxacin (CIP), clindamycin (CLI), rifampicin (RIF), and trimethoprim/sulfamethoxazole (TMP/SMX), against clinical MRSA isolates at standard and high inoculums. Minimum inhibitory concentration (MIC) of the six antimicrobial agents against MRSA was determined by a broth microdilution method. The summation of fractional inhibitory concentration (ΣFIC) was used to determine the effects of drug combinations at standard and high inoculums. Sixty-five of 71 (92 %) MRSA isolates were sensitive to FA, RIF and TMP/SMX. Using standard and high inoculums, antagonism was observed in two MRSA isolates for FA+TMP/SMX at standard inoculum and synergism at low frequencies, except for FA+DOX combination at high inoculum. These findings should assist in further studies to determine the appropriate antibiotic combinations for treatment of MRSA infection in Thailand.

Keywords: methicillin-resistant *Staphylococcus aureus*, combination drug inhibition test, fusidic acid

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of deep organ infections, such as osteomyelitis and prosthetic joint infection, which require prolonged antibiotic treatment, and, thus, oral anti-MRSA agents play an important role in reducing long-term intravenous antibiotic treatment (Liu *et al*, 2011; Osmon *et al*, 2013). Currently, relatively few oral agents are available for treatment of MRSA infection, with linezolid being commonly recommended (Liu *et al*, 2011); however, long term use is associated with thrombocytopenia and peripheral neuropathy (irreversible in some cases) (Lee *et al*, 2003; Bressler *et al*, 2004; Choi *et al*, 2019). Linezolid functions as an inhibitor of initiation of bacterial protein synthesis by preventing formation of the initiation complex (Zurenko *et al*, 2001).

Fusidic acid (FA), a steroid antibiotic that inhibits protein synthesis at the elongation step demonstrates potent *in vitro* activity against *S. aureus* including MRSA (Jones *et al*, 2011; Hortiwakul *et al*, 2014). In addition to its high *in vitro* activity, FA does not demonstrate cross-resistance with other antimicrobials (Lowbury *et al*, 1962; Collignon and Turnidge, 1999; Turnidge, 1999; Chen *et al*, 2010). Despite these favorable properties, FA has slow bactericidal/bacteriostatic activity against *S. aureus* (Turnidge, 1999) and emergence of FA resistance during treatment has been documented especially in high inoculum infections (Fantin *et al*, 1993; Craft *et al*, 2011). Thus, FA in combination with other anti-MRSA antibiotics has been suggested to improve its activity and repress emergence of resistance (Whitby, 1999). However, there is a lack of evidence on the most suitable FA combination, but FA plus rifampicin (RIF) is commonly used for oral treatment of bone and joint infections (Aboltins *et al*, 2007). On the other hand, there is the worry that use of RIF could induce selection of RIF-resistant *Mycobacterium tuberculosis* in TB endemic regions (Glaziou *et al*, 2014). Currently, there are limited reports regarding other oral agents for use with FA against both standard and high inoculums of MRSA (Wang *et al*, 2012).

Here, a study was conducted to determine *in vitro* activity of FA alone and in combination with five other oral antimicrobial agents that possess anti-MRSA activity, namely, ciprofloxacin (CIP), clindamycin (CLI), doxycycline (DOX), RIF, and trimethoprim/sulfamethoxazole (TMP/SMX), against MRSA at standard and high inoculums. The result from the study might provide other options for oral treatment of MRSA infection that requires long term antimicrobial therapy.

MATERIALS AND METHODS

Antibiotics source

FA was from Sigma-Aldrich (St Louis, MO); DOX and RIF were from Bio Basic Canada Inc (Ontario, Canada) and CIP, CLI and TMP/SMX were from the Bureau of Drug and Narcotics, Ministry of Public Health, Nonthaburi Province, Thailand.

MRSA isolates source

MRSA isolates were from clinical specimens of hospitalized patients at Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University, Songkhla Province, Thailand obtained between April 2013 and December 2014. Isolates were produced by culturing on mannitol salt agar (OXOID, Hampshire, UK) and *S. aureus* isolates were identified using standard biochemical tests (Church, 2016) methicillin resistance was determined by a cefoxitin disk diffusion method (CLSI, 2014), with *S. aureus* ATCC 29213 used as control strain. The isolates were stored at -80°C until used.

The research protocols were approved by the Ethics Committee, Faculty of Medicine, Prince of Songkla University (no. 57-268-14-1). Prior written consent was waived because *in vitro* research poses no risk to subjects and names were redacted from samples.

MRSA inoculum preparation

MRSA inoculum was prepared in cation-adjusted Mueller-Hinton II broth (CAMHB) (Becton, Dickinson and Co, Sparks, MD) and bacterial suspension visually inspected for turbidity and a direct colony suspension was prepared at 0.5 McFarlan unit ($1.5x10^8$ colony forming unit (CFU)/ml) (CLSI, 2012). Turbidity of the bacterial suspension was adjusted to 10^5 CFU/ml (standard inoculum) and 10^8 CFU/ml (high inoculum).

Determination of minimum inhibitory concentrations (MICs)

MICs of CIP, CLI, DOX, CIP, RIF, and TMP/SMX were determined by a microdilution method in CAMHB (CLSI, 2012) carried out in a 96-well microtiter plate (CLSI, 2014). For standard inoculum, each antimicrobial was tested with a series of two-fold serial dilutions of CIP ranging 0.063-128 μg/ml, CLI 1-2,048 μg/ml, DOX

0.016-32 μg/ml, FA 0.004-8 μg/ml, RIF 0.008-16 μg/ml, and TMP/SMX 0.031/0.594-64/1,216 μg/ml); and for high inoculum, with CIP ranging 0.063-512 μg/ml, CLI 0.016-512 μg/ml, DOX 1-2,048 μg/ml, FA 0.004-8 μg/ml, RIF 2-4,267 μg/ml, and TMP/SMX 0.031/0.594-64/1,216 μg/ml. MIC values for CIP, CLI, DOX, RIF, and TMP/SMX were determined according to CLSI guidelines (CLSI, 2014) while MIC of FA was according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2014). TMP/SMX MIC is reported as that of TMP. *S. aureus* ATCC 29213 was used as control strain. Each experiment was carried out in duplicate.

FA drug combination assay of MRSA

In order to test the effects of FA combined with other antimicrobials on clinical MRSA isolates (n = 12), a checkerboard assay was performed for both standard and high inoculums. The antimicrobial combinations (FA + CIP, FA + CLP, FA + DOX, FA + RIF, and FA + TMP/SMX) were carried out using range of concentrations and conditions as described above. *S. aureus* ATCC 29213 was used as control strain. Then, the summation of fractional inhibitory concentration (ΣFIC) for each antimicrobial pair at standard and high inoculums was calculated as follows: ΣFIC = (MIC of drug A + drug B/MIC of drug A alone) + (MIC of drug B + drug A/MIC of drug B alone). Synergic, additive, and antagonistic effect were defined as ΣFIC = ≤0.5, >0.5-1.0, and ≥4.0, and any other values defined as indifferent, respectively (Hindler and Humphries, 2016).

RESULTS

Clinical MRSA isolates (n = 71) were collected from various sites of infections: from sterile sites [blood (n = 10), body tissue (n = 8) body fluid (n = 2), and cerebrospinal fluid (n=1)] and from non-sterile sites [sputum (n = 28), other non-normally sterile body fluid (n = 15), urine (n = 3), and other sources (n = 4)].

FA, RIF and TMP/SMX were the most active agents against MRSA (>90% susceptibility) followed by DOX (47% susceptibility) (Table 1). MRSA isolates were highly resistant to CLI and CIP (<5% susceptibility). At high inoculum (10^8 CFU/ml), MICs of all antimicrobial agents were markedly increased (Table 2).

Using standard inoculum (10^5 CFU/ml), combination of FA+DOX and FA+RIF showed synergism in 4/12 (33%) and 4/12 (33%) tested isolates, whereas FA+TMP/SMX showed antagonism in only 2/12 (17%) isolates. However, at high inoculum, tests of FA antimicrobial combinations were unable to be performed in 8-42% of the test isolates as MIC values of antimicrobials for some test isolates could not be determined (Table 2); nonetheless,

Table 1

Minimum inhibitory concentration range, 50th and 90th percentiles, percent of susceptible isolates of antimicrobials against methicillin-resistant *Staphylococcus aureus* clinical isolates from Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University, Songkhla Province, Thailand (April 2013 - December 2014)

Antimicrobial	MIC (μg/ml)			Percent of susceptible isolates[a] Number (%) (N = 71)
	MIC50	MIC90	MIC range	
Fusidic acid	0.25	1	0.062-2	65 (92)
Trimethoprim/ sulfamethoxazole	0.062[b]	2[b]	<0.031-16[b]	65 (92)
Rifampicin	<0.008	1	<0.008-16	65 (92)
Doxycycline	8	16	<0.016->32	34 (48)
Ciprofloxacin	64	64	0.125-128	23(32)
Clindamycin	1,024	2,048	<1->2,048	3 (4)

[a]antimicrobial susceptible strains were defined based on their MIC value including ciprofloxacin ≤1 μg/ml, clindamycin ≤0.5 μg/ml, doxycycline ≤4 μg/ml, fusidic acid ≤1 μg/ml, rifampicin ≤1 μg/ml, trimethoprim/sulfamethoxazole ≤2/38 μg/ml

[b]Reported as trimethoprim concentration

MIC: minimum inhibitory concentration; MIC50: 50th percentile MIC; MIC90: 90th percentile MIC; μg/ml: microgram per milliliter

where MIC values were available for both antimicrobials present in the combination, combination of FA with CLI, CIP, TMP/SMX, and DOX showed synergism in 3, 3, 3, and 6 of the 12 tested isolates, respectively (Table 3).

DISCUSSION

Deep-seated infections due to MRSA such as osteomyelitis or prosthetic joint infections require long duration of antibiotic treatment (Aboltins *et al*, 2007). Use of oral anti-MRSA agents after adequate IV antibiotic could reduce patients' hospital length of stay and cost. FA is frequently used in this manner in some countries including Thailand due to the high cost of linezolid and the low prevalence of FA resistance. The susceptibility rate of MRSA to FA

Table 2

Effect of inoculum size on antimicrobial minimum inhibitory concentrations of methicillin-resistant Staphylococcus aureus clinical isolates (n = 12) from Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University, Songkhla Province, Thailand (April 2013 - December 2014)

Antimicrobial	MIC range (μg/ml)	
	10^5 CFU/ml	10^8 CFU/ml
Fusidic acid	0.062-2	0.5-≥8
Trimethoprim/sulfamethoxazole	≤0.031-16*	≥64*
Rifampicin	≤0.008-2	16.7-≥4,267
Doxycycline	≤0.016-16	128-≥2,048
Ciprofloxacin	0.125-128	64-≥512
Clindamycin	0.031-≥512	0.5-≥512

*Reported as trimethoprim concentration

CFU: colony forming unit; MIC: minimum inhibitory concentration; ml: milliliter; μg/ml: microgram per milliliter

is approximately 97-100% based on several reports from 2013 to 2019 in different region of Thailand (Wongsuk and Nutalai, 2015; Chatreewattanakul *et al*, 2015; Bunnueang *et al*, 2016; Division of Microbiology, 2020). In the current study, clinical MRSA isolates were still highly susceptible (>90%) to FA, RIF and TMP/SMX, although *in vitro* activity of these three antibiotics was reduced in the high inoculum experiments. Efficacy of other oral anti-staphylococcal drugs was limited: <5% of MRSA strains were susceptible to CIP and CLI and only 50% were susceptible to DOX. The results would indicate precluding use of these latter agents in monotherapy to treat MRSA infection as well as the former set in situations of high inoculum. Additionally, emerging resistance of bacterial subpopulations is a concern for FA monotherapy (Okusanya *et al*, 2011). Earlier, Chang *et al* (2000) demonstrated oral FA monotherapy results in FA resistance in 33% of previously FA susceptible strains.

In vitro assays of clinical MRSA isolates at standard inoculum to FA combinations, we observed synergisms

Table 3

Effects of fusidic acid antimicrobial combinations against standard and high inoculums of methicillin-resistant Staphylococcus aureus clinical isolates from Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University, Songkhla Province, Thailand (April 2013 - December 2014)

Antimicrobial combination	Standard inoculum (105 CFU/ml) Number of isolates (%), out of 12 isolates (range of ΣFIC)				High inoculum (108 CFU/ml) Number of isolates (%), out of 12 isolates (range of ΣFIC)				
	Synergistic[a]	Additive[b]	Antagonistic[c]	Indifferent[d]	Synergistic[a]	Additive[b]	Antagonistic[c]	Indifferent[d]	ND
FA + CLI	2 (17) (0.37-0.5)	5 (42) (0.59-0.75)	0 (0) -	5 (42) (1.01-2.67)	3 (25) (0.26-0.5)	3 (25) (0.75-1.0)	0 (0) (-)	5 (42) (3.0-3.0)	1 (8) (-)
FA + CIP	1 (8) (0.49)	3 (25) (0.52-1.0)	0 (0) (-)	8 (67) (1.02-2.67)	3 (25) (0.25-0.5)	2 (17) (0.63-0.75)	0 (0) (-)	2 (17) (1.02-1.13)	5 (42) (-)
FA + TMP/SMX	2 (17) (0.46-0.49)	4 (33) (0.57-0.96)	2 (17) (4.33-17.67)	4 (33) (1.02-1.03)	3 (25) (0.13-0.5)	2 (17) (0.51-1.0)	0 (0) (-)	3 (25) (1.01-2)	4 (33) (-)
FA + RIF	4 (33) (0.25-0.5)	7 (58) (0.55-0.92)	0 (0) (-)	1 (8) (1.25)	1 (8) (0.5)	3 (25) (0.52-0.75)	0 (0) (-)	5 (42) (1.01-1.50)	3 (25) (-)
FA + DOX	4 (33) (0.02-0.36)	6 (50) (0.52-0.96)	0 (0) (-)	2 (17) (1.07-3.17)	6 (50) (0.04-0.26)	2 (17) (0.51-0.56)	0 (0) (-)	4 (33) (1.01-1.01)	0 (0) (-)

[a]ΣFIC of ≤0.5; [b]ΣFIC of >0.5 - 1.0; [c]ΣFIC of ≥4.0; [d]ΣFIC of any other values

ΣFIC: the summation of fractional inhibitory concentration for each antimicrobial pair which was calculated as (MIC of drug A + drug B)/(MIC of drug A alone) + (MIC of drug B + drug A)/(MIC of drug B alone)

CFU: colony forming unit; CIP: ciprofloxacin; CLI: clindamycin; DOX: doxycycline; FA: fusidic acid; MIC: minimum inhibitory concentration; ml: milliliter; ND: not able to determine; RIF: rifampicin; TMP/SMX: trimethoprim/sulfamethoxazole

of FA with DOX and with RIF, and antagonism with TMP/SMX in only a minority of isolates. At high inoculum, although combination assays for 8-42% of isolates could not be performed as MIC values were not measurable for one or both of the antimicrobials, synergisms were observed in a minority of isolates for all FA combinations. It is worth noting that synergism of FA with DOX was obtained with 50% of isolates. Antagonism was observed in two MRSA isolates for FA+TMP/SMX at standard inoculum. Thus, all five FA combinations could be used at both standard and high inoculums, although at standard inoculum there was a small possibility of antagonism in combination of FA with TMP/SMX.

Biedenbach *et al* (2010) reported synergistic or additive effects for FA + RIF combination in all MRSA isolates tested. Although FA and DOX act by inhibiting protein synthesis, FA acts at 50S and DOX at 30S ribosome (Biedenbach *et al*, 2010), thereby explaining the absence of antagonism. Beppler *et al* (2017) reported combinations of inhibitors of protein and DNA synthesis result in antagonistic interactions, providing an explanation for the antagonism of FA + TMP/SMX combination as each of the latter two antibiotics inhibit different enzymes involved in folic acid metabolism required for DNA synthesis (MacDougall, 2018).

This study has several limitations. Firstly, the number of MRSA isolates studied was low. Secondly, findings should be applied with caution in clinical situations since *in vitro* study might not predict or correlate with clinical outcome. Thirdly, all clinical MRSA isolates were from one hospital and confirmation from other hospitals in the country is required. Fourthly, genetic confirmation of antibiotic resistance of MRSA isolates was not performed. And fifthly, although prevalence of community-acquired (CA)-MRSA infections is <3% (Jenkins and Schuetz, 2012; Wongsuk and Nutalai, 2015), the findings might not be applicable to CA-MRSA isolates. Mekviwattanawong *et al* (2006) reported <5% of *S. aureus* isolated from patients with community onset sepsis are resistant to oxacillin.

In summary, the study shows clinical MRSA isolates (collected from 2013 to 2014) were still susceptibility to fusidic acid. No antagonisms were observed for fusidic acid combinations with four other antimicrobials, namely, ciprofloxacin, clindamycin, doxycycline, and rifampicin. Synergism in drug combinations were observed at low frequencies, except for fusidic acid/doxycycline combination at high inoculum. Further clinical investigations of fusidic/doxycycline for bone and joint MRSA infections appear warranted.

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CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

Aboltins CA, Page MA, Buising KL, *et al*. Treatment of staphylococcal prosthetic joint infections with debridement, prosthesis retention and oral rifampicin and fusidic acid. *Clin Microbiol Infect* 2007; 13: 586-91.

Beppler C, Tekin E, White C, *et al*. When more is less: emergent suppressive interactions in three-drug combinations. *BMC Microbiol* 2017; 17: 107.

Biedenbach DJ, Rhomberg PR, Mendes RE, Jones RN. Spectrum of activity, mutation rates, synergistic interactions, and the effects of pH and serum proteins for fusidic acid (CEM-102). *Diagn Microbiol Infect Dis* 2010; 66: 301-7.

Bressler AM, Zimmer SM, Gilmore JL, Somani J. Peripheral neuropathy associated with prolonged use of linezolid. *Lancet Infect Dis* 2004; 4: 528-31.

Bunnueang N, Kongpheng S, Yadrak P, Rattanachuay P, Khianngam S, Sukhumungoon P. Methicillin-resistant *Staphylococcus aureus*: 1-year collection and characterization from patients in two tertiary hospitals, southern Thailand. *Southeast Asian J Trop Med Public Health* 2016; 47: 234-44.

Chang SC, Hsieh SM, Chen ML, Sheng WH, Chen YC. Oral fusidic acid fails to eradicate methicillin-resistant *Staphylococcus aureus* colonization and results in emergence of fusidic acid-resistant strains. *Diagn Microbiol Infect Dis* 2000; 36: 131-6.

Chatreewattanakul T, Thunyaharn S, Samosornsuk W, Visawapoka U, Samosornsuk S. SCC mec type and antimicrobial susceptibility pattern of MRSA isolated from blood stream infection in Phramongkutklao Hospital. *J Med Tech Phy Ther* 2015; 27: 152-61. [in Thai]

Chen Y, Koripella RK, Sanyal S, Selmer M. *Staphylococcus aureus* elongation factor G-structure and analysis of a target for fusidic acid. *FEBS J* 2010; 277: 3789-803.

Choi GW, Lee JY, Chang MJ, *et al*. Risk factors for linezolid-induced thrombocytopenia in patients without haemato-oncologic diseases. *Basic Clin Pharmacol Toxicol* 2019; 124: 228-34.

Church DL. Identification of Gram-positive bacteria. In: Leber A, editor. Clinical Microbiology Procedures Handbook. 4th ed. Washington, DC: ASM Press; 2016.

Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests f or Bacteria That Grow Aerobically; Approved Standard-Ninth Edition. CLSI document M07-A9. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.

Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility testing; Twenty-Fourth Informational Supplement. CLSI document M100-S24. Wayne, PA: Clinical and Laboratory Standards Institute; 2014. Collignon P, Turnidge J. Fusidic acid *in vitro* activity. *Int J Antimicrob Agents* 1999; 12 (Suppl 2): S45-58.

Craft JC, Moriarty SR, Clark K, *et al*. A randomized, double-blind phase 2 study comparing the efficacy and safety of an oral fusidic acid loading-dose regimen to oral linezolid for the treatment of acute bacterial skin and skin structure infections. *Clin Infect Dis* 2011; 52 (Suppl 7): S520-6.

Division of Microbiology. Percentage of susceptible bacteria, Songklanagarind Hospital Jan - Dec 2019, 2020 [cited 2022 Feb 14]. Available from: URL: http://www.pathology.psu.ac.th/images/PathoDoc/PathoDoc/MicroDrugSense/MicroDrugSense20191.png

Fantin B, Leclercq R, Duval J, Carbon C. Fusidic acid alone or in combination with vancomycin for therapy of experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1993; 37: 2466-9.

Glaziou P, Sismanidis C, Floyd K, Raviglione M. Global epidemiology of tuberculosis. *Cold Spring Harb Perspect Med* 2014; 5: a017798.

Hindler JA, Humphries RA. Synergism testing: broth microdilution checkerboard and broth macrodilution methods. In: Leber A, editor. Clinical Microbiology Procedures Handbook. 4th ed. Washington, DC: ASM Press; 2016.

Hortiwakul T, Siripaitoon P, Ingviriya N. In vitro activities of vancomycin, fosfomycin, fusidic acid and linezolid against methicillin-resistant *Staphylococcus aureus*, Year 2011-2012. *Songkla Med J* 2014; 32: 231-6.

Jenkins SG, Schuetz AN. Current concepts in laboratory testing to guide antimicrobial therapy. *Mayo Clin Proc* 2012; 87: 290-308.

Jones RN, Mendes RE, Sader HS, Castanheira M. *In vitro* antimicrobial findings for fusidic acid tested against contemporary (2008-2009) Gram-positive organisms collected in the United States. *Clin Infect Dis* 2011; 52 (Suppl 7): S477-86.

Lee E, Burger S, Shah J, *et al*. Linezolid-associated toxic optic neuropathy: a report of 2 cases. *Clin Infect Dis* 2003; 37: 1389-91.

Liu C, Bayer A, Cosgrove SE, *et al*. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011; 52: e18-55.

Lowbury EJ, Jackson DM, Cason JS, Miller RW. Fucidin for staphylococcal infection of burns. *Lancet* 1962; 2: 478-80.

MacDougall C. Sulfonamides, trimethoprim-sulfamethoxazole, quinolones, and agents for urinary tract infections. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw-Hill Education; 2018.

Mekviwattanawong S, Srifuengfung S, Chokepaibulkit K, Lohsiriwat D, Thamlikitkul V. Epidemiology of *Staphylococcus aureus* infections and the prevalence of infection caused by community-acquired methicillin-resistant *Staphylococcus aureus* in hospitalized patients at Siriraj Hospital. *J Med Assoc Thai* 2006; 89 (Suppl 5): S106-17.

Okusanya OO, Tsuji BT, Bulitta JB, *et al*. Evaluation of the pharmacokinetics-pharmacodynamics of fusidic acid against *Staphylococcus aureus* and *Streptococcus pyogenes* using *in vitro* infection models: implications for dose selection. *Diagn Microbiol Infect Dis* 2011; 70: 101-11.

Osmon DR, Berbari EF, Berendt AR, *et al*. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2013; 56: e1-25.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters, Version 4.0, 2014 [cited 2022 Feb 14]. Available from: URL: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_4.0.xls

Turnidge J. Fusidic acid pharmacology, pharmacokinetics and pharmacodynamics. *Int J Antimicrob Agents* 1999; 12 (Suppl 2): S23-34.

Wang JL, Tang HJ, Hsieh PH, *et al*. Fusidic acid for the treatment of bone and joint infections caused by meticillin-resistant *Staphylococcus aureus*. *Int J Antimicrob Agents* 2012; 40: 103-7.

Whitby M. Fusidic acid in the treatment of methicillin-resistant *Staphylococcus aureus*. *Int J Antimicrob Agents* 1999; 12 (Suppl 2): S67-71.

Wongsuk T, Nutalai D. Susceptibility testing of vancomycin, daptomycin and linezolid against methicillin-resistant *Staphylococcus aureus*. *J Med Health Sci* 2015; 22: 25-33. [in Thai]

Zurenko GE, Gibson JK, Shinabarger DL, Aristoff PA, Ford CW, Tarpley WG. Oxazolidinones: a new class of antibacterials. *Curr Opin Pharmacol* 2001; 1: 470-6.