The Susceptibility Pattern of *Staphylococcus Aureus* and *Streptococcus Pyogenes* to Fusidic Acid and Mupirocin in Superficial Pyoderma

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Abstract: The most common causes of superficial pyoderma are *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pyogenes* (*S. pyogenes*). Currently, many regions have reported of *S. aureus* and *S. pyogenes* resistance to fusidic acid and mupirocin, whereas there are regions that still susceptible. Antibiotic resistance is a health issues in many countries, which increase the morbidity and mortality. The susceptibility test is one of methods to determine the resistance problems. About 27 and 12 of *S. aureus* and *S. pyogenes* isolates, consecutively, were collected from 44 specimen samples of superficial pyoderma patients. All isolates were subjected to susceptibility test to fusidic acid and mupirocin using broth microdilution methods. This study showed differences between *S. aureus* to fusidic acid versus mupirocin, whereas *S. aureus* 8 times more susceptible to fusidic acid than mupirocin significantly (PR = 8.312; $p = 0.001$); *S. pyogenes* is more susceptible to fusidic acid than mupirocin significantly ($p = 0.000$). This study has been show *Staphylococcus aureus* and *S. pyogenes* are more susceptible to fusidic acid than mupirocin

1 INTRODUCTION

Superficial pyoderma is a bacterial skin infection that affects the epidermis, beneath the stratum corneum and hair follicles (Nirwati,2013). Approximately 30% of superficial pyoderma in developing countries occurs at below 15 years old (Depari, 2016). The 14 meta analysis collected by World Health Organization (WHO), reported that in tropical countries superficial pyoderma primarily caused by *Staphylococcus aureus (S. aureus)* and *Streptococcus pyogenes (S. pyogenes),* whereas in developing countries is *S. aureus* (Depari, 2016). Inadequate superficial pyoderma therapy may lead to complications either extending to the layer beneath the epidermis or other organs, therefore requiring immediate empirical therapy (Milet, 2012). Empirical therapy can trigger antibiotic resistant of bacterial strains and treatment failure, especially when used irrationally. The widespread use of topical antibiotics is one of the causes of antibiotic resistance (Poovelikunnel, 2015) (Antonov,2015)

Currently various studies have reported resistance of *S. aureus* and *S. pyogenes* both to fusidic acid and mupirocin in various regions, but there are still regions where *S. aureus* and *S. pyogenes* are susceptible to both agent (Koning,2012) The objective of this study is to determine the susceptibility of *S. aureus* and *S. pyogenes* to fusidic acid and mupirocin in Dermatology and Venereology Policlinic of Dr. Mohammad Hoesin General Hospital Palembang and analyzed the differences between *S. aureus* and *S. pyogenes* susceptibility to fusidic acid and mupirocin

2 METHODS

This is an observational analytical laboratory study with cross sectional design conducted from July to October 2017 at Dermatologic Infection Division, DV Department, Clinical Pathology and Microbiology Department of Dr. Mohammad Hoesin

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General Hospital Palembang, and Health laboratory for Palembang. The 44 study samples that fullfiled the inclusion criteria, then were subjected to culture examination and identified. Each *S. aureus* and *S. pyogenes* isolates that grow later were subjected to susceptibility test using broth microdilution methods.

3 RESULTS

The study samples included in this study from < 1 to15 years old, majority of the subjects (59.1%) were in the 1-5 years old group, with same ratio of male and female (1:1). The majority of the subjects (36.4%) of this study was in the middle socioeconomic level and poor environmental conditions (27.4%). The sample of this study mostly normoweight (70.5%). A total of 30 subjects (68.2%) using antibiotics where as 11 subjects using appropriate antibiotics questioned by researchers i.e amoxicillin, chloramphenicol, and gentamicin. Based on clinical manifestation, the majority of diagnosis found in the study sample was vesicobullous impetigo (38.6%) (**Table 1**).

Table 1. Sosiodemografic characteristic of sample

Characteristic	N	%
Age (years old), mean ± SD	5,02±3,65	
Age		
• < 1 years old	3	6,8
• 1 - 5 years old	26	59,1
• 6 - 10 years old	11	25,0
• 10 – 15 years old	4	9,1
Sex, n (%)		
• Male	22	50
• Female	22	50
Sosioeconomic Condition		
• Low	13	29,5
• Middle	16	36,4
• High	12	27,3
• Very high	3	6,8
Environment		
• Good	27	61,4
• Poor	17	38,6
Body Mass Index		
• *Underweight*	10	22,7
• *Normoweight*	31	70,5
• *Overweight*	3	6,8

Among 44 specimens obtained from 44 subjects, 48 isolates were found in culture, 4 of which were mixed. The most bacteria found were *S. aureus*, 27 isolates (61,3%) and *S. pyogenes* 12 isolates (27,2%).

The susceptibility test for fusidic acid, found that 77.8% of *S. aureus* isolates and all *S. pyogenes* isolates (100%) were susceptible to fusidic acid (**Table 2**). While, susceptibility test result for mupirocin showed that 29.6% isolates of *S. aureus* susceptible to mupirocin and only 8.3% of *S. pyogenes* isolates were susceptible to mupirocin (**Table 2**). There was a difference between *S. aureus* susceptibility to fusidic acid and mupirocin, with *S. aureus* 8 times more susceptible to fusidic acid than mupirocin significantly (**Table 3**). In addition, *S. pyogenes* are more susceptible to fusidic acid than mupirocin significantly (**Table 4**).

Table 2. Susceptibility of *S. aureus* dan *S. pyogenes* to fusidic acid and mupirocin

Antibiotic	*S. aureus*		*S. pyogenes*	
	Susceptible	Resistant	Susceptible	Resistant
Fusidic acid	21 (77,8)	6 (22,2)	12 (100)	0 (0)
Mupirocin	8 (29,6)	19 (70,4)	1 (8,3)	11 (91,7)

Table 3. Comparasion of *S. aureus* susceptibility between fusidic acid to mupirocin

Characteristic	Susceptibility of *S. aureus*		Total	PR* (CI 95%)	*p value**
	Susceptible	Resistant			
Antibiotic					
Fusidic acid	21	6	27	8,312	0,001
Mupirocin	8	19	27	(2,437-28,354)	
Total	29	25	54		

**chi-square* test

Table 4. Comparasion of *S. pyogenes* susceptibility between fusidic acid to mupirocin

Chracteristic	Susceptibility of *S. pyogenes*		Total	PR* (CI 95%)	*p value**
	Susceptible	Resistant			
Antibiotic					
Fusidic acid	12	0	12		0,000
Mupirocin	1	11	12	-	
Total	13	11	24		

* *Fisher's* exact test

4 DISCUSSION

The incidence of superficial pyoderma is influenced by host factors (immune status and skin barrier state), environment and agent (Nirwati,2013) (Milet, 2012). Predisposing factors are associated with superficial pyoderma, including age, sex, socioeconomic status, environmental condition, and nutritional status of the patient **(**Depari,2016) (Karimkhani,2014)

The results of this study indicate that *S. aureus* and *S. pyogenes* are still sensitive to fusidic acid and have good in vitro effectiveness. Low susceptibility of *S. aureus* and *S. pyogenes* to mupirocin in this study, suggesting in vitro resistance of *S. aureus* and *S. pyogenes* to mupirocin. Susceptibility patterns are influenced by factors including geographic factors (environmental contamination, population density, and population migration), socioeconomic, prevalence of MRSA or antibiotic resistant bacteria, and antibiotic usage[7,12]. Antonov et al., Found a strong association between mupirocin resistance and some factors were: history of mupirocin use (19.2% - 26.5%, p <0.001), MRSA isolates (55.4%, p <0.001), and history of other topical and systemic antibiotics (OR 3.6, p <0.006) (Antonov, 2015)

Mupirocin resistance is caused by point mutations in the *ileS* gene, as well as the transmission of MupA or MupB genes via plasmid-mediated intergene bacteria to form gene modification *ileS.* This modification gene is the form of "eukaryotic-like" genes RNA synthetase that has no affinity for mupirocin[6]. MupA genes are also known to be present in plasmids bacteria that are resistant to some other antibiotics that may cause cross resistance with other antibiotics via a plasmid conjugation mechanism. **(**Poovelikunnel, 2015) (Cadilla, 2011)

High resistance of *S. aureus* and *S. pyogenes* isolates to mupirocin versus fusidic acid in this study may be due to antibiotic usage (Poovelikunnel,2015) (Cadilla, 2011)The use of antibiotics with chemical structures resembling mupirocin is known to cause horizontal transfer between bacterial carriers of resistant genes against the antibiotic. Candilla et al., found that the MupA gene was strongly associated with MDR (p <0.0001), 23% among 837 antibiotic-resistant samples of the β-lactam and non-β-lactam groups were MupA carriers. In addition mupirocin-

resistant bacteria had a 9-fold (OR 9.83%) risk for resistance to at least 4 β-lactam and non-β-lactam antibiotics (erythromycin, tetracycline, chloramphenicol, gentamicin, ofloxacin, or trimethoprim-sulfamethoxazole). (Cadilla, 2013)

Fusidic acid has a unique and very different chemical structure. The carbon chains in the chemical structure of fusidic acid are similar to steroids than antibiotics so rarely cause cross-resistance[10]. The *in vitro* efficacy of antibiotics is more significant if proven to be *in vivo*. In vitro sensitivity is not entirely predictable for *in vivo* effect. In addition, *in vitro* resistance is common, but not necessarily related to treatment failure (McNeil,2014)

5 CONCLUSION

The results of this study showed that there has been *in vitro* resistance of *S. aureus* and *S. pyogenes* to mupirocin. In addition, *S. aureus* and *S. pyogenes* are more susceptible to fusidic acid than mupirocin. *In vitro* effectivity of fusidic acid was better than mupirocin. The emergence of resistance in this study is influenced by various factors, especially the use of antibiotics that causes cross resistance between bacterial carrier resistant genes.

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