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Original Article

Efficacy of 5% permethrin-2% fusidic acid cream compared to 5% permethrin-placebo in the treatment of impetiginized scabies

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Abstract

Introduction: Scabies is caused by *Sarcoptes scabiei* var *hominis*, often causing secondary bacterial infections, especially by *Streptococcus pyogenes* and *Staphylococcus aureus*. Permethrin 5% cream is the first-line of treatment that is recommended, combined with Fusidic acid 2% cream as the first-line topical antibiotic. We investigated the efficacy of a combination of permethrin 5% cream and fusidic acid 2% cream for the treatment of impetiginized scabies.

Methodology: A double-blind, randomized clinical trial was organized at two Islamic boarding schools in Bogor, West Java, Indonesia. Forty subjects were randomly allocated into the intervention group (permethrin 5% and fusidic acid 2%; n = 20), and the control group (permethrin 5% and placebo; n = 20). Treatment efficacy was determined through the visual analogue scale (VAS) for pruritus and pain, and by examining bacterial cultures.

Results: Treatment efficacy in the intervention group was higher than in the control group on day 7 (80% vs. 35%) and day 14 (95% vs 35%, $p \leq 0.001$, RR 2.714) with decreasing VAS for pruritus ($p = 0.04$) and pain ($p = 0.035$). The most common bacterium was *Staphylococcus aureus*. Some minor adverse effects such as itch and heat occurred temporarily.

Conclusions: Treating impetiginized scabies with permethrin 5% and fusidic acid 2% cream is more effective than treating with only 5% premethrin. The most common bacterium causing secondary infection in impetiginized scabies is *Staphylococcus aureus*.

Key words: impetiginized scabies; fusidic acid; permetherin; visual analogue scale; efficacy; *Staphylococcus aureus*.

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Introduction

Scabies is a communicable skin disease caused by *Sarcoptes scabiei* var *hominis* infection [1]. It is endemic to tropical and sub-tropical regions [2], including Africa, South America, the Caribbeans, Central and South Australia and Asia [3,4]. The Global Burden of Disease 2010 report estimated that globally, scabies affects around 100 million people [5]. The global prevalence of scabies ranges from 0.2% to 71.4%. Data from Cipto Mangunkusumo General Hospital (RSCM), a tertiary referral hospital in Jakarta, Indonesia, show that 768 outpatients and 54 inpatients were diagnosed with scabies from January 2012 to October 2017 [unpublished data]. Scabies is more commonly found in children compared to teenagers and adults [6].

The signs and symptoms of scabies include nocturnal pruritus, pathognomonic skin lesions, itching found in several people in a communal dwelling, and microscopic finding of the parasite. Skin lesions appear with a predilection towards areas between the fingers, the flexor surface of wrists, elbows, genitals, axilla, periumbilical area, nipples, bottoms, and penile shafts [7].

Patients with scabies experience great discomfort due to intense itch, causing scratching that may lead to secondary infections, especially by *Streptococcus pyogenes* and *Staphylococcus aureus* [8]. *Staphylococcus aureus* is part of the skin's normal microbiota and generally does not cause disease in normal skin but can be pathogenic in certain conditions [9]. Host factors that influence staphylococcal infections pathogenesis include immunocompromised status, long-term use of corticosteroids, and atopic dermatitis. Trauma and inflammation (post-surgery wounds, burns, traumatic wounds, dermatitis), insect bites, and poor hygiene also play important roles in susceptibility to infection [10]. Many *Streptococcus* species are part of the skin's normal flora and colonize the upper respiratory tract as commensals. Colonization of *S. pyogenes* is rare but can be found in impetigo-endemic regions [11]. Impetiginized scabies can

progress to cellulitis, rheumatic fever, glomerulonephritis, and even sepsis [12]. Complications due to secondary infections by *S. pyogenes* and *S. aureus* are often found in children in developing countries [8,13]. Prevalence of impetiginized scabies varies by regions; the Solomon Islands reported a prevalence of 41.1% [14], a dermatovenereology outpatient clinic in a hospital in Bandung, Indonesia reported 7% of outpatients were diagnosed with impetiginized scabies [15], and Sungkar *et al*. [16] described 26% of their study subjects in an Islamic boarding school (pesantren) in Jakarta had impetiginized scabies.

The main therapy for scabies is scabicidal topical preparations, such as permethrin 5% cream, 1% lindane lotion/cream, 10% and 20% benzyl benzoate emulsion/lotion, and 2-10% sulfur precipitate ointment. Permethrin cream is considered the first-line agent in scabies treatment [17]. The *Sarcoptes scabiei* mite produces Scabies Mite Inactivated Protease Paralogues (SMIPPs) and Serpins (SMSs, Scabies mite serine protease inhibitors) which inhibit complement activation and promotes bacterial growth in vitro, preventing complement-mediated mite eradication [18]. This parasite protective mechanism indicates a need for antibiotics in the management of impetiginized scabies. Antibiotic therapy can be given topically or systemically, depending on the severity of the disease [19].

Mass scabies treatment in boarding schools can decrease scabies cases by up to 56% [20]. Romani *et al*. reported a 54% decrease in cases after mass administration of permethrin 5% cream [21]. Several studies investigated the efficacy of giving a combination of topical permethrin cream and oral antibiotics [21,22] but to date, no studies have compared the efficacy of prescribing permethrin 5% cream in combination with topical antibiotics. This study investigates the efficacy of giving permethrin 5% cream with fusidic acid 2% compared to permethrin 5% cream with a placebo cream as a combination treatment for impetiginized scabies.

Methodology

Study design

We performed a double-blind clinical trial in two Islamic boarding schools in Bogor, West Java, Indonesia (Pondok Pesantren Al-Islami and Pondok Pesantren Gaza Al-Islami), from September 2018 to March 2020. We calculated a minimum sample size of 46 subjects (with a 10% predicted drop-out rate) using the two proportions hypothesis test. This trial was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

Inclusion and exclusion criteria

We included students who consented to enrolment in the trial and provided signed informed consent forms from their legal guardians. Subjects had lived in the school campus for at least four weeks, were diagnosed with scabies, and presented with pustules, pus, purulent bullae, and yellow-brown crusts. Students with fever, enlarged lymph nodes, individuals who had received topical or systemic antibiotics in the last 24-72 hours before examination, subjects with positive history of hypersensitivity to permethrin 5% or fusidic acid 2%, positive history of atopic dermatitis, diabetes mellitus, HIV/AIDS, chronic renal failure, long-term systemic drug use, and students who were lost to follow-up were excluded. This ensured that the subjects were treated only with topical antibiotics, and the results were not complicated by other factors.

Treatment protocol

Students who fit our inclusion and exclusion criteria signed informed consent forms and obtained consent from their guardians. Subjects were randomized to two groups: intervention (permethrin 5% cream and fusidic acid 2% cream) or control (permethrin 5% cream and placebo). Randomization was performed by the research assistant using a randomization table; investigators and subjects were blinded.

Patient history was recorded, and physical examination, skin scraping, and Gram-staining of pus were performed. The treatment was administered by research assistants. A glycerol-based cream (Biocream®, Merck, Indonesia) was used as placebo. In addition to treatment interventions, all subjects were given 0.9% NaCl compresses and sterile gauze. Follow-up visits were done on days 7 and 14.

Evaluation

Clinical resolution of the disease was assessed by subjective and objective complaints. Subjective complaints were assessed using visual analogue scale (VAS) for pain and pruritus. Objective complaints were assessed clinically, by observing new scabies lesions and resolution of impetigo lesions or the presence of residual macule or fibrotic tissue on day 7 and day 14. If any discrepancies were found between subjective and objective complaints, the worse criteria were assumed. Adverse events were assessed subjectively (pruritus, stinging sensation, heat, headache, paresthesia) and objectively (presence of contact dermatitis or irritation).

Table 1. Characteristics of study subjects.

Characteristics	Intervention (n = 20)	Placebo (n = 20)	*p*
Age (years), median (min-max)	14 (13-17)	14 (13-17)	1.000
Gender, n (%)			
Male	13 (65.0)	13 (65.0)	1.000^
Female	7 (35.0)	7 (35.0)	
Shower frequency, n (%)			
Once a day	0 (0.0)	2 (10.0)	**< 0.001**
Twice a day	20 (100.0)	8 (40.0)	
> Twice a day	0 (0.0)	10 (50.0)	
Soap usage, n (%)			
Yes	20 (100.0)	19 (95.0)	1.000*
No	0 (0.0)	1 (5.0)	
Type of soap used, n (%)			
Antiseptic soap	20 (100.0)	20 (100.0)	-
Moisturizing soap	0 (0.0)	0 (0.0)	
Nail condition, n (%)			
Dirty	17 (85.0)	16 (80.0)	1.000*
Clean	3 (15.0)	4 (20.0)	
Body mass index (BMI), n (%)			
Malnourished	7 (35.0)	9 (45.0)	0.24**
Normal	12 (60.0)	11 (55.0)	
Overweight	1 (5.0)	0 (0.0)	

Mann-Whitney test; ^ Chi Square test; * Fisher Exact test, ** Kolmogorov-Smirnov test.

Table 2. Efficacy of combination Fusidic acid 2% and permethrin 5% on impetiginized scabies, VAS and side effect after treatment.

Criteria	Intervention (n = 20)	Placebo (n = 20)	*p*	RR (CI 95%)
Cured in Day 7				
Yes	16 (80.0)	7 (35.0)	**< 0.001***	**2.286 (1.210-4.318)**
No	4 (20.0)	13 (65.0)		
Cured in Day 14				
Yes	19 (95.0)	7 (35.0)	**< 0.001***	**2.714 (1.481-4.974)**
No	1 (5.0)	13 (65.0)		
VAS Pruritus				
Day 0	6 (2-9)+	5 (3-8)+	0.529**	-
Day 14	1 (0-6)+	3 (0-6)+	0.076**	-
Delta VAS	-4 (-9~1)+	-3 (-7~3)+	**0.040****	-
VAS Pain				
Day 0	3 (2-4)+	3 (2-4)+	0.758**	-
Day 14	0 (0-3)+	0 (0-4)+	**0.018****	-
Delta VAS	-2 (-4~0)+	-1 (-4~ -2)+	**0.035****	-
Adverse effects				
Yes	4 (20.0)	0 (0.0)	0.106*	
No	16 (80.0)	20 (100.0)		
Subjective complaints (n = 4)				
Heat	3 (75.0)	0	N/A	
Pruritus	1 (25.0)	0		

* Fisher Exact test; ** Mann-Whitney test; + Median (minimum-maximum).

Statistical analysis

Analysis was done per protocol using SPSS version 22.0. A significance level of 5% was used, *p* was considered significant at < 0.05 level.

Results

Scabies prevalence in Pondok Pesantren Al Islami was 36.7% (187 out of 509 subjects), 12.3% (23 out of 187 subjects) of whom were diagnosed with impetiginized scabies. In the other school, Pondok Pesantren Gaza Al-Islami, scabies was found in 29.7% (66 out of 222) subjects, 28.8% (19 out of 66) of whom were impetiginized. Of all the students who had scabies, 16.6% (42 out of 253) were diagnosed with impetiginized scabies, met our inclusion criteria, and were included in the study. Students who did not provide consent or dropped out received treatment but were excluded from the analysis. Subjects were randomized using a randomization table: 20 subjects in the intervention group and 20 subjects in the placebo group (control).

No significant differences were observed in mean age and sex distribution in the two groups (Table 1). However, there was significant difference in the number of showers taken, where 50% of the control group showered more than twice a day and 100% of the intervention group showered twice a day. The majority of subjects used antiseptic soap during showers and had dirty nails (80-85%). Both groups had similar nutritional status.

Based on follow-up visits on days 7 and 14 (Table 2), we found statistically significant differences in treatment efficacy between the intervention and control groups. The cure rate on day 14 in the intervention group was 95%, notably higher than in the control group (35%). Relative risk on day 14 was 2.714, indicating that the intervention group was 2.7 times more likely to be cured than the control group.

On day 14, the proportion of subjects with a visual analogue scale (VAS) for pruritus of 0 was higher in the intervention group, and the median delta VAS before and after treatment was also higher in the intervention group compared to the control group (-4 vs -3, respectively). No significant difference was found in median VAS for pain on the baseline. After treatment, more subjects had VAS of 0 in the intervention group, with a statistically significant difference in median delta VAS for pain (-2 in the intervention group vs -1 in the control group).

There were some minor adverse effects in the intervention group. Three subjects reported heated sensation after application of treatment creams, and one subject reported itch; however, these complaints were found to be temporary and did not cause notable discomfort, so subjects in both groups followed through with their assigned treatments comfortably.

Table 3. Characteristics of bacteria and parasites on initial assessment.

Criteria	Intervention (n = 20)	Placebo (n = 20)	*p*
GRAM			
Bacteria < 1 (rare)	0 (0.0)	0 (0.0)	0.827*
Bacteria 1-5 (low)	8 (40.0)	8 (40.0)	
Bacteria 6-30 (moderate)	11 (55.0)	10 (50.0)	
Bacteria > 30 (high)	1 (5.0)	2 (10.0)	
Leukocyte < 1 (rare)	0 (0.0)	0 (0.0)	0.157*
Leukocyte 1-9 (low)	2 (10.0)	2 (10.0)	
Leukocyte 10-25 (moderate)	16 (80.0)	11 (55.0)	
Leukocyte > 25 (high)	2 (10.0)	7 (35.0)	
KOH			
Mites found on skin-scraping	3 (15.0)	2 (10.0)	0.634**
Swab Culture			
Staphylococcus aureus	11 (55.0)	10 (50.0)	-
Staphylococcus saprophyticus	1 (5.0)	2 (10.0)	-
Acinetobacter sp + S. aureus	1 (5.0)	2 (10.0)	-
Escherichia coli + S. aureus	1 (5.0)	2 (10.0)	-
Bacillus sp	1 (5.0)	1 (5.0)	-
Enterobacter aerogenes	1 (5.0)	1 (5.0)	-
Enterobacter gergoviae	2 (10.0)	-	-
Acinetobacter baumannii	1(5.0)	-	-
Acinetobacter sp	1 (5.0)	-	-
Enterobacter cloacae + S. aureus	-	1 (5.0)	-
Staphylococcus saprophyticus + Streptococcus alfahemolytic	-	1 (5.0)	-

* Kolmogorov Smirnov test; ** Fisher Exact test.

Characteristics of bacteria and parasites

We found no statistically significant differences in the proportion of bacteria found on Gram staining. Moderate levels of bacterial colonization were found in 55% of the intervention group and in 50% of the control group, shown in Table 3. Moderate leukocyte levels were found in 80% of the intervention group and in 55% of the control group. Mites were found in KOH skin scraping in 5% of the intervention group and in 10% of the control group.

Bacterial culture showed single species growth in 32 samples (80%) and two species in 8 samples (20%). The most commonly identified bacteria were *S. aureus* (52.5%), followed by *S. saprophyticus*. When two bacterial species were present, they were mostly *S. aureus* with *Acinetobacter* sp and *Escherichia coli*. *S. aureus* was the most common isolate, both on its own and with other bacteria. Gram-negative bacteria found in cultured samples included *Enterobacter cloacae*, *Enterobacter aerogenes*, *Enterobacter gergoviae*, *Acinetobacter* sp, *Acinetobacter baumannii*, and *Escherichia coli*.

Antibiotic sensitivity test for *Staphylococcus aureus* showed sensitivity to cefadroxil and resistance to cefixime (Table 4). Amoxicillin with clavulanic acid, erythromycin, clindamycin, and azithromycin were found to be effective against *S. aureus*. *S. saprophyticus* was sensitive to cefadroxil and amoxicillin-clavulanic acid, but resistant to cefixime. Among the Gram-negative bacteria, *Acinetobacter* sp. was sensitive to azithromycin and amoxicillin-clavulanic acid, and *Enterobacter* sp. was sensitive to cefixime and azithromycin.

Discussion

All the study subjects showered using antiseptic soap. A study by Larson [23] reported showering or washing hands using antiseptic soap can reduce the number of bacteria on the skin, but can also disrupt the skin's barrier, leading to pathogenic colonization of *S. hominis, S. aureus*, Gram-negative bacteria, and *Candida* sp. Thus, using antiseptic soap may contribute to the subjects' susceptibility to impetiginized scabies, but it did not affect the treatment outcomes. Dirty nails can act as a source for secondary bacterial infection. Several studies described an association between hygiene status and bacterial infection as a complication of scabies [24-26].

Nutritional status in 60% of the intervention group and in 55% of the control group was normal ($p = 0.524$). Tasani *et al.* concluded that there were no significant associations between nutritional status and treatment

Table 4. Antibiotic sensitivity of the most commonly found Gram-positive and Gram-negative bacteria.

Bacteria/Antibiotics	Sensitive	Intermediate	Resistant	Total
Staphylococcus aureus				**24**
Cefadroxil	24	0	0	
Erythromycin	23	1	0	
Clindamycin	23	0	1	
Amoxicillin - clavulanic acid	11	1	0	
Cefixime	6	1	17	
Azithromycin	23	0	1	
Staphylococcus saprophyticus				**4**
Cefadroxil	4	0	0	
Erythromycin	2	0	2	
Clindamycin	2	0	2	
Amoxicillin - clavulanic acid	3	0	0	
Cefixime	0	0	4	
Azithromycin	2	0	2	
Acinetobacter sp				**5**
Cefadroxil	2	0	3	
Erythromycin	1	4	0	
Clindamycin	0	0	5	
Amoxicillin - clavulanic acid	5	0	0	
Cefixime	1	0	4	
Azithromycin	5	0	0	
Enterobacter sp				**5**
Cefadroxil	2	1	2	
Erythromycin	0	1	4	
Clindamycin	0	0	5	
Amoxicillin - clavulanic acid	0	2	3	
Cefixime	5	0	0	
Azithromycin	3	0	2	

success in impetiginized scabies [27]. Korte *et al*. also reported the lack of association between malnutrition and treatment success in scabies, despite the high prevalence of the disease in malnourished populations; malnutrition was associated with poor socioeconomic status [28].

Treatment efficacy

Previous studies have compared the efficacy of a combination of permethrin or ivermectin with oral antibiotics (single-dose azithromycin) vs topical treatment with no antibiotics [21,22]. However, we found no studies had compared the efficacy of a combination of permethrin 5% cream with fusidic acid 2% cream and permethrin 5% cream alone.

A study by Romani in 2019 found a significant decrease in impetiginized scabies prevalence after treatment with ivermectin and azithromycin one year after treatment administration, compared to treatment with only ivermectin [21]. This highlighted the benefits of giving antibiotics to treat impetiginized scabies in order to prevent impetigo. Romani's finding contradicts a study by Marks in 2019, in which no difference was found between using a combination of ivermectin and azithromycin, and only ivermectin in treating scabies and impetiginized scabies (relative reduction 75% vs 73%; $p = 0.49$) [22]. Marks also described that giving azithromycin in mass treatments in children can reduce mortality from bacterial infections [22]. Lawrence *et al.* [29] found that impetigo prevalence decreased from 40% to 20% after a 1 year follow up when a scabies-infected population was treated with permethrin or oral ivermectin without antibiotics. They found that despite a substantial amount of group A *Streptococcus* on the children's hands, no impetigo was observed due to intact skin, while having scabies increased children's susceptibility to impetigo. Therefore, if the prevalence of scabies is decreased, the prevalence of impetigo or impetiginized scabies will also decrease. Lawrence suggested prescribing penicillin to cases of impetiginized scabies to improve clinical symptoms and prevent complications [29].

We used fusidic acid cream as an antibiotic to treat secondary bacterial infections. A Cochrane systematic review published in 2012 described fusidic acid 2% and mupirocin creams as the most effective topical antibiotics against mild to moderate impetigo, with mild adverse effects and no gastrointestinal discomfort [30]. We found a relative risk of 2.714 when permethrin cream was used in combination with fusidic acid cream, which means treatment success was 2.7 times more likely compared to using permethrin cream only. Prescribing fusidic acid 2% cream can improve treatment success rates in impetiginized scabies, thus preventing further bacterial infections.

On the 14th day follow-up, we found subjects with a VAS for pruritus of 6 despite having been declared as cured of scabies. This was possible due to the presence of post-scabetic itch, which can persist for 2-4 weeks after adequate treatment. Post-scabetic itch can be differentiated from re-infection or persistent infection by looking for new lesions [31,17].

There were no significant differences in pain between the two groups, but we found more subjects with VAS but zero pain in the intervention group, which may be a positive effect from fusidic acid despite having no anti-inflammatory actions [32]. Topical application of fusidic acid 2% cream for 7-14 days was considered adequate to resolve bacterial infections that cause inflammation, thus reducing overall inflammation and pain in most subjects in the intervention group. This finding is supported by a study by Powers which reported that VAS for pain would decrease in cutaneous bacterial infections if improvements in skin lesions are seen [33].

In the intervention group, 20% of the subjects complained of heat and itching after treatment, yet it was minor and temporary. These adverse effects were also reported in Morley *et al.*'s study [34], in which 1 out of 191 subjects (0.52%) complained of a burning sensation, pruritus, irritation, contact dermatitis, and a sticky sensation as side effects of 2% sodium fusidate cream. Mild adverse effects were also reported by White *et al*. [35] who found a small number of subjects with pruritus and burning sensations after applying 2% sodium fusidate ointments. In contrast, a study by Gilbert *et al.* [36] in Canada found no adverse effects after treatment with fusidic acid 2% cream, consistent with the general knowledge of fusidic acid 2% cream having a favorable safety profile and mild side effects, if any.

Characteristics of bacteria and parasites

Our study found moderate to high bacterial count in samples from both groups. In samples where low bacterial counts were observed, clinical judgment showed the presence of secondary bacterial infections and bacterial growth in cultures. Brooks *et al.* [37] found Gram staining to be less sensitive compared to culture, especially when the bacterial load was minimal. Samples need to have at least 10^5 organisms/mL to be visible when stained, while cultures only need 10^2-10^3 organisms/mL to show colonization. In terms of leukocyte counts, 67.5% of our subjects had moderate

levels of leukocytes, 22.5% had high leukocyte levels, and 10% had low levels. No statistically significant differences were found between the two groups.

Based on clinical judgment, the characteristics of bacterial culture were similar between the two groups. All subjects in both groups had at least one culture isolated. Most of the bacterial growth was *S. aureus,* consistent with previous studies describing *S. aureus* as the most common etiology of impetiginized scabies [22]. However, a study by Tasani *et al.* [27] observed that *S. aureus* was the second most common bacteria causing impetiginized scabies, after Group A *Streptococcus*. We did not find any Group A *Streptococcus* in our study, but differences in pathogenic species did not affect the diagnosis of impetiginized scabies or treatment. In some (20%) culture samples, Gram-negative bacteria like *Acinetobacter* sp, *Escherichia coli,* and *Enterobacter cloacae* were found alongside *S. aureus*. The samples were taken from the buttocks area and the growth of these bacteria in culture media might suggest poor personal hygiene. Positive growth in bacterial culture shows the need for antibiotic treatment in impetiginized scabies.

Mites were found in only 5 skin scrape samples. Skin scrape samples were taken from only one predilection area, which may explain the lack of mites in our study, while in everyday practice, skin scraping is usually repeated on several regions until the mites are found. We suggest performing skin scrapes on at least three locations with no excoriations or inflammations, using scalpels or object-glass. Despite 100% specificity, sensitivity of skin scraping to find mites is considered low (43.5%). Walter *et al.* [38] proposed the use of dermoscopy to improve the sensitivity of skin scraping. Through dermoscopy, the delta wing sign can be found, which indicates the presence of mites.

Antibiotic sensitivity

We found *S. aureus* to be 100% sensitive to cefadroxil, 95% to erythromycin, clindamycin, amoxicillin-clavulanic acid, and azithromycin, while only 25% were sensitive to cefixime and the other 70% were resistant. *S. saprophyticus* had 100% sensitivity to cefadroxil, 75% to amoxicillin-clavulanic acid, and 50% to clindamycin, erythromycin, and azithromycin.

Cefadroxil was found to be effective in all cases of impetigo, as previously described by Ladhani *et al.* in 2015 [39]. Cefadroxil was considered as effective as cefalexin and dicloxacillin. Cefalexin was used in the IDSA (Infectious Diseases Society of America Guidelines) guidelines as the first-line empiric therapy for impetigo, while the first-line therapy for impetigo in the Indonesian Society of Dermatology and Venereology's guidelines was dicloxacillin [40,41]. Cefalexin is considered more favourable than cefadroxil due to more affordable prices in the United States, but cefalexin is rarely prescribed in Indonesia. Amoxicillin with clavulanic acid is also a first-line treatment for impetigo. Erythromycin, clindamycin, and azithromycin are macrolides that can be given as second-line agents for impetigo [41]. Empiric antibiotic choices were based on the assumption that *S. aureus* is the most common bacterial cause of impetigo, as found in our study. No methicillin-resistant *S. aureus* (MRSA) were found in our study. Antibiotic stewardship needs to be applied in prescribing antibiotics. Fusidic acid was used in our study as dictated by the Indonesian Society of Dermatology and Venereology's guidelines for mild impetigo [41]. A systematic review by Koning *et al.* found fusidic acid 2% cream to be as effective as oral antibiotics [30].

We found *Acinetobacter* sp to be the most common Gram-negative bacteria, and it was sensitive to azithromycin and amoxicillin-clavulanic acid. Meanwhile, *Enterobacter* sp was most sensitive to cefixime, followed by azithromycin. Previous studies have described usage of azithromycin as a part of mass treatment of impetiginized scabies in a community [22]. We found that Gram-positive and negative bacteria in our samples were still sensitive to azithromycin. Despite its potential use, in Indonesia azithromycin is used for yaws, as regulated in the Indonesian Ministry of Health's Decree, and cefadroxil is suggested as a first-line agent for impetiginized scabies.

Study limitations

Several limitations are present in our study: skin scrapes were only performed on one predilection area, thus causing many negative results, lack of Gram-staining and culture evaluations post-treatment, a long period of time was needed to recruit samples, only 20 out of 21 samples per group was obtained due to the COVID-19 pandemic, no sensitivity test to fusidic acid cream was performed due to unavailable discs in Indonesia, and 28 subjects were not tested for sensitivity to amoxicillin-clavulanic acid due to technical problems in the laboratory.

Conclusions

A combination of permethrin 5% cream and fusidic acid 2% cream was more effective in treating impetiginized scabies compared to permethrin 5% cream and placebo on day 7 ($p \leq 0.001$, RR = 2.286)

and day 14 ($p \leq 0.001$, RR = 2.714). A significant reduction in VAS for pruritus was seen in the treatment group after 14 days of treatment ($p = 0.04$). VAS for pain was also reduced in the treatment group after 14 days of treatment ($p = 0.035$). There are some minor adverse effects in the intervention group as itch and heat that affect temporarily. *S. aureus* followed by Gram-negative bacteria were the most common etiology.

A combination of permethrin 5% cream with fusidic acid 2% cream can be considered as a first-line agent in impetiginized scabies treatment. More studies on other topical antibiotics, microbiological follow-up examinations, and periodic community surveillance on impetigo-causing bacteria are needed.

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