Original Research Article

Role of probiotic for impetigo in children

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Abstract

Back ground: Impetigo is the most common bacterial infection in children. This acute, highly contagious infection of the superficial layers of the epidermis is primarily caused by *Staphylococcus aureus* or *Streptococcus Pyogenes*. The Objective of this study is to find out the role of probiotic among children suffering from impetigo.

Materials and methods: This was a prospective, randomized, single-blinded interventional study, conducted in Paediatric OPD, Dermatology OPD and Paediatric Ward in Rajah Muthiah Medical College and Hospital for a period of 6 months. A total of 50 patients were enrolled in the study as per the inclusion criteria. They were treated with probiotic (50 million spores of *Lactobacillus sporegenes*, *Streptococcus faecalis* 30 million spores, *Clostridium butyricum* 2 million spores, *Bacillus mesentericus* 1 million spores) twice daily for 5 days. As a conventional treatment, Azithromycin 10 mg/kg/day once a day for 5 days given along with probiotic. Microbiological examination of pus from the first swab was used to prepare smears and was stained by Gram's method. The pus from the second swab was inoculated on blood agar and Mc Conkey's agar.

Results: Bacteriological response and the clinical response were highly significant from baseline to the fifth day of treatment with probiotic along with azithromycin.

Conclusion: The result of our study explores a new possibility in the horizon of treatment of impetigo. Since the adverse effects caused by probiotic are minimal and tolerable, it could be further exploited for the treatment of other inflammatory or immune conditions that are refractory to treatment with current chemotherapeutic agents.

Key words

Impetigo, *Staphylococcus aureus, Streptococcus pyogenes, MRSA (Methicillin Resistant Staphylococcus Aureus),* Probiotic, Azithromycin.

Introduction

Impetigo is a highly contagious infection of the superficial epidermis. The onset of impetigo on the otherwise normal skin is abrupt. When impetigo occurs as a secondary complication of another skin disorder, the onset can be insidious and it can be difficult to recognize. Impetigo may affect any age group but is most commonly encountered in preschool and school-aged children. The infection usually heals without scarring, even without treatment. *Staphylococcus aureus* is the most important causative organism. *Streptococcus pyogenes* (i.e., group A beta-hemolytic *Streptococcus)* causes fewer cases, either alone or in combination with *Staphylococcus aureus* [1]. The two types of impetigo are nonbullous impetigo (i.e., impetigo contagiosa) and bullous impetigo. Nonbullous impetigo represents a host response to the infection, whereas a *Staphylococcus* toxin causes bullous impetigo and no host response is required to manifest clinical illness [1]. The diagnosis usually is made clinically and can be confirmed by gram stain and culture, although this is not usually necessary. Culture may be useful to identify patients with nephritogenic strains of *Streptococcus pyogenes* during outbreaks of post-streptococcal glomerulonephritis or those in whom methicillin-resistant *Staphylococcus Aureus* is suspected [1]. The extensive disease may occur if early symptoms are neglected, or if there is an underlying pruritic skin disorder such as atopic dermatitis or scabies. Very few organisms have the innate ability to penetrate the skin; they must gain access through the skin by physical means such as by an arthropod vector, trauma, surgery or intravenous catheter, while the papovavirus (warts) appears to be an exception. It has also been suggested that cytokine production in the skin (i.e. TNF-α, interleukin (IL) – 1) may serve directly in antimicrobial defense, for example by inhibiting adherence of *Streptococcus pyogenes,* in addition to their role in activating inflammatory immune defences [2]. Probiotics, defined as live microbial food ingredient beneficial to health, are normal commensal bacteria of the healthy human gut microflora [3]. The most frequently used generally are lactobacilli and bifido bacteria [4], and the best documented current therapeutic application is in the prevention and treatment of diarrhoeal disease. Impetigo is an under recognized disease and in conjunction with scabies, comprises a major childhood dermatological condition with potentially lifelong consequences if untreated. Probiotic contribute to balancing of the gut microbiota by producing factors while inhibiting pathogens and other commensal bacteria. Probiotics have been shown to promote the mucus secretion and mucin expression, contributing both to the exclusion of pathogens and to barrier function. Probiotic can also directly inhibit the growth of or kill pathogens by the production of antimicrobial molecules including bacteriocins or microcins. Moreover, probiotic stimulate host antimicrobial defense pathways, thus excluding pathogens indirectly by stimulating the synthesis of defending and by activating its propeptide form. The mechanisms whereby probiotic elicit pathogen exclusion also includes augmentation of the immune response to pathogens through the stimulation of IgA secretion and anti-inflammatory cytokines. They also regulate proinflammatory cytokines and promote epithelial barrier function. The effect of probiotic in ameliorating intestinal barrier dysfunction has been evaluated in numerous studies, in cell culture models exposed to enteropathogens or proinflammatory cytokines. Probiotic may counteract inflammatory responses beyond the intestinal m ilieu [5]. Numerous studies have evaluated the potential efficacy of probiotic in the prevention and treatment of allergic disease in general, and of atopic eczema in particular. Clinical improvement in atopic eczema following

probiotic supplementation has been reported in some published studies and the therapeutic effects of probiotic on atopic dermatitis seemed to be encouraging. In atopic eczema, secondary infection can cause impetigo. Since probiotic showed clinical improvement in atopic eczema, based on updated information, the topic of administration of probiotic is addressed in this study. So this study was undertaken as there is increasing interest in the potential beneficial role of probiotic supplementation among children suffering from impetigo.

Materials and methods

This was a prospective, randomized, single blinded interventional study was conducted in the Out Patient Department of Dermatology in collaboration with Department of Paediatrics in Rajah Muthiah Medical College and Hospital, Annamalai University, Chidambaram for a period of 6 months. The protocol for the study was approved and prior permission was also taken from the institutional human ethics committee of Rajah Muthiah Medical College and Hospital, Chidambaram. A total of 50 patients were enrolled in this study as per the inclusion criteria. Written informed consent obtained from either of the parents before participation into the study. They were treated with probiotic (50 million spores of *Lactobacillus sporegenes*, *Streptococcus faecalis* 30 million spores, *Clostridium butyricum* 2 million spores, *Bacillus mesentericus* 1 million spores) twice daily for 5 days along with conventional treatment of Azithromycin 10mg/kg/day once daily for 5 days. Probiotic was administered two hours before meals and Azithromycin were administered two hours after meals. Inclusion criteria

- Patients aged between 1 to 15 years of both genders.
- Patients with local signs and symptoms of impetigo as pain or tenderness, purulent discharge, erythema with or without induration, swelling, localized warmth. Patients with a number of lesions up to 10 or area of lesions not exceeding 100 cm sq.

Exclusion criteria

- Patients aged less than one year.
- Patients with complicated acute bacterial skin and skin structure infections or with a chronic or underlying skin condition at the site of infection.
- Parent of the children unwilling or unable to comply with the study procedures. The primary parameters include bacteriological cure assessed by culture of the samples taken from the lesions, clinical cure defined as the approximate size of the lesions before and after treatment, clinical cure defined as the number of lesions before and after treatment.

The patients were monitored two times in the study, once at the baseline, and later at the end of the fifth day of treatment. General physical and systemic examination was done and patients were enquired for the incidence of adverse effects. Wound size area was determined by measuring the greatest length of the wound in two perpendicular dimensions with a standard metric ruler. The two measurements were multiplied together to provide an estimate of the overall wound size. Surrounding erythema was not included in the measurement. A collection of specimen intact pustules was cleaned with spirit and then ruptured with a sterile needle. Pus was expressed and collected into two sterile cotton swab. In crusted lesions, normal saline was used to clean the wound. Two swabs were rubbed over the pus or the edge of the ulcer. The swabs were then immediately transported to the microbiology laboratory for further processing. Microbiological examination of pus from the first swab was used to prepare smears and was stained by Gram's method. The pus from the second swab was inoculated on blood agar and MacConkey's agar. The culture plates were inoculated at 37^{o}C for 24-48 hours, aerobically.

Statistical Analysis

The statistical analysis was carried out with SPSS VER. 16.0 Software. All the data were presented as mean, standard deviation, and percentage of efficacies. Paired 't' test is used to evaluate the statistical significance between the baseline and end of five days' treatment. In this study, (P <0.05) was considered as significant.

Results

Figure – 1, 2 showed the patients in the age group of 1 to 15 years were included in the study. Majority of the patients in our study comprised of age group 1 to 5 years. 29 (58%) patients are in the age group of 1 to 5 years. 16 (32%) patients are in the age group of 6 to 10 years. 5 (10%) patients are in the age group of 11 to 15 years. The incidence of impetigo was more common among male children compared to female children.

Figure – 3 showed the most common organism cultured at baseline is *Staphylococcus aureus* and *Streptococcus pyogenes* is cultured in 15 patients followed by *Staphylococcus aureus* is cultured in 28 patients, both the pathogens were cultured in 4 patients and MRSA (Methicillin Resistant *Staphylococcus aureus)* cultured in 10 patients. At the end of treatment (day 5*) Staphylococcus aureus* cultured in 1 patient. *Streptococcus pyogenes* cultured in 1 patient, both the pathogens cultured in 2 patients and MRSA cultured in 1 patients. P value <0.001 in *Staphylococcus aureus*, *Streptococcus pyogenes*, and MRSA confirms that there is a highly significant difference between the baseline and 5th day of treatment.

Figure - 1: Demographic characteristics of Impetigo children (Age).

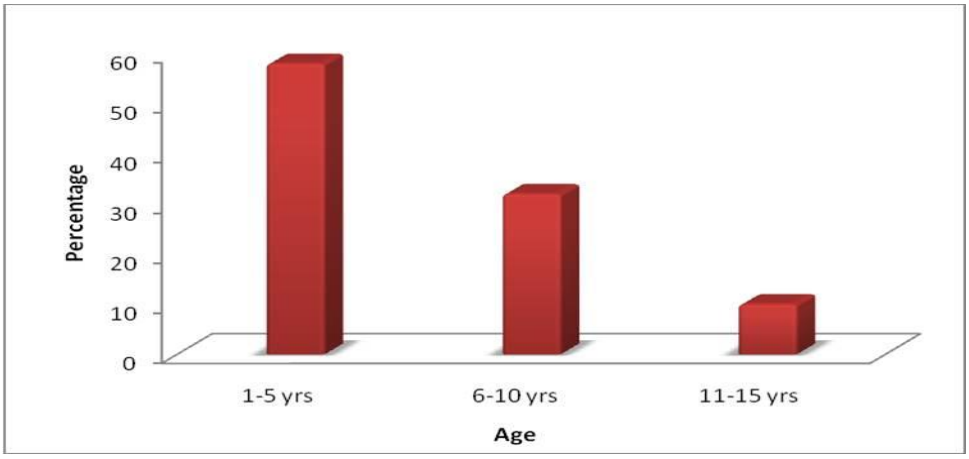

Figure - 2: Demographic characteristics of Impetigo children (Gender).

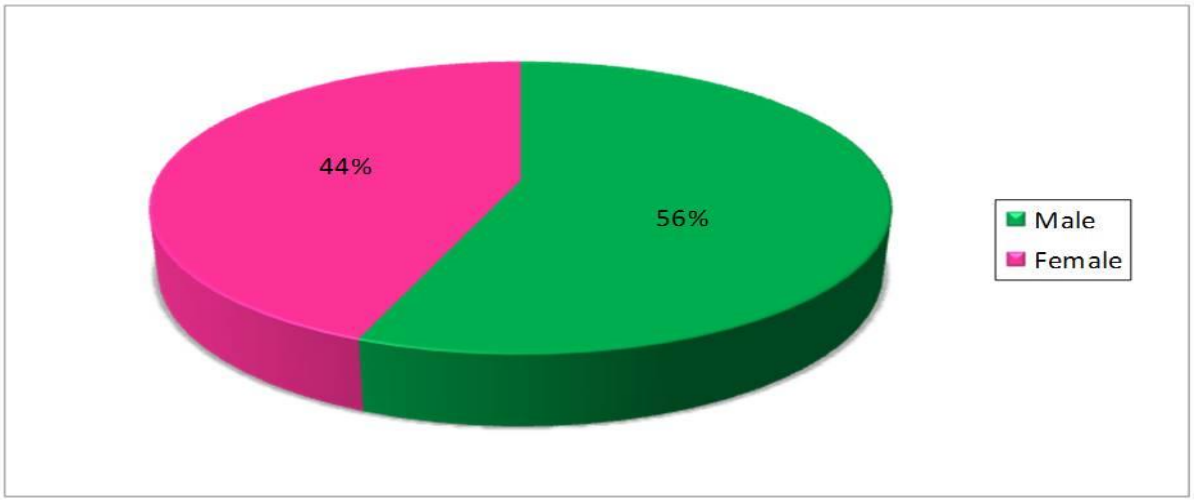

Figure - 3: Bacteriological Response in Treated Patients.

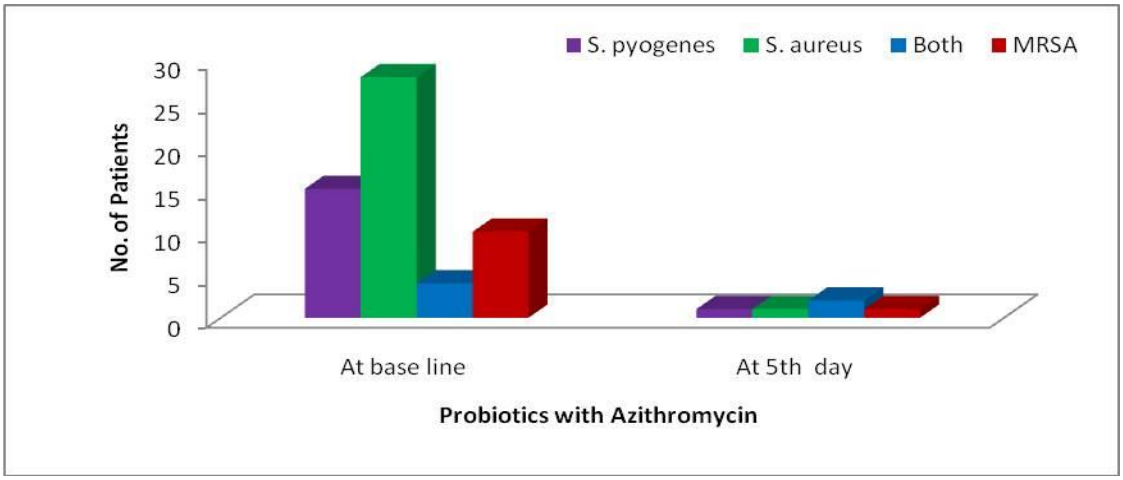

Figure - 4: Assessment of Efficacy based on Bacteriological Response.

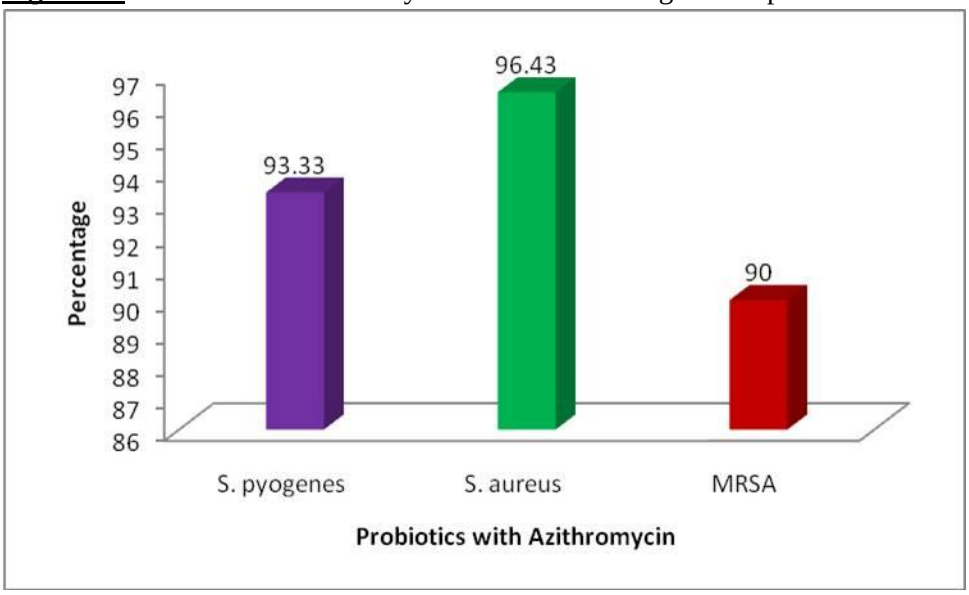

Figure - 5: Distribution of Bullous and Non-Bullous Lesions in Different Areas of the Body.

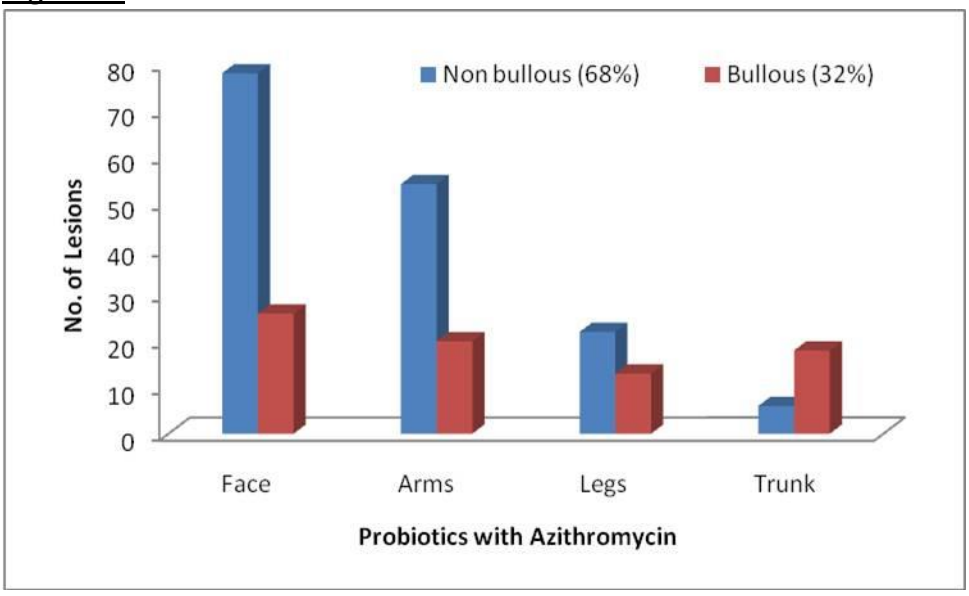

Figure - 6: Effect of Probiotic with azithromycin on Number of Lesion and Mean Wound Area.

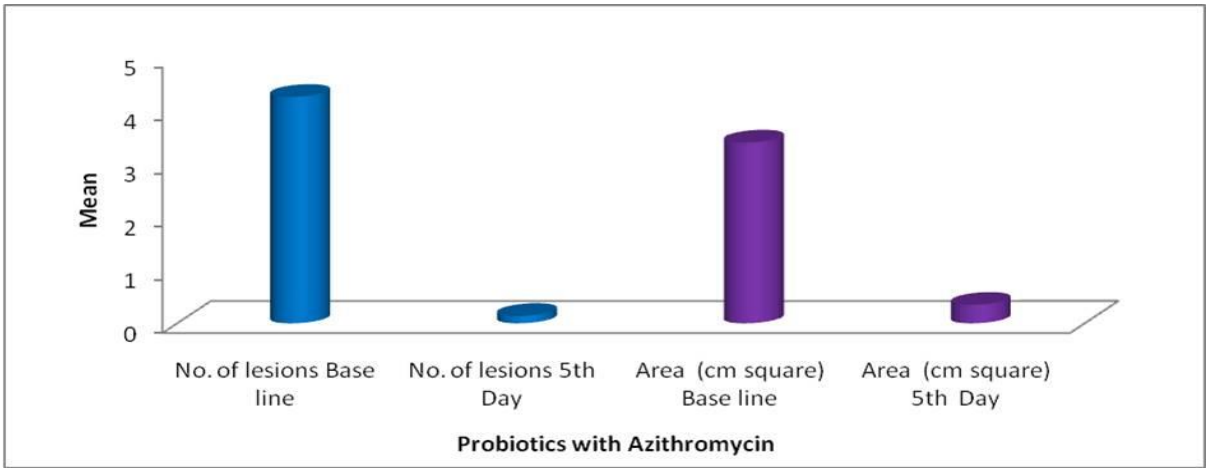

Figure - 7: Incidence of Adverse Events in Study Group.

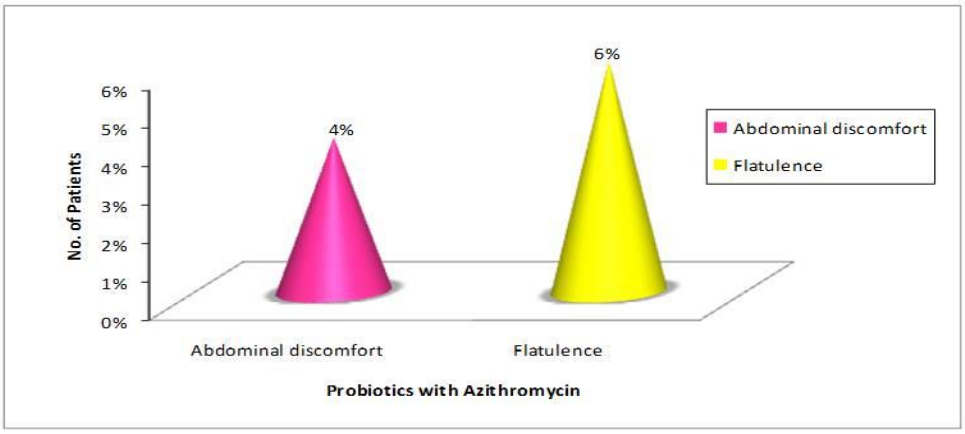

Figure – 4 showed per pathogen bacteriological success rates were 93.33% for *Streptococcus pyogenes*, 96.43% for *Staphylococcus aureus* and 90% for MRSA (Methicillin Resistant *Staphylococcus aureus*).

Figure – 5 showed the total numbers of lesions were 237 in number among which nonbullous lesions were 68% and bullous lesions were 32% seen most commonly in the face followed by arms, legs, and trunk.

Figure – 6 showed Paired 't' test is carried out to test the significant difference between the wound area, from baseline to fifth day and the number of lesions, from baseline to the fifth day. The mean wound area of 3.40 with standard deviation 0.91 at baseline decreased to 0.34 with standard deviation 1.19 after treatment. The mean number of lesions is 4.26 with a standard deviation of 0.80 at baseline decreased to mean a number of lesions is 0.14 with standard deviation 0.700 after treatment. From the mean wound area, mean number of lesions the P value <0.001 confirms that there is the highly significant difference between the baseline and fifth day of treatment.

Table – 1 showed that 48 patients out of 50 are completely cured (absence of lesions) and 2 patients are not cured (presence of lesions). Probiotic with Azithromycin shows 95% of clinical efficacy.

Table - 1: Clinical Response and Clinical Efficacy of Probiotic with Azithromycin.

Lesions	**Probiotics with Azithromycin**
Cured (Absence of lesions)	48
Not cured (Presence of lesions)	2
Efficacy (%)	95.83 (%)

Figure – 7 showed all the adverse events observed in patients treated with probiotic with Azithromycin were mild and these resolved within 24 hours after they appeared. Flatulence is seen in 6% of patients and 4%of patients with abdominal discomfort (**Photo – 1, 2**).

Photo – 1: Probiotic with Azithromycin before treatment.

Photo – 2: Probiotic with Azithromycin after treatment.

Discussion

Probiotics are bacteria or yeasts considered to confer a benefit on the host organism. Probiotics derived from six different genera – *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus* and *Bacillus* alone or in combination are tried in many studies to prevent or treat many infective conditions. Two bacteriae which are most prevalent in the intestine are bifidobacterium and lactobacillus. Saavedra JM, et al., (1994) [6] proved that oral administration of 2 other probiotics, *B. bifidum*, and *S. thermophiles*, reduced the incidence of diarrhea in a double blind, placebo-controlled trial in 55 hospitalized infants. Probiotics might prevent infection because they compete with pathogenic viruses or bacteria for binding sites on epithelial walls. Staphylococci were the main bacterial causative agents of bullous impetigo while in nonbullous impetigo, *Streptococcus pyogenes* in addition to *Staphylococci* predominantly *Staphylococcus aureus* were the predominant causative agents. Susceptibility to this infection depends on host immune factors, as well as the virulence of the organisms. Preschool and young school age children are most often affected. It predominates in males and large outbreaks may be troublesome in barracks and similar communities [7]. In our study, the patients are in the age group of 1 to 15 years. Majority of the patients are in the age group between 1 to 5 years i.e. 58%. Moreover, 56% of male children were diagnosed as impetigo, it showed a higher preponderance of males. Asha C. Bowen, et al., (2015) [8] estimated that global population of children suffering from impetigo is around 162 million and were distributed predominantly in tropical countries based on the data from studies published since 2000 in low and low middle-income countries. Many studies show a higher prevalence of *Staphylococcus aureus* and this organism is reported as the main cause for impetigo. In our study, the most common organism cultured at baseline is *Staphylococcus aureus* followed by *Streptococcus pyogenes*, MRSA (Methicillin Resistant *Staphylococcus aureus*) and both the pathogen (*S. aureus* and *S. pyogenes*). Probiotic with azithromycin treated patient resulted in a bacteriological success rate, with the P value <0.001 confirms that there is a highly significant difference between the baseline and fifth day of treatment. Almost all MRSA strains i.e. community-associated MRSA (C = MRSA) isolated from outpatients with impetigo and Staphyloccocal scaled skin syndrome were reported to carry type IV Staphylococcal Cassette Chromosome (SCC) SCCmec and were susceptible to various antibiotics other than β-

lactam antibiotics. However, the reduced susceptibility of C-MRSA to macrolides and aminoglycosides has also been reported [9]. Studies reported by Senthilkumar and Venniyil, et al., from South India with the prevalence of MRSA of 46% and 78% respectively [10, 11]. MRSA was seen to be more common in the southern part of India than in the west (20.33%) or north (18.88%). In our study, 20% of MRSA was isolated and the bacteriological success rate was 90%. Per pathogen, bacteriological success rates are 93.33% for *Streptococcus pyogenes* and 96.43% for *Staphylococcus aureus*. Clinical epidemiological study of vesiculobullous disorders in pediatric age group by Vinit Gupta, et al., the face was affected in 50% of patients, and in 19% of patients lower limbs were affected by impetigo [12]. In our study, the total number of lesions were 237 in number among which nonbullous lesions were 68% and bullous lesions were 32% seen most commonly in the face followed by arms, legs, and trunk. Probiotic with azithromycin treated patients showed the number of the lesion is reduced from the mean value of 4.26 ± 0.80 on the 1st day to 0.14 ± 0.70 on the 5th day, the wound area from the initial mean value of 3.40 ± 0.91 was found to be reduced to 0.34 ± 1.19. The study group resulted in a reduction in a number of lesions and wound area on the 5th day of treatment. Rosenfeldt, et al., (2003, 2004) [13, 14] performed two trails in 2003 and 2004, evaluating the effect of a mixture of *Lactobacillus rhamnosus* and *L. reuteri* in children with moderate to severe atopic dermatitis. Results of these trials showed a moderate improvement of clinical severity of eczema in children supplemented with a mixture of probiotic strains with a more pronounced effect in patients with a positive skin Prick test. Moreover, Rosenfeldt, et al., (2003, 2004) demonstrated that probiotic supplementation may stabilize intestinal barrier function with clinical benefit for children with atopic dermatitis. In our present study 48 out of 50 patients are completely cured without any lesions and 2 patients were not cured and had lesions, it also showed 95% clinical efficacy. Rautio M, et al., (1999) [15] stated that rare complication including endocarditis and liver abscess have been associated with *Lactobacillus rhamnosus* use. In our study, a most common adverse event reported was flatulence in 6% of patients and abdominal discomfort in 4% of patients. It has been well established that probiotic may counteract inflammatory response beyond the intestinal milieu. Probiotic may enhance the production of anti-inflammatory cytokines in epithelial cells as well as in monocytes and macrophages. Probiotics contribute to regulating allergic hypersensitivity reactions by suppressing the Th2 mediated response that helps in balancing Th1/Th2 immune responses and by increasing Treg mediated immune responses [16]. Probiotic effects also may be mediated via control of the balance between pro and anti-inflammatory cytokines. Impetigo is an infectious disease in which probiotics added along with the conventional treatment of azithromycin which showed an enhancement of immune response to infection. Thereby helping in speedy recovery and healing of the lesion. Our current study proves that addition of probiotic with azithromycin can cure the symptoms of impetigo. It reduced the number of lesions and the causative microorganisms. This may be due to the probiotic induced improvement of immune response or may be due to its anti-inflammatory action.

Conclusion

Probiotic (50 million spores of *Lactobacillus sporegenes*, *Streptococcus faecalis* 30 million spores, C*lostridium butyricum* 2 million spores, *Bacillus mesentericus* 1 million spores) twice daily along with azithromycin 10 mg/kg/day once daily for 5 days given to children aged under fifteen years resulted in shortening of the duration of illness and faster healing of the lesion in impetigo. Large scale community-based efficacy and effectiveness trials are needed to confirm these results.

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