Impetigo:An Assessment of Etiology and Appropriate Therapy in Infants and Children

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Impetigo contagiosa is one of the most common skin infections in children. As its name implies,it is a contagious superficial infection of the skin. The infection begins as a vesicular or pustular skin lesion and develops into exudative and crusting stages. Unless there is trauma to the lesion, superinfection or an abscess develops, the lesion heals completely without scarring.

Until the early 1980s, impetigo was considered primarily a streptococcal infection; however, during the past decade, several studies have documented a predominantly staphylococcal cause. In a study of 101 children with impetigo from Miami, U.S.A., Schachner et al cultured *S.aureus* from 86 per cent of cases (77% of cultures yielded *S. aureus* only; 9% yielded *S. aureus* and B-strepto-cocci)(1). Barton et al identified *S.aureus* in cultures from 83 per cent of 100 cases with impetigo(2). Domidovich et al found *S. aureus* in 81 per cent of 73 patients with impetigo(3). In Thailand, Suthatvoravut et at cultured *S.aureus* from 64 per cent of cases in a study reported in 1980(4). Ngamvasinont et al identified *S. aureus* in cultures from 73 per cent of 88 patients with impetigo(5).

Issues relating to the management of impetigo continue to be discussed. Recent experiences suggest that erythromycin, intramuscular benzathine penicillin G as well as clindamycin, cefaclor and amoxicillin with clavulanic acid are extremely effective (6-9). Since the cost of such drugs is very expensive for Thai patients, we are studying the etiology of the disease and are searching for a cheaper drug for use in developing countries, such as Thailand, especially for Chiang Mai in the North of Thailand.

We recently completed a study of 110 patients with impetigo to delineate the actual causative agents and thus the appropriate antibiotics for the management of impetigo in children. This study compares the effectiveness of treatment of impetigo by using two common antibiotics; penicillin V potassium and cloxacillin orally.

MATERIAL AND METHOD

The subjects were 110 patients cared for in the pediatric outpatient department of Maharaj Nakhon Chiang Mai Hospital between December 1988 and November 1990. Children under 15 years of age with a clinical diagnosis of impetigo were invited to participate in the study. The patients were examined by Dr. Chulaporn Pruksachatkunakorn or Dr. Tasnawan Vaniyapongs. Exclusion criteria included a history of adverse reaction to penicillin or cloxacillin, antibiotic therapy within the past week, primary or secondary immunodeficiency, and concurrent infection that would require additional antibiotic therapy. Patients

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who received topical antibiotic therapy were not excluded from the study participation. The study was explained to each child's guardian prior to enrollment.

Demographic data including age, sex, and address were obtained, together with clinical information related to location, number, and description of lesions. The severity of impetigo, based on the number of lesions, was classified as mild (fewer than six), moderate (six to 20), and severe (over 20).

Nonbullous lesions beginning as vesicles, rapidly becoming pustular, then developing thick, yellow crusts, have been previously described as typical occurrences in streptococcal impetigo. Forty-two patients seen during this investigation had lesions of this sort with pustular and crusted lesions. Color Fig.1 is an illustration of such lesion.

Bullous lesions, considered to be the classical form of pure staphylococcal impetigo, were seen in sixty-eight patients. The color photograph in Fig. 2 illustrates several bullous lesions. In addition to intact bullae, recently ruptured lesions are also seen. Ruptured lesions of this sort form a very thin crust which is quite difficult to elevate or remove.

Patients or their parents were asked to estimate how long the lesions had been present prior to the study enrollment. Other data collected that might affect the success of therapy were a past history of impetigo in the patient, and preexisting skin disorders and impetiginous lesions in household members.

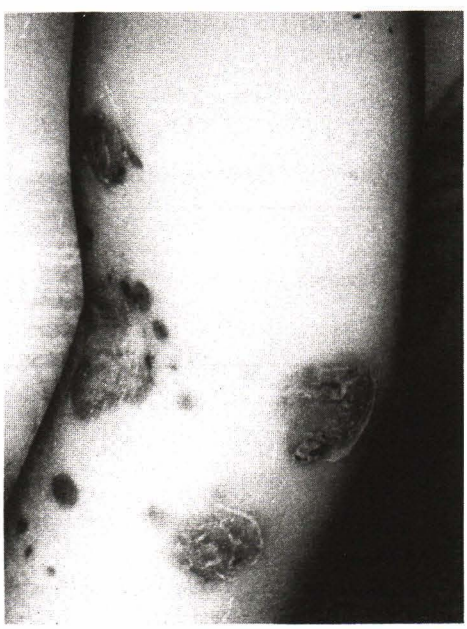
Lesion culture was obtained from a representative impetiginous lesion by unroofing the lesion, swabbing it, and then transfering to Stuart transport media. Bacterial culture was placed on blood agar plate. Antibiotic sensitivity tests were performed on all *S.aureus* and streptococci isolates by Kirby-Bauer method. Participants were randomly assigned to received either oral penicillin V potassium 50 mg/kg/day or cloxacillin sodium 50 mg/kg/day four times a day for 7 days. Patients returned seven days after their first visit for reexamination and repeat lesion culture. If lesions either failed to improve or worsened, therapy was altered based on initial antibiotic sensitivities. Patients were asked to bring their medicine bottles back so that compliance could be evaluated. The investigators use the clinical and bacteriologic findings as the criteria and classify into four groups:

1) cured (healed lesions and negative follow-up culture)

2) bacteriologic failure (healed lesions but positive follow-up culture)

3) clinical failure (non-healed lesions and negative follow- up culture)

4) clinico-bacteriologic failure (non-healed le-



sions and positive follow-up culture).

Statistical analysis

1. Percentage

2. The difference was tested for significance by 2 x 2 contingency table analysis using Chi-square test with continuity correction and Fisher's exact test. Two-tailed p value of 0.05 were calculated.

RESULTS

This study focused on 110 patients, ranging in age from 1 month to 8 years, (median age of 3.5 years). Sixty-four patients were male and forty-six were female. The prevalence of impetigo was found to be related to the season. During both years (1989-1990) of the study, impetigo was observed to increase during the rainy season. Sixty-two patients (56%) had recurrence and prolonged history of impetigo. Multiple cases of impetigo in families were observed in fifty patients (45%).

Factors which predispose or contribute to the development of impetigo are identified in the following summary. Sixty-two had insect bites, thirty had atopic dermatitis, and eighteen had no predisposing factors. Although most children were reported to receive a daily bath, skin hygiene was obviously poor in forty-four cases (40%).

The duration of impetigo ranged from one day to sixteen days. Sixty-six patients (60%)had impetigo lesions which lasted between 4 and 7 days, twenty-five (23%) in 1-3 days, and nineteen (17%) more than seven days.

The distribution of lesions varies. The predominant sites are face and extremities. Patients or parents were questioned regarding allergic or adverse reactions to their medications at the 7- day follow-up visit. No allergic or adverse reactions were reported.

Bacteriology of impetigo lesions

Table 1 shows the correlation between the appearance of impetigo lesions and culture results. Thirty - five (32%) of the 110 cultures yielded *S. aureus* alone, forty-two (38%) yielded *S.aureus* and GABHS. Fourteen (13%) yielded GABHS alone, and eleven patients (10%) yielded no organism. Forty per cent of bullous impetigo patients grew a pure culture of *S.aureus*. Thirty-four per cent grew both *S.aureus* and GABHS from bullous form and 45 per cent from nonbullous. There was a statistically significant relationship between frequency of the bullous type and the solitary presence of *S.aureus*.

Seventy - seven patients whose lesions cultured *S.aureus* alone, or with GABHS were resistant to penicillin. Nineteen per cent of the *S.aureus* isolates were resistant to cloxacillin and 31 per cent to erythromycin.

Treatment Results

Of the 110 patients enrolled in the study, 90 were fully evaluated; 9 were unavailable for follow-up, and 11 were negative to cultures taken on the first visit. Of these nine patients, four grew *S.aureus*

Table 1. Bacteriology of lesions

Organisms	No. of patient (%)		P value
	Nonbullous	Bullous	
S. aureus	8 (19)	27 (40)	0.0119*
GABHS	8 (19)	6 (9)	0.059
S. aureus + GABHS	19 (45)	23 (34)	0.1156
Other	5 (12)	3 (4)	0.0707
No growth	2 (5)	9 (13)	0.0750

*statistically significant

Table 2. Results of treatment

Results	No. of patient (%)		P value
	Penicillin-treated	Cloxacillin-treated	
Cure	27 (60)	38 (84)	0.004*
Bact-fail	3 (7)	4 (9)	0.3469
Clin-fail	1 (2)	0	0.1573
Clin-Bact fail	14 (31)	3 (7)	0.0015*

*statistically significant

Table 3. The relationship between clinical severity and results

Severity	No. of cured patient		P value
	Penicillin-treated	Cloxacillin-treated	
Mild	9/16	7/9	0.1409
Moderate	6/10	13/16	0.1173
Severe	12/19	18/20	0.0234*
Total	27/45	38/45	

*statistically significant

alone, four grew *S.aureus* and GABHS and one grew GABHS alone. The responses to the two antimicrobial regimens were compared at the 7- day follow-up examination and repeated culture. The remaining ninety patients were evaluated at one week follow-up.

As shown in Table 2, of forty-five patients who received penicillin, twenty-seven (60%) were clinically cured. Of forty-five patients who received cloxacillin, thirty-eight (84%) were clinically cured. There was a statistically significant relationship between type of antibiotic and result of treatment. Cloxacillin was more effective and fewer clinicobacteriologic failures were observed with cloxacillin than with penicillin therapy. All patients who experienced penicillin-treatment failure were retreated with cloxacillin and responded well. Those for whom cloxacillin-treatment failed were retreated with erythromycin (due to the antibiotic sensitivity) and showed good responses. Of the eighteen penicillin-treatment failures, those for whom cultures had initially produced penicillin-resistant *S.aureus* included ten who were of the bullous type and eight were of the nonbullous type. Also three of seven patients with cloxacillin-treatment failure had initially produced cloxacillin-resistant *S.aureus*. Two were identified as bullous form and five were nonbullous.

Table 3 shows the correlation between clinical severity and cure rates for the two antibiotics. Eighteen of twenty (90%) who were initially classified as belonging to the severe group were cured by cloxacillin while twelve of nineteen (63%) were

Table 4. Results of resistant *S. aureus*

Antibiotic resistance	No. of cured patient (%)		P value
	Penicillin-treated	Cloxacillin-treated	
Penicillin	22/38(58)	25/31 (81)	0.0218*
Cloxacillin	5/8 (63)	4/ 7 (57)	0.4163
Erythromycin	6/14(43)	6/10 (90)	0.0093*

*statistically significant

Table 5. Comparison of isolation from impetiginous lesions

Authors	No. of pt.	% of *S.aureus* alone	% of GABHS alone	% of *S. aureus* and GABHS
Burnett,1962 [20]	60	32	23	27
Hughes, 1967 [20]	62	23	18	30
Dillon, 1968 [10]	497	11	32	54
Estery,1970 [11]	166	37	27	36
Dajani, 1973 [12]	150	13	24	58
Schachner, 1980 [1]	101	77	1	9
Suthatvoravut, 1980 [4]	62	45	11	19
Barton, 1987 [2]	100	53	3	30
Ngamvasinont, 1987 [5]	88	58	13	15
Demidovich, 1990 [3]	73	62	8	19
This study, 1991	110	32	13	38

Table 6. Comparison of cured patients

	Schachner [1] 1980	Suthatvoravut [4] 1980	This study 1991
Penicillin	53 %	77 %	
60	%		

cured by penicillin. In the severe group, cloxacillin was significantly more effective than penicillin therapy.

Responses to the two antimicrobial regimens were also compared in cases of resistant *S.aureus* as shown in Table 4. Of seventy-seven who yielded penicillin-resistant *S.aureus,* eight patients dropped out. The 69 remaining patients were analyzed. In penicillin-resistant group, twenty-five (80%) were cured by cloxacillin while twenty - two (58%) were cured by penicillin. In erythromycin-resistant group, nine (90%) were cured by cloxacillin and six (43%) were cured by penicillin, there were statistically significant differences in these two groups. Only one patient yielded both cloxacillin and erythromycin-resistant *S.aureus* but experienced good response to cloxacillin regimen.

DISCUSSION

The impetigo observed in this population demonstrated that boys were more likely than girls to have impetigo. It was postulated that in Thai culture, boys were more active and more likely than girls to become infected.

Suthatvoravut commented that impetigo reached a peak incidence in the rainy months in her geographical area (Bangkok, Thailand)[4]. The present study shows distinct peaks during the rainy season of each of the two years of the study period. The seasonal incidence varies considerably in different geographical areas but infection is most prevalent in humid weather and may occur year-round in tropical areas.

Classically, impetigo is a disease of pediatric age group and particularly involves younger children. In the 88 cases which were studied by Ngamvasinont, the predominant age of the patients was one year to five years [5]. Our patients were mostly under five years of age.

Environment and hygiene play important roles in impetigo. Our study agreed with earlier studies in Thailand in the point that impetigo is more frequent among low income populations than in the more affluent sector of society.

The distribution of lesions was similar to the observation of Suthatvoravut and Ngamvasinont [4,5]. Face and extremities are the most common sites and also the preferable sites of atopic dermatitis and insect bites. Differences in the duration of skin infection prior to medical intervention may have resulted from striking appearance of bullous lesions prompting an earlier clinic visit. Whether or not mimor skin trauma plays a significant role in bullous impetigo remains uncertain, but certainly most children with streptococcal impetigo were reported to have had mosquito or insect bites which subsequently became infected. The available evidence suggests that the streptococcal skin infection is spread from patients with active lesions to siblings or others in close contact, without prior respiratory infection or colonization being a prerequisite for the individual developing the disease. The role of intermediate vectors such as flying insects in possibly spreading such infection is still uncertain[10].

Data collected in the United States 20 years ago identified GABHS as the predominant pathogen in nonbullous impetigo and *S. aureus* as a secondary invader[11-15]. Recently, studies performed in such geographically disparate areas as England, Australia and Egypt have shown a predominance of staphylococci in both bullous and nonbullous lesions [16-18]. In Thailand, investigations performed in the 1980s in Bangkok also pointed to the importance of *S.aureus* as indicated by both increased frequency of isolation, as well as failure of therapy not directed at predominantly penicillin-resistant organisms [4,5]. Suthatvoravut's study revealed that the most commonly isolated organisms was *S.aureus* alone (45%),mixed *S.aureus* and GABHS (19%), or GABHS alone (11%) [4]. There were no treatment failures with cloxacillin or dicloxacillin in contrast to a 23 per cent failure rate in cases treated with penicillin alone[4]. Ngamvasinont also found an overwhelming predominance of *S.aureus* isolates in his patients with impetigo[5]. Data in the present study showed that *S.aureus* and GABHS were that the most isolated organisms (38%), *S.aureus* alone (32%) and GABHS alone (13%). A comparison of isolated organisms is summarized in Table 5. The bullous type yields mainly staphylococcal in etiology, while nonbullous type is associated with streptococci, with or without staphylococci . Good correlation has been found between type of impetigo and kind of isolated organisms. The findings of the present study are in agreement with earlier observations.

Available evidence suggests that mixed cultures of streptococci and staphylococci results from secondary invasion of the lesion by one organism following an initial infection with the other [10,12]. In the present study, it seems likely that staphylococci are more often the secondary invaders, rather than the primary infection agent. Several findings support this statement, including inability to distinguish clinically those lesions positive for both streptococci and staphylococci from lesions which are positive for streptococci alone. It has been shown by others that *S.aureus,* in contrast with streptococcus pyogenes, frequently inhibit normal reaction of the skin[21]. Staphylococci might be inoculated into streptococcal lesions simply by scratching or irritating the lesion. Some strains of *S.aureus* inhibit growth of GABHS so that the cultures that appeared to be pure growths of *S.aureus* and might mask the presence of GABHS[22,23]. Furthermore, faulty culture technique, including failure to remove crusts or swabbing skin around a lesion, may result in isolation of staphylococci which were present on crusts or skin, yet not truly contribution to the infection.

This study did not identify the strain of streptococci and *S. aureus.* In Thailand, there have

been a few studies in this area. Sukonthaman's study found that GABHS isolated from impetigo were M-type 13,19,49,52,55,63 and PS 346[24].

Dillon's studies of 10 years ago revealed a penicillin resistance in the staphylococcal bullous impetigo of approximately 50 per cent, while an increasing degree of resistance has been noted by several other authors[25]. Schachner showed that greater than 98 per cent of all *S.aureus* grown from the superficial skin infection were resistant to penicillin[1]. This study finds the degree of resistance overwhelming, with 100 per cent of *S.aureus* grown from impetigo resistant to penicillin. Although there were no cloxacillin resistant *S.aureus* in Bangkok [4,5]. Nineteen per cent of the *S.aureus* in the present study were cloxacillin-resistant. These data suggest a basic difference in the epidemiology of staphylococcal skin infections in different geographic areas.

The present investigation demonstrates that cloxacillin is more effective than penicillin. This is in general accord with the results of the studies of Schachner and Suthatvoravut as shown in Table 6 [1,4]. However, patients with mild to moderate forms of impetigo respond as well to penicillin, as cloxacillin. Interestingly, cloxacillin is appropriate for severe impetigo. Cloxacillin was statistically effective in treating *S.aureus* which resisted either penicillin or erythromycin. Data in the present study are insufficient to permit conclusion that penicillin and cloxacillin are equally effective therapy in cases of cloxacillin-resistant *S.aureus*. Periodic re-evaluation of antimicrobial susceptibility patterns and therapeutic efficacy may necessitate future revision of this recommendation.

In addition to treatment results, cost, patient compliance and associated untoward reaction are all significant factors in selection of treatment option for impetigo. We are surprised that no untoward reactions were reported by any of our patients even though we specifically asked them if adverse reactions had been experienced. Economic issues include not only the cost of the medication, but the money lost by parents who must take time off from work to care for the child until the child is free from impetigo lesions and can return to day care or school. Of the two regimens, cloxacillin appeared to be more effective than penicillin. The antibiotics, such as cloxacillin and erythromycin, remain our therapeutic choice for patients with impetigo.

SUMMARY

We found that mixed organisms of *S.aureus* and GABHS were the most common cause of impetigo in chlidren in our study; that, of the two regimens evaluated, cloxacillin is the most effective treatment; that penicillin is equally effective in cases of mild to moderate forms and may be preferred on the basis of cost-effectiveness.

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สาเหตุและการรักษาโรคผิวหนังชนิด impetigo ในผู้ป่วยเด็กและทารก

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ศึกษาผู้ป่วยเด็กที่เป็น impetigo จำนวน 110 รายแบบไปข้างหน้า เพื่อหาเชื้อที่เป็นสาเหตุและทดลองใช้ยาปฏิชีวนะ 2 อย่าง ณ.แผนกผู้ป่วยนอก โรงพยาบาลมหาราชนครเชียงใหม่ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ โดยแบ่งชนิดของความรุนแรงตามจำนวนรอยโรคเป็นชนิดอ่อน, ชนิดปานกลาง, และชนิดมาก นอกจากนี้ได้เพาะเชื้อแบคทีเรียจากรอยโรคและให้ยา Penicillin 50 มก./กก./วัน หรือยา Cloxacillin 50 มก./กก./วัน รับประทานนาน 7 วัน จากผลการเพาะเชื้อพบว่าขึ้นเชื้อ group A β – hemolytic streptococci (GABHS)และ *Staphylococcus aureus (S.aureus)* ร้อยละ 38, เชื้อ *S.aureus* อย่างเดียวร้อยละ 32, และเชื้อ GABHS อย่างเดียวร้อยละ13 จากผลการรักษาพบว่าผู้ป่วยที่มีความรุนแรงชนิดอ่อนหรือชนิดปานกลางอาจพิจารณาใช้ยา Penicillin หรือยา Cloxacillin ก็ได้ขึ้นกับเศรษฐานะของผู้ป่วย ผู้ที่ดื้อยา Penicillin ต้องใช้ cloxacillin แต่ผู้ป่วยที่มีความรุนแรงมากควรใช้ Cloxacillin และถ้าดื้อยา Cloxacillin ให้ใช้ Erythromycin.

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