

**THE EFFECTIVENESS OF LONG-ACTING PENICILLIN  
(PENIDUR) IN PREVENTING RECURRENCES OF  
DERMATOLYMPHANGIOADENITIS(DLA) AND CONTROLLING  
SKIN, DEEP TISSUES, AND LYMPH BACTERIAL FLORA IN  
PATIENTS WITH "FILARIAL" LYMPHEDEMA**

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**ABSTRACT**

*Dermatolymphangioadenitis (DLA) is a common and serious complication of so-called "filarial" and bacterial non-filarial lymphedema of the limb, affecting skin, lymphatics and lymph nodes. In our previous studies, we demonstrated that more than 60% of patients revealed presence of bacterial isolates in deep tissues, tissue fluid and lymph from the lymphedematous limbs. The question remained open whether elimination or suppression of bacteria dwelling in lymphedematous tissues by administration of low doses of penicillin for long time periods would prevent recurrence of DLA attacks. In this study, we retrospectively evaluated a self/community-selected group of patients with lymphedema of the lower limbs with respect to the efficacy of long-acting penicillin in preventing episodes of DLA. There were no microfilariae or anti-filarial antibodies detected in the investigated group. The questions we asked were: a) how effective is the benzathine penicillin in preventing recurrences of DLA attacks and b) how does its long-term administration influence the bacterial spectrum of leg skin, deep tissues, lymph and lymph nodes and sensitivity to antibiotics. Two randomly selected groups of*

*patients, receiving and not receiving penicillin during the same period of time, were compared. Evidently lower recurrence rate of DLA was observed in the treated group ( $p < 0.002$ ). There was increased prevalence of cocci and gram-positive bacilli with a concomitant decrease of gram-negative bacilli on the foot and calf skin surface. Simultaneously, decreased prevalence of gram-positive cocci and gram-negative bacilli isolates in limb deep tissues and lymph was seen. No resistance to penicillin and other tested antibiotics developed in isolates from the skin surface, deep tissues and lymph. We conclude that long-lasting penicillin is effective in preventing recurrent DLA attacks.*

Lymphedema of the limbs is a pathological condition affecting, according to the World Health Organization, around 300 million of the earth's inhabitants. In India, Africa and Pacific islands, one of the causative factors primarily damaging limb lymphatics has been suggested to be *Filariae* such as *Wucheria bancrofti* and *Brugia malayi*. The parasites penetrating lymph vessels may impair lymphatic drainage of tissues that leads to stoppage of transport away of microorganisms penetrating the sole and palm skin. In most inhabitants, primary

bacterial penetration and inflammation without filarial infestation seems to be the etiological factor leading to development of lymphedema. This is most frequently seen in the barefoot walking population. In consequence of tissue colonization, frequent acute attacks of dermatolymphangioadenitis (DLA) take place. DLA is a common and serious complication of limb in so-called "filarial" patients (those without evidence of filarial infection but living in endemic area) as well as non-filarial lymphedema affecting skin, lymphatics and lymph nodes (1,2). The symptoms are: circumscribed or diffuse erythema of skin, red streaks along superficial lymphatics on the medial aspect of the limb, tender enlarged inguinal lymph nodes and high fever reaching in some cases 41.5°C. The inflammatory changes persist after an acute episode at a subclinical level and occasionally undergo overt exacerbation. They can be demonstrated on histopathological sections of skin specimens (3). The dense mononuclear infiltrates at the epidermo-dermal junction, evidently more intense than in the subcutis, lymphatics and lymph nodes, suggest reaction to the activated skin bacterial flora (3). Bacterial isolates have been found in tissue fluid, lymph and lymph nodes of the lymphedematous limbs both in the so-called "filarial" and non-filarial lymphedema. In the Indian group above 60% and in the European group above 40% of patients revealed presence of bacteria in deep tissues, tissue fluid and lymph of the lymphedematous limbs (4-6). Bacterial strains of the same phenotype and antibiotic sensitivity were identified on the toe-web surface and in the tissue fluid, lymph and lymph nodes (5). Blood bacterial isolates were identified in 46% of patients during and immediately after the acute attacks of DLA (7).

The question remains open whether bacteria, and if so which, participate in the pathomechanism of the DLA attacks and progression of obstructive lymphedema. If true, long-term low-dose administration of antibiotics would be justified as a useful

prophylactic modality. Recently, we have carried out an open trial on the prevalence of DLA in 45 European patients given parenterally long-acting benzathine penicillin for a period of 12 months. The frequency rate of DLA episodes decreased after penicillin administration by more than 90% (8,9). These results prompted us to investigate whether a similar effect could be obtained in the so-called "filarial" lymphedema patients.

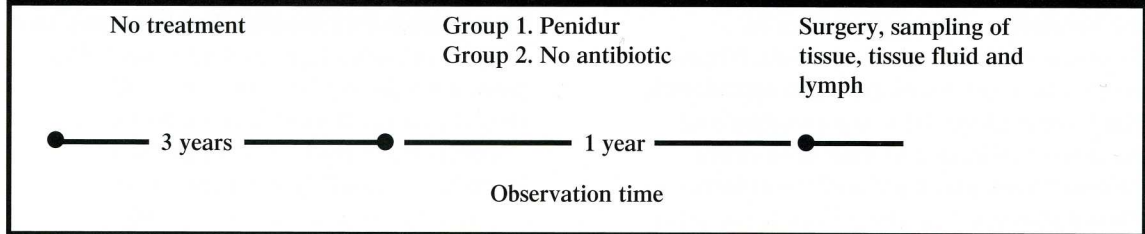
In this study, we retrospectively evaluated a randomly selected group of patients with "filarial" lymphedema of lower limbs with respect to the efficacy of long-acting penicillin in preventing recurrent episodes of DLA. The specific questions we asked were: a) how effective is the benzathine penicillin in preventing recurrences of acute DLA attacks and b) how does its long-term administration influence the bacterial spectrum of leg skin, deep tissues, lymph and lymph nodes and bacterial sensitivity to antibiotics. Two groups of patients, those receiving and not receiving penicillin in the same period of time, were compared.

## MATERIALS AND METHODS

### *Patient Selection and Penicillin Administration*

Seventy-four patients, with so-called "filarial" lymphedema of lower limbs, stage I to IV calling at the lymphedema outpatient clinic in Thanjavur (25), Chennai (25), and Varanasi (24), consecutively registered as they appeared in our outpatient clinic and were included into this retrospective evaluation. All patients were referred to us by the local practitioners upon our request, without information on the purpose of the visit. Prior to being seen by the practitioner, all patients suffered over the last 3 year period from recurrent attacks of dermatolymphangioadenitis (DLA) not treated in most cases, as the acute symptoms subsided after 3-5 days. In the areas patients with lymphedema came from, 99% of them complain about incidents of DLA. The local

**TABLE 1**  
**The Time Setting of the Observations of Patients with Lymphedema-  
 Treated and Non-Treated with Penidur**



practitioners advised all patients to take penidur (Wyeth, GB) injections according to the standard protocol—1,200,000u i.m. every 2-3 weeks for a period of 12 months. No other antibiotics were given during this period of time. The patient cohort divided itself into two groups with self or community factors influencing their choice. For example, 40 patients had the possibility to receive injections in their villages while another 34 patients were not treated with penidur because of negligence, or there was lack at their location of personnel permitted to make injections. The villages were located in similar hygienic and socio-economic areas. The percentage of treated and non-treated patients was similar in all three locations: Thanjavur, Chennai and Varanasi. The time setting of the observations is shown on *Table 1*.

There were 42 males and 32 females, aged 23 to 73. Duration of lymphedema ranged between 5 to 22 years. Stage I comprised patients with edema of the foot, stage II those with edema of the foot and lower leg, stage III patients with edema reaching the mid-thigh level and stage IV those with edema involving the entire extremity. The average frequency of DLA attacks for all stages was  $5.1 \pm 6.3$  (range 1-24/year). Patients were screened for the presence of blood microfilariae and were found negative in all cases. No filarial antigen was detected in serum, lymph and tissue fluid. Despite lack of evidence of filarial infestation, customarily in India cases with

lymphedema are called “filarial,” and we are using this convention.

All patients had indications for surgical revision of the inguinal lymph nodes and microsurgical lymph-venous shunts and were admitted to the department of surgery. The indications for surgery were: (a) recurrent DLA attacks, and (b) in stage I and II: soft, pitting edema partly subsiding after night rest and a continuously increasing limb volume; in stage III and IV: heavy leg, limited movements in ankle and knee joints, rapidly developing skin hyperkeratosis and fibrosis. At the time of surgery, tissue, tissue fluid, lymph, and lymph node samples were taken for bacteriological studies. We routinely harvest skin and tissue fluid for identification of microorganisms in long-term cultures. This is necessary for isolation of bacteria from hair follicles and skin glands not detected in skin surface swabs. Cannulation of lymphatics is a minimally invasive procedure. It is done in the biopsy wound by introducing a 0.5 mm diameter plastic cannula. The knowledge of types of bacteria colonizing tissues and their antibiograms are indispensable for treatment of DLA and perioperatively during debulking surgery. The consent of local ethical committees has been obtained for these diagnostic/research procedures.

As controls for the bacteriology of deep tissues and fluids, 20 patients without edema of legs undergoing elective orthopedic surgery were studied.

## *Laboratory Investigations*

### *Collection of Material for Bacteriological Cultures*

Collection of the biological material for bacteriological investigations was performed in the operating theater. All specimens were collected by the same surgeon, under strictly sterile conditions. They were put into transport media and coded. Swabs, tissue fragments or fluid samples were taken from skin of lower calf, calf biopsy wound, thigh and groin tissues and inguinal lymph nodes, as well as from calf tissue fluid and lymph from cannulated lymphatics.

### *Skin Biopsy*

Wet swabs were taken, before disinfection, by rubbing the skin surface on the calf at the ankle level 20 times. In addition, skin biopsy 0.5 x 0.3 cm fragments were sent for bacteriological study (see calf biopsy wound).

### *Calf Biopsy Wound*

Skin was disinfected consecutively three times for 2 min. with a isopropyl alcohol and allowed to dry. An incision was made, and a 0.5 x 0.3 cm skin fragment was taken. At the same time a swab was dipped in the wound for 30 sec not touching the wound edges. The same procedures were carried out in the thigh and groin.

### *Lymph Node Biopsy*

A 0.5 x 0.5 cm fragment was harvested at the time of groin revision and lympho-venous shunt operation.

### *Tissue Edema Fluid*

Tissue fluid spontaneously filling the calf biopsy wound was collected in sterile syringes, and 2-5 ml were injected into bottles

containing Hemoline medium (bioMerieux, Lyon, France).

### *Lymph*

In patients with patent lymphatics, a superficial lymph vessel draining skin of the foot and lower part of calf was cannulated with a siliconized polyethylene cannula (PE-10). Lymph was collected in sterile test-tubes containing 0.1 ml of heparin (Novo, Copenhagen, Denmark). The collection period lasted for 6-24 hours. Five ml of lymph was transferred to Hemoline media.

### *Culture Media*

The following media were used: Hemoline liquid medium (Biomerieux), Columbia blood agar base enriched with 5% sterile defibrinated sheep blood, MacConkey's agar, Chapman's agar, Sabouraud's agar (malt agar), and brain heart infusion (BHI) (all from Difco, Detroit, MI).

### *Identification of Bacterial Strains*

The cultures were incubated at 37°C and examined at 24 and 48 hr for aerobic bacterial growth. After 48 hr of incubation, BHI cultures were transferred into blood agar and examined after another 24-hr culture. Skin biopsy material and lymph nodes were transferred from transport media to BHI medium. These cultures were examined every day for up to 10 days and, if positive, inoculated onto blood agar slants. After 10 days, all negative cultures were transferred to blood agar. Tissue fluid, lymph, and venous blood were placed in Hemoline medium and examined every day for 14 days. If growth was observed, material was then inoculated onto blood agar and incubated at 37°C for an additional 24 and 48 hr. In cases where there was no aerobic growth, additional cultures for anaerobic growth were established. Isolates were identified by standard procedures using the Analytical Profile Identification (API)

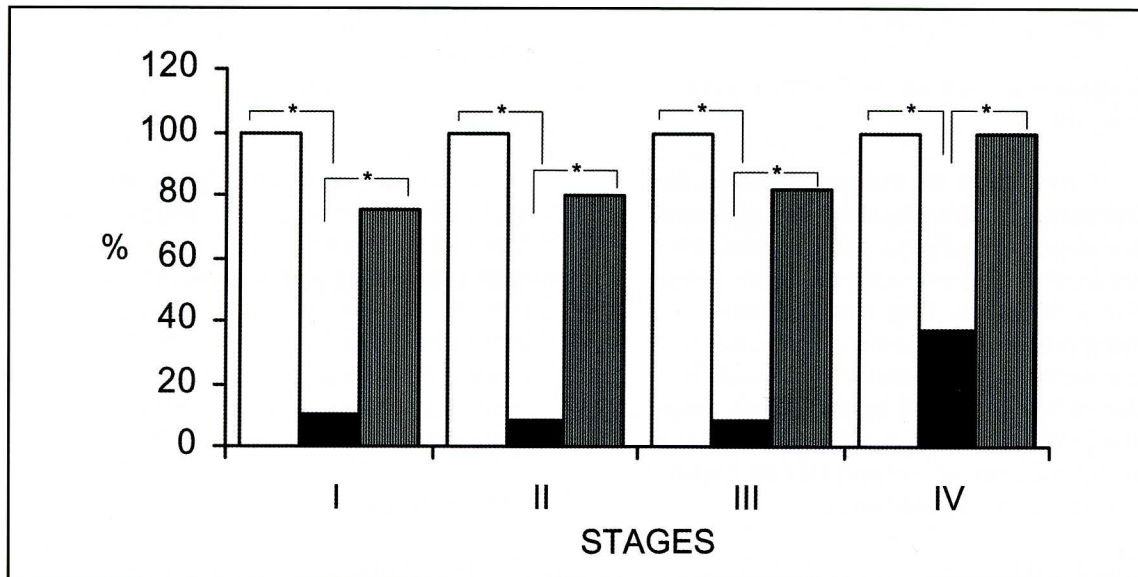


Fig. 1. The incidence rate of attacks of dermatolymphangioadenitis (DLA) before treatment with penidur (open bar), after 12 months of treatment (black bar) and in the non-treated group (dotted bar) in various stages of lymphedema. \*  $p < 0.05$ .

System (Biomerieux). Aerobic cocci of the *Micrococcaceae* family were identified using the API-Staph system. Bacteria of *Streptococcaceae* family were identified with API 20 Strep. Members of the genus *Corynebacterium* (gram-positive coryneform and pleomorphic rods) were identified with API Coryne. Gram-negative rods were identified using API 20E. Gram-positive spore-forming bacilli (*Bacillus* spp.) were identified by evaluating the fermentation of sugars or polyalcohols. The sensitivity of isolated bacterial strains to antibiotics was examined using the ATB system (Biomerieux). Analysis of antibiotic sensitivity was performed using the ATB-Plus reader (Biomerieux).

#### Statistical Evaluation

The differences in the frequency rate of DLA attacks in the treated and non-treated patients were evaluated using the Student t-test. For correlation between the DLA rate after treatment and the prevalence of isolates in lymph and lymph nodes the Pearson

correlation coefficient was calculated.

Statistical evaluation of prevalence of isolates in the treated and non-treated patients made use of the Student t-test. The level of significance was set at  $p < 0.05$ .

#### RESULTS

##### *Recurrence Rate of DLA in Penidur-Treated and Non-treated Groups*

The percentage of patients suffering from recurrent acute DLA attacks was, during the 12-months observation period, 15.6% in the penidur-treated and 76.4% in the non-treated group. The difference between the groups was significant ( $p < 0.002$ ). When the treated group was stratified according to the stage of the disease, the treated patients in stage I to III had 8-10% and those in the most advanced stage IV 37% recurrences (decrease significant at  $p < 0.05$  in all treated groups). For comparison, the recurrence rate in the non-treated group was 66 to 100% (Fig. 1).

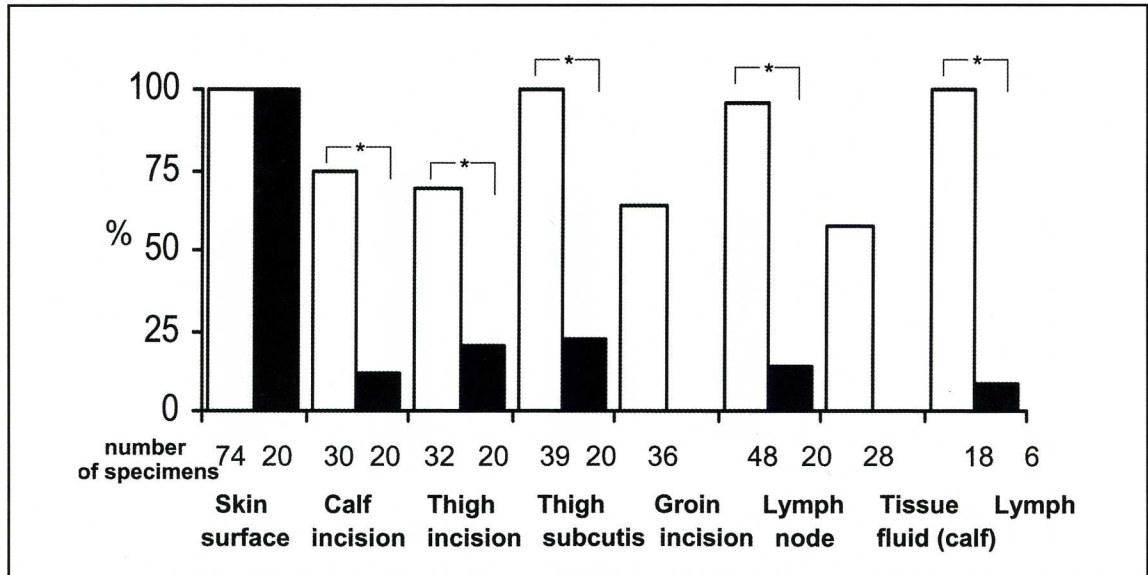


Fig. 2. The numerical prevalence of isolates from specimens obtained from various anatomical sites of 74 patients (open bars) and non-lymphedema controls (black bars). \* difference in prevalence between lymphedema and controls. \* $p < 0.05$ .

#### Prevalence of Bacterial Isolates from Specimens Isolated from Different Anatomical Sites

The percentage of isolates from specimens obtained from different anatomical sites in treated and non-treated patients as well as the non-lymphedematous controls is shown in Fig. 2. The subcutaneous tissue, tissue fluid, lymph and lymph nodes contained higher numbers of isolates than controls. The difference in prevalence was statistically significant ( $p < 0.05$ ).

#### Spectrum of Bacterial Species on Skin of the Lymphedematous Limbs in the Treated and Non-treated Groups

Bacteria were isolated from 100% of skin surface swabs in both penidur-treated and non-treated groups. Differences in the prevalence of bacterial strains between the treated and non-treated group were found. Significantly more gram-positive cocci and sporulent bacilli were found on calf skin

surface of the treated than non-treated patients ( $p < 0.05$ ). Concomitantly, there were fewer gram-negative bacilli ( $p < 0.05$ ) (Fig. 3). The prevalence of corynebacteria isolates did not differ between groups and that of gram-negative cocci was rather negligible in both groups. Among the population of gram-positive cocci, there were 60% more Micrococci isolates, 20% coagulase-negative Staphylococci, and 20% Aerococci ( $p < 0.05$ ) (Fig. 4). In the treated compared with the non-treated group there were 40% more Enterobacter ( $p < 0.05$ ), and there were fewer Acinetobacter by 50% and Proteus by 43% ( $p < 0.05$ ) (Fig. 5) than in the non-treated group.

#### Sensitivity to Antibiotics of Bacterial Isolates from the Skin of Lymphedematous Limbs

**Gram-positive cocci.** A slight decrease in the percentage of gram-positive cocci and gram-negative bacilli sensitive to penicillin was observed (Table 2). The differences were not statistically significant. Among the

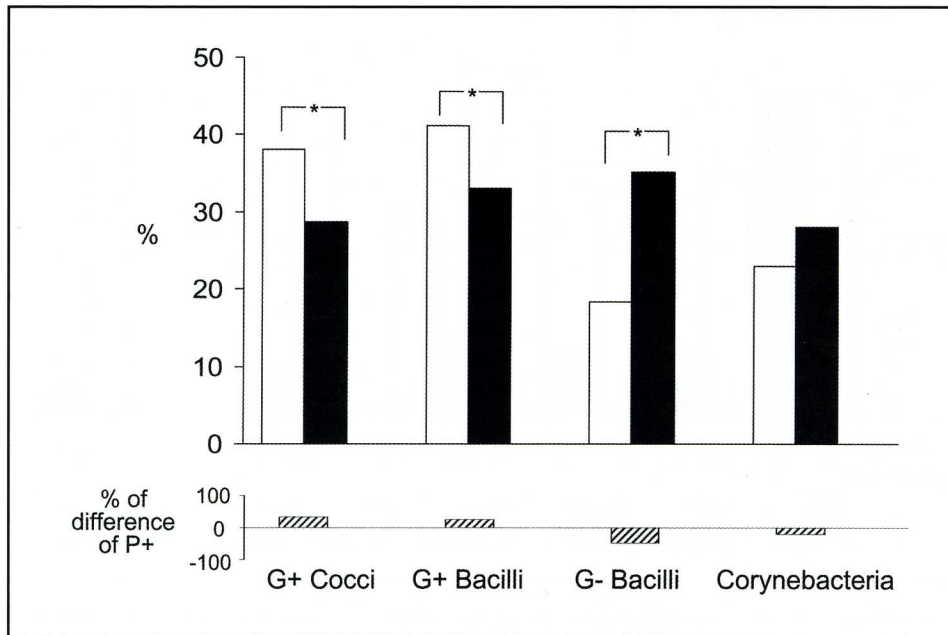


Fig. 3. The percentage of various species of isolates from the limb surface of the 12 month treated (open bars) and non-treated (black bars) patients. The mean difference between two groups expressed in percent (P+ penidur treated). \*  $p < 0.05$ .

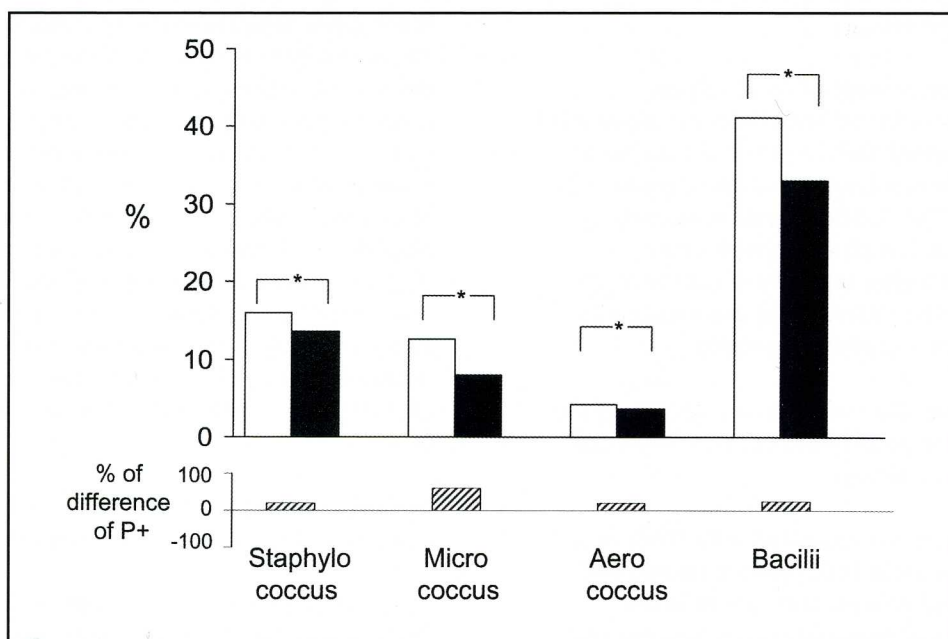


Fig. 4. The percentage of various strains of isolates from the limb surface of the 12 month treated (open bars) and non-treated (black bars) patients. The mean difference between two groups expressed in percent (P+ penidur treated). \*  $p < 0.05$ .

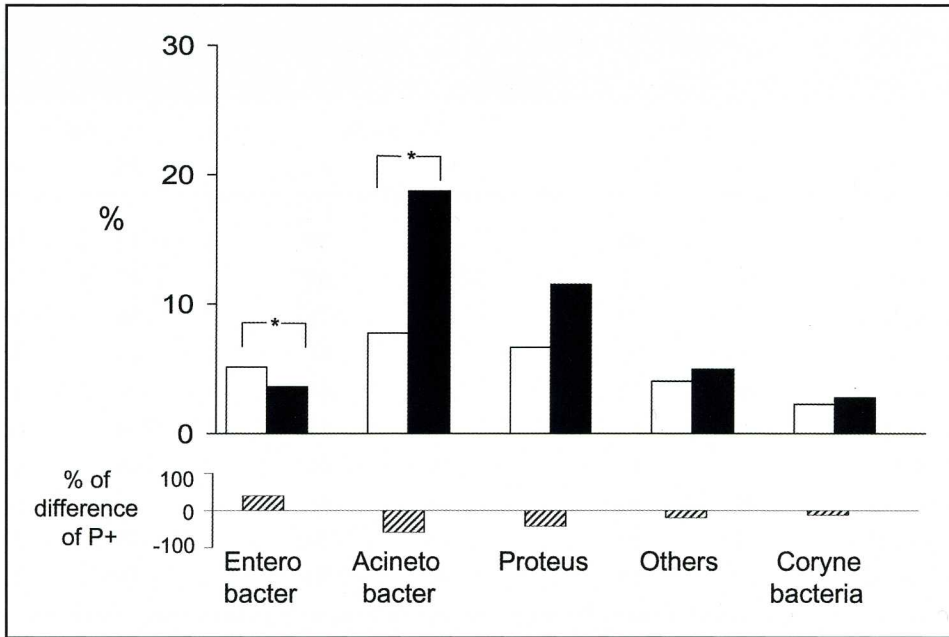


Fig. 5. The percentage of various strains of isolates from the limb surface of the 12 month treated (open bars) and non-treated (black bars) patients. The mean difference between two groups expressed in percent (P+ penidur treated). \*  $p < 0.05$ .

strains that became partly resistant were *Micrococcus spp* and *Enterococcus* (Table 3). However, the latter was a rather rare isolate on the skin surface.

**Sporulent bacilli.** There was no effect of penidur on the sensitivity to the antibiotics studied.

**Gram-negative bacilli.** Penidur had no effect on the sensitivity to antibiotics. A slight drop in sensitivity was only noted in the *Enterobacter spp.* population.

**Corynebacteria.** There was no effect of penidur on sensitivity to antibiotics.

**Gram-negative cocci.** A slight decrease in the percentage of strains sensitive to penicillin, oxacillin, erythromycin, vancomycin and rifampicin was observed. However, the number of gram-negative cocci isolated from skin surface was negligible.

#### *Spectrum of Bacterial Species in the Deep Tissues and Fluids of the Lymphedematous Limb in the Treated and Non-treated Groups*

The mean percentage of isolates from deep tissues and fluids was 36.4% in the treated compared to 50.1% in the non-treated group ( $p < 0.05$ ). The gram-positive bacilli were isolated in 22.1% in the treated and 25.7% in the non-treated group, the gram-negative bacilli in 50% and 14.6% ( $p < 0.05$ ) and the gram-positive cocci in 9.3% and 19.1% ( $p < 0.05$ ), respectively. Among the gram-positive bacilli the most common was *Bacillus cereus* and among cocci *Staph. epidermidis*. Major differences were found in the distribution of isolates in deep tissues, tissue fluid and lymph (Figs. 6-8). Generally, there was a lower prevalence of gram-positive cocci and gram-negative bacilli in penidur-treated group by 48 to 90%. Figure 9 summarizes the changes in prevalence of isolates from deep tissues and fluids after 12



**TABLE 2**  
**Mean Percentage of Isolates from the Skin Surface Sensitive to Various Antibiotics**

	G+ Cocci		G+ Bacilli		G- Bacilli	
	P+	P-	P+	P-	P+	P-
Penicillin	34*	41	28	29	12	50
Tobramycin	64	72	64	68	47	52
Gentamycin	75	73	71	71	56	55
Tetracyclin	75	72	74	67	52	52
Erythromycin	56	62	68	43	nd	nd
Lincomycin	60	51	51	45	nd	nd
Rimfapicin	73	63	50	41	nd	nd
Vancomycin	87	87	91	80	nd	nd
Cotrimoxazole	69	82	83	80	49	55
Ciprofloxacin	20	21	41	50	70	71

\* sensitivity score +++, P+ penidur-treated, P- non-treated, nd – not done

**TABLE 3**  
**Prevalence of Sensitivity to Antibiotics of Leg Skin Surface Selected Bacterial Strains in Patients with Lymphedema Treated with Penidur for 12 Months and Non-Treated (% of Sensitive Strains)**

	Bacterial Strains									
	Staphylococcus coag.		Micrococcus		Enterococcus		B. Cereus		Enterobacter	
	P+	P-	P+	P-	P+	P-	P+	P-	P+	P-
Penicillin	31**	39	51	83	16	5	10	7		n
Tobramycin		n		n	0	50	54	74	37	64
Gentamycin		n	72	100		n		n		n
Kanamycin		n	66	82		n	47	70		n
Erythromycin		n		n	0	100		n		n
Tetracyclin		n		n	39	89		n		n
Lincomycin		n		n	0	50		n		n
Rimfapicin		n		n	6	50		n		n
Vancomycin		n		n		n		n	73	91
Cotrimoxazole		n	61	100		n		n		n

P+ penidur treated; P- non-treated; \*\* sensitivity score +++; n – no difference

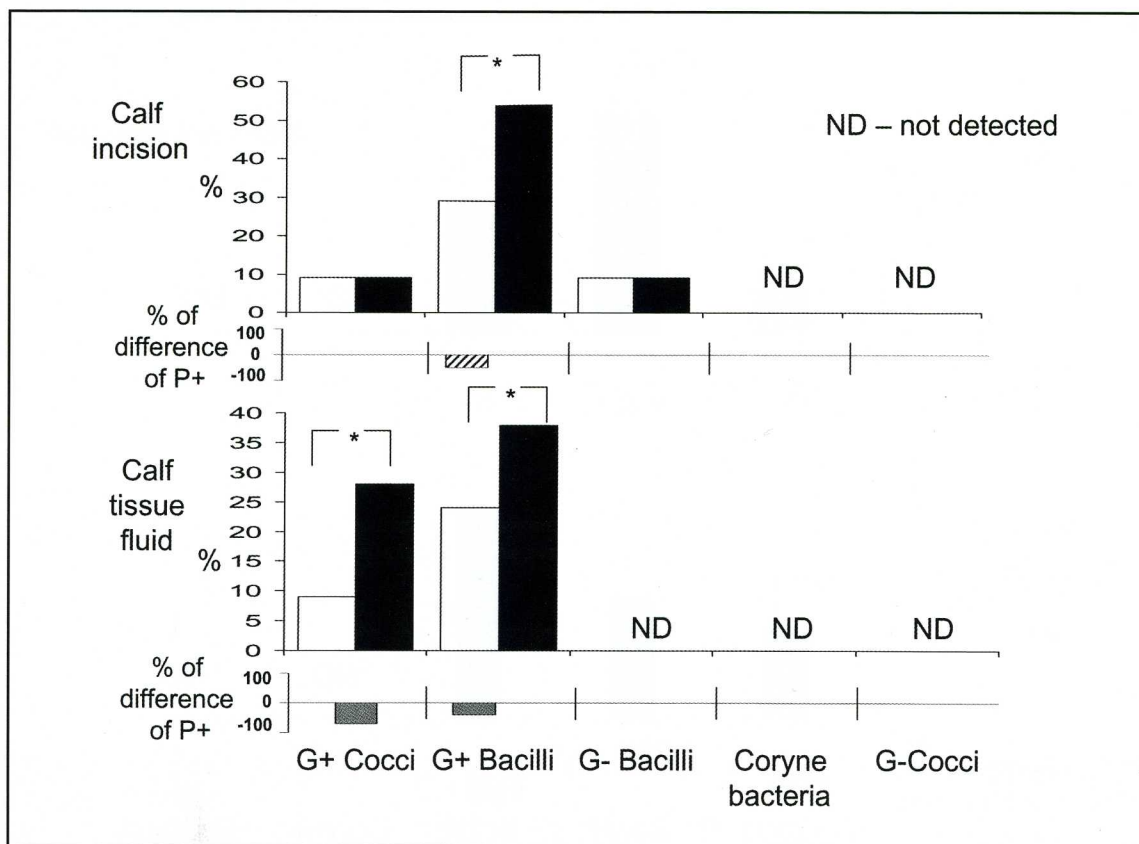


Fig. 6. The percentage of various strains of isolates from the limb deep tissues and fluids of the 12 month treated (open bars) and non-treated (black bars) patients. The mean difference between two groups expressed in percent (P+ penidur treated). \*  $p < 0.05$ .

months administration of penidur. With respect to tissue localization of gram-positive cocci evidently fewer of them were found in the treated group in the calf tissue fluid, thigh incision, thigh subcutis, lymph node and lymph. The prevalence of gram-positive bacilli was lower in calf tissues but higher in the thigh tissues and lymph nodes.

#### *Sensitivity to Antibiotics of Bacterial Isolates from the Deep Tissue and Fluids in the Penidur Treated and Non-treated Groups*

The sensitivity of bacterial isolates of gram-positive cocci, gram-positive and gram-negative bacilli did not change after

12 months of penidur administration (Tables 4 and 5). There were no differences in sensitivity of *Bacillus cereus* and *Staph. epidermidis*, *hominis*, *haemolyticus* and *cohnii*.

#### *Correlation Between the DLA Rate after Treatment and the Prevalence of Isolates in Lymph and Lymph Nodes*

The correlation between the decreasing DLA rate after treatment with penidur and the decreasing prevalence of cocci in tissue fluid, lymph and lymph nodes was  $R_p = 0.92$ . No correlation was found with respect to gram-positive bacilli.

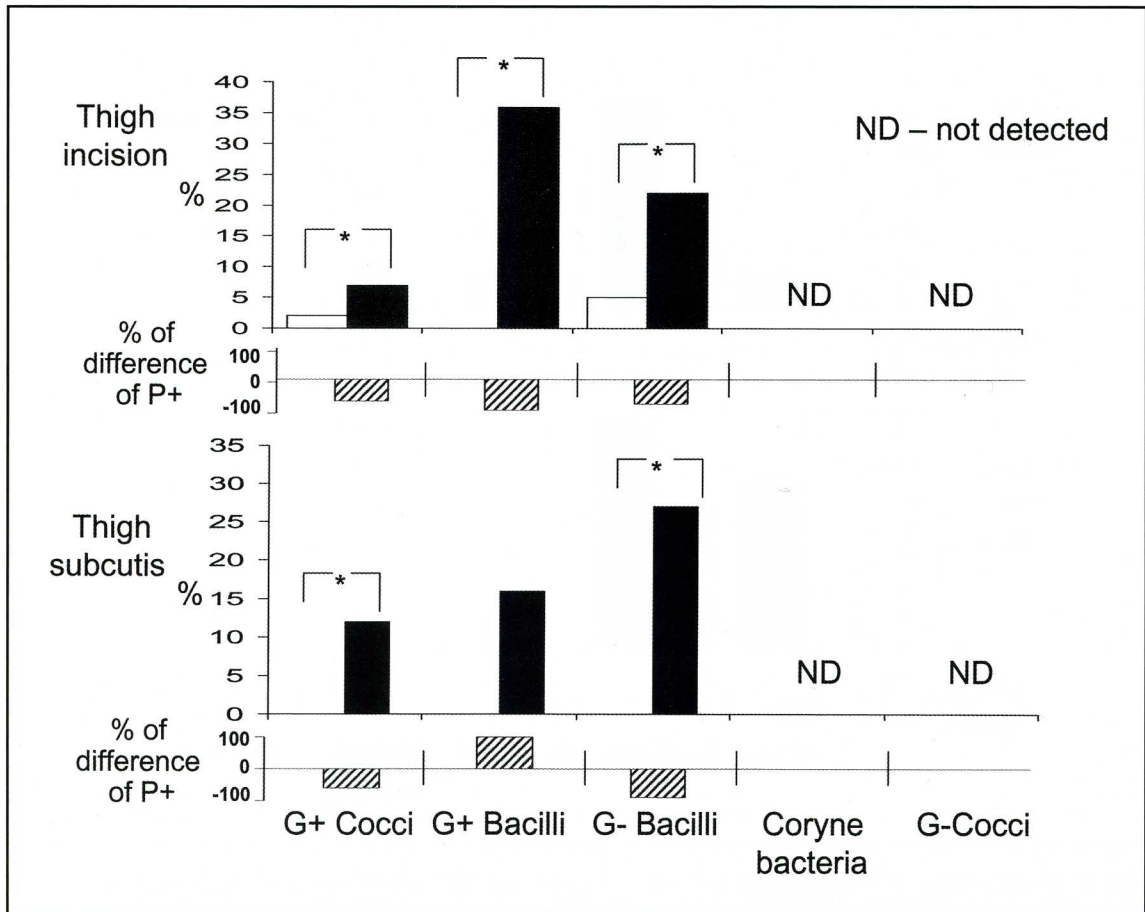


Fig. 7. The percentage of various strains of isolates from the limb deep tissues of the 12 month treated (open bars) and non-treated (black bars) patients. The mean difference between two groups expressed in percent (P+ penidur treated). \*  $p < 0.05$ .

## DISCUSSION

This study has provided the following information on the effects of long-acting penicillin (penidur) administration in patients with lymphedema suffering from recurrent DLA attacks: (a) an evidently lower recurrence rate of DLA, (b) increased prevalence of cocci and gram-positive bacilli with a concomitant decrease of gram-negative bacilli on the foot and calf skin surface, (c) decreased prevalence of gram-positive cocci and gram-negative bacilli isolates in limb deep tissues and lymph, and (d) no significant changes in the sensitivity to

penicillin and other tested antibiotics of bacterial strains isolated from the skin surface, deep tissues and lymph.

The decrease in frequency of DLA attacks should be attributed to the action of penicillin. This effect suggests that the bacterial factor is responsible for the outbursts of inflammatory reactions in the skin, lymphatics and lymph nodes. The results obtained corroborate our previous observations from a group of European patients with obstructive lymphedema of limbs receiving long-acting penicillin, whose frequency rate of DLA decreased by 94% (9). Also Shenoy et al (11) showed some positive

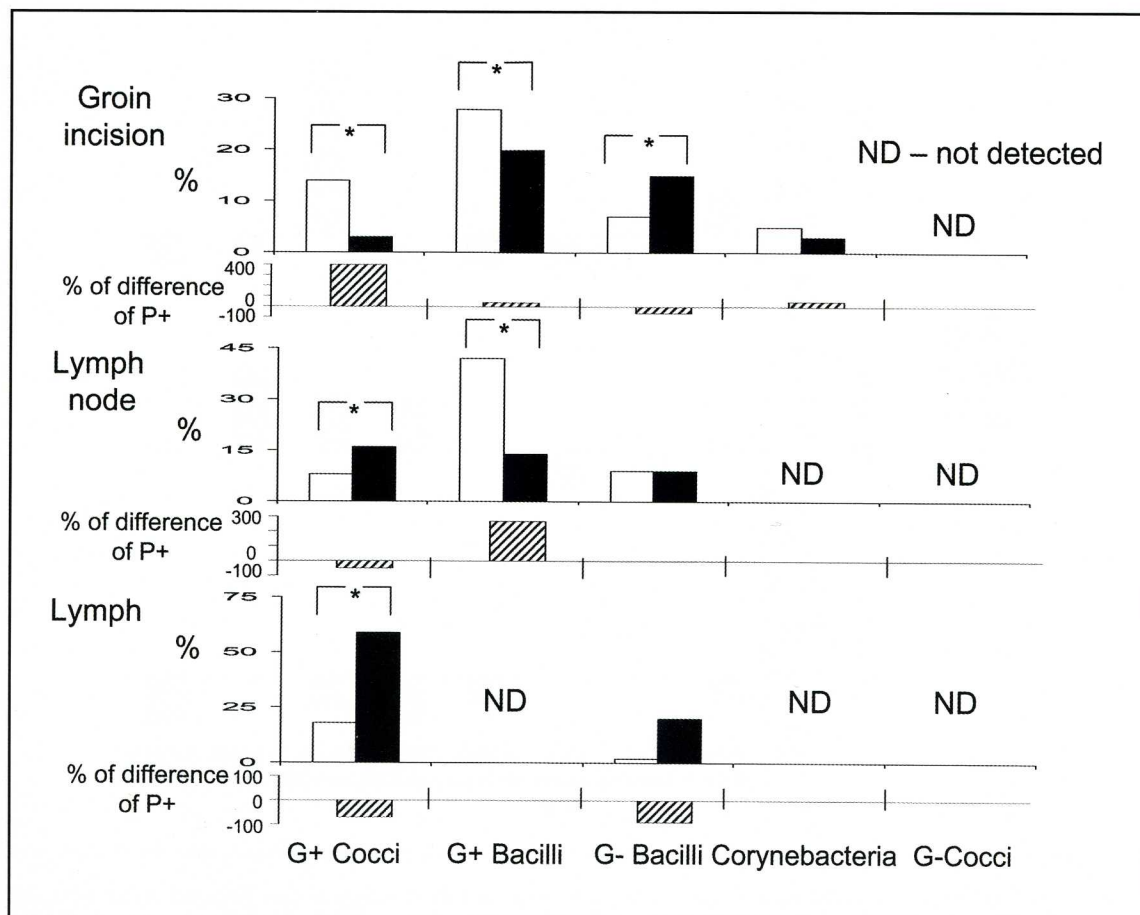


Fig. 8. The percentage of various strains of isolates from the limb deep tissues and fluids of the 12 month treated (open bars) and non-treated (black bars) patients. The mean difference between two groups expressed in percent (P+ penidur treated). \*  $p < 0.05$ .

effect of penicillin in preventing DLA attacks in lymphedema in patient with brugian filariasis. Badger et al (12) reported a decrease in the number of inflammatory episodes in the penicillin-treated groups.

We also looked at the effects of long-term penicillin administration on the bacterial flora of limb skin surface and deep tissues. The prevalence of cocci and gram-positive bacilli increased on the limb skin surface, although this change was rather small when compared to the non-treated group. The increased prevalence of these species might be accounted for by their slight increase in resistance to antibiotics, although statistically

non-significant. Interestingly, we did not observe differences in the spectrum of bacterial strains on the skin surface of the lymphedematous and contralateral normal limbs (data not included).

The change in prevalence of bacterial strains, under the influence of penidur, in deep tissues remained at variance with that of skin flora. A decrease in prevalence of cocci and gram-negative bacilli was observed in deep tissues that was not observed on the skin surface. This difference may be attributed to the expected differences in concentration of penicillin penetrating dermis and sweat glands compared with the

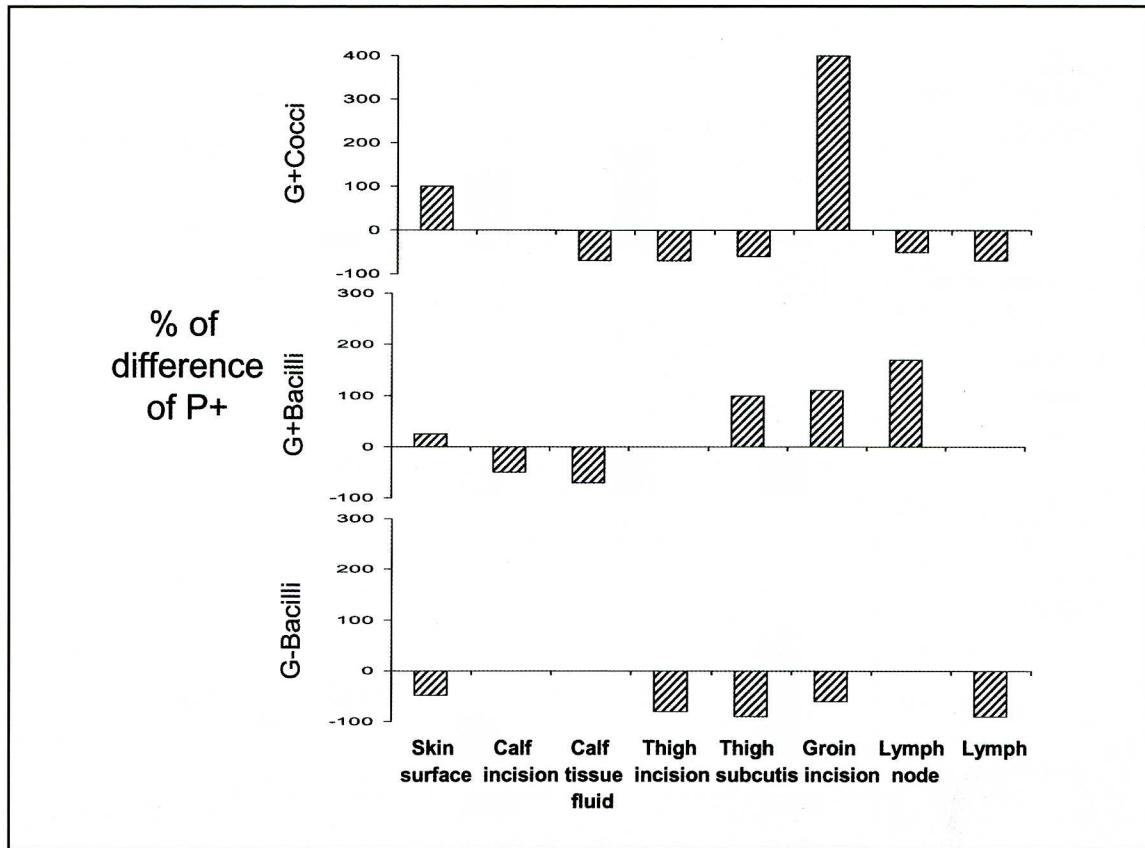


Fig. 9. Mean differences in prevalence of various isolates from various anatomical sites between the treated and non-treated group in percent.

subcutaneous tissue, lymph node tissue, interstitial fluid and lymph as well as to a different biochemical environment for bacterial colonization. The observed decrease in prevalence of cocci in deep tissues and lymph is clinically important, as the coagulase-negative Staphylococci evoke chronic inflammatory reaction following skin penetration (13,14) and are frequently isolated from the lymphedematous skin (6,7). The coincidence of lower frequency of cocci in deep tissues and lymph with a drop of the DLA rate may not be accidental. The calculated correlation coefficient was high.

An interesting observation was that of a relatively high prevalence of bacteria in the thigh and groin tissue of patients treated with

penidur and to a certain degree in lymph nodes, compared with the calf tissue fluid and lymph. This finding may be accounted for by the transport of microbes in lymph to the upper parts of the limb (15,16) as well as physiological colonization of the groin by certain strains and poor hygiene.

Another clinically important finding was lack of development of resistance to penicillin and other antibiotics by the deep tissue and fluid isolates. This observation may be explained by a low dose of administered penidur and subsequently low concentration of this antibiotic in the recipient tissues and fluids, as well as the fact that the subject's own bacterial skin flora was not previously exposed to the wide-spectrum antibiotics.

**TABLE 4**  
**Mean Percentage of Isolates from the Deep Tissues and Fluids Sensitive to Various Antibiotics**

	G+ Cocci		G+ Bacilli		G- Bacilli	
	P+	P-	P+	P-	P+	P-
Penicillin	44	59	53	31	58	57
Tobramycin	80	81	68	59	56	36
Gentamycin	84	86	72	65	89	64
Tetracyclin	84	77	66	70	52	54
Erythromycin	76	73	86	82	nd	nd
Lincomycin	84	76	79	41	nd	nd
Rimfapicin	92	95	100	100	nd	nd
Vancomycin	92	91	96	94	nd	nd
Cotrimoxazole	72	78	94	94	83	92

\* sensitivity score +++, nd – not done

**TABLE 5**  
**Prevalence of Sensitivity to Antibiotics of Leg Deep Tissues and Fluids Selected Bacterial Strains in Patients with Lymphedema Treated with Penidur for 12 Months and Non-Treated (% of Sensitive Strains)**

	Bacterial Strains									
	Staphylococcus coag.		Micrococcus		Enterococcus		B. Cereus		Enterobacter	
	P+	P-	P+	P-	P+	P-	P+	P-	P+	P-
Penicillin	43**	56	60	79	15	15	15	12		n
Tobramycin		n		n	40	50	50	70	45	60
Gentamycin		n	80	92		n		n		n
Kanamycin		n	75	85		n	50	70		n
Erythromycin		n		n	60	100		n		n
Tetracyclin		n		n	50	80		n		n
Lincomycin		n		n	40	48		n		n
Rimfapicin		n		n	21	45		n		n
Ciprofloxacin		n		n		n		n	80	90
Cotrimoxazole		n	61	100		n		n		n

P+ pendur treated; P- non-treated; \*\* sensitivity score +++; n – no difference

In the few cases with recurrence of DLA in stage IV, no specific bacterial strains were identified nor was there resistance to antibiotics detected. We suggest that bacterial load rather than the type of bacterial species is responsible for lack of penicillin effects.

In conclusion, we showed that long-acting penicillin (penidur) in low doses effectively lowers the frequency rate of DLA; there is a lower prevalence of the gram-positive cocci and gram-negative bacilli most likely responsible for recurrence of DLA, in deep tissues and lymph; and no resistance to penicillin and other antibiotics develops after a 12 month treatment.

#### ACKNOWLEDGMENTS

This study was supported by funds from the Indian National Science Academy, India and the State Committee for Scientific Research, Poland.

#### FINANCIAL DISCLOSURE

The author(s) have no financial interest in penidur or in Wyeth Pharmaceutical.

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