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TETRACYCLINE-RESISTANT HAEMOLYTIC STREPTOCOCCI IN PATIENTS WITH LEG ULCERS

An Argument for Changing the Topical Treatment

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Abstract. Tetracycline-resistant (t-r) haemolytic streptococci occurred in 17 of 145 patients with leg ulcers, 58 of whom had been treated with terramycin-polymyxin B powder. The number of t-r streptococci isolated fell when the use of terramycin-polymyxin B powder was replaced by local chlorhexidine, but increased again when the use of terramycin-polymyxin B powder was resumed for a shorter period. Patients with ulcers of long duration appear to be particularly exposed to infection with t-r streptococci and with *Serratia marcescens* simultaneously. The number of t-r streptococci in the dermatological ward and the other departments of the hospital are compared. The change in treatment from terramycin-polymyxin B powder to chlorhexidine does not appear to have any influence on the course of the disease.

Some months after the opening of the dermatological outpatient clinic, tetracycline-resistant (t-r) streptococci were isolated from leg ulcers. Consequently it was found of interest to study the epidemiology, conditions which might favour selection of t-r streptococci, and finally if there was any difference in healing time and complications between those patients harbouring resistant streptococci and those without.

The first report of *in vivo* acquired tetracycline resistance by streptococci was published by Lowbury & Cason (3) in 1954. This was followed by publications by, for example, Kuharic et al. (1) who found that 20% of group A strains were t-r, while Mitchell & Baber (4) reported their findings as 32%. Robertson (6) found in successive studies carried out in south-west Essex (England) that the percentage of t-r strains remained at approximately 30. Reports of group G t-r streptococci are given by Köhler (2), Pulverer (5) and Robertson (6).

MATERIALS AND METHODS

Patients. This study covers the period from July 1969 to December 1970, a total of 18 months. The number of patients being treated for leg ulcers increased throughout the period from 31 to 107 per month. The study comprises 145 patients with leg ulcers of various etiology, though venous ulcers constitute the majority.

In the beginning the standard treatment was a powder containing oxytetracycline 3% and polymyxin B 0.1% (Pfizer). In January 1970 the use of terramycin-polymyxin B powder was changed to chlorhexidine ointment or powder. Apart from this the treatment of leg ulcers was unchanged throughout the period, viz. compression bandaging. Routinely the patients were seen once a week.

Bacteriological examinations. On every visit the ulcers were swabbed. Swabs from nose and throat of the staff were examined December 1969 and December 1970.

Culture was started on the same day with primary sensitivity testing on the medium described by Frølund Thomsen (7) and with tablets manufactured by "Rosco". As resistant to tetracycline were recorded strains with zones of 22 mm or less, corresponding to a minimal inhibitory concentration of 4 μg/ml, or more.

Group and type determinations were performed at the Streptococcus Department, Statens Serum Institut, Copenhagen.

RESULTS

The haemolytic streptococci isolated in the period July 1969 to December 1970 are shown in Table I.

The group distribution of the streptococci from the dermatological department differed from that found from the rest of the hospital. In the dermatological department the streptococci of group G comprised approximately half of the total number of haemolytic streptococci isolated and they were 30–35 times more frequent in the specimens than in those from the rest of the hospital. Fifty to seventy per cent of the group G strains from the

Table I. *Incidence of haemolytic streptococci isolated July 1969–December 1970 from patients in the Dermatological Department compared with the other departments of the hospital*

Incidences of tetracycline-resistant streptococci are given in parentheses

		Group					Total no. of specimens
		A	B	G	Others	Total	
July–December 1969	Derm. Dept.	16 (3)	3 (2)	15 (11)	5 (0)	39 (16)	736
	Other Dept.	88 (2)	52 (17)	17 (0)	42 (0)	199 (19)	19 807
January–June 1970	Derm. Dept.	21 (2)	4 (1)	19 (14)	4 (0)	48 (17)	848
	Other Dept.	91 (0)	67 (17)	26 (3)	39 (0)	223 (20)	21 718
July–December 1970	Derm. Dept.	13 (1)	4 (0)	21 (12)	5 (0)	43 (13)	698
	Other Dept.	55 (0)	49 (17)	40 (3)	35 (2)	179 (22)	22 014

dermatological department were resistant to tetracycline compared with 0–10% in the rest of the hospital.

From 6 patients in other departments, t-r streptococci of group G were isolated. Two of these had been referred to the dermatological outpatient clinic for treatment of leg ulcers and both of these patients had been treated with terramycin-polymyxin B powder.

There are very few streptococci of group B in our patients (Table I) and only one isolated from a leg ulcer.

The patients were divided into two groups according to the presence of streptococci (Table II). There is a predominance of men in the group with t-r streptococci ($\chi^2 = 4.8$, $f = 1$, $0.02 < P < 0.05$). The duration of treatment in the latter group is twice as long as that of the other group. Furthermore it is seen that three-quarters of the patients with t-r streptococci had been treated with terramycinpolymyxin B powder as opposed to approximately one-third of the other group ($\chi^2 = 7.2$, $f = 1$, $P < 0.01$).

Table II. *A survey of two groups of patients with leg ulcers*

I. 128 patients without growth of tetracycline-resistant streptococci
II. 17 patients with growth of tetracycline-resistant streptococci

	♂	♀	Average age	No. of patients treated with T-P-powder[a]	Average duration of outpatient treatment (days)
I	47	81	64	46 (36%)	121
II	11	6	65	12 (71%)	242

[a] T, tetracycline; P, polymyxin B.

The amount of terramycin-polymyxin B powder used during the period is shown in Fig. 1 (lower section). The total consumption in the latter half of 1969 was 1 059 g, while the corresponding consumption for the whole of 1970 was 284 g. However, a considerable amount of powder was used in the summer of 1970 as a new assistant treated the patients with terramycin-polymyxin B powder, not being aware that the study was in progress.

Fig. 1 (upper section) shows the month in which the t-r streptococci were first isolated, the sex distribution and the groups to which the streptococci belonged. The upper curve shows the prevalence of patients with t-r streptococci. A comparison between the two figures shows that there is a time lag between the use of terramycin-polymyxin B powder and the appearance of t-r streptococci in the ulcers. In the beginning the spread of the t-r streptococci occurred only in the male ward. No new case appeared in the spring of 1970, but t-r streptococci reappeared following the resumption of treatment with terramycin-polymyxin B powder. An average of 55 days passed from the patient's first visit in the clinic to the appearance of the t-r streptococci.

In Table III, a comparison is made of the bacteria isolated from the ulcers of 46 patients

without t-r streptococci (I), 12 patients with t-r streptococci (II), both groups treated with terramycin-polymyxin B powder and 5 patients not so treated but having t-r streptococci (III). The table shows that a higher incidence of gram negative rods occurred in patients with t-r streptococci. The presence of *Serratia marcescens* is conspicuous as only 7 of the 145 patients had growth of *Serratia marcescens*, compared with 5 out of 12 (Table III) with t-r streptococci. Fifteen patients had t-r streptococci of group G and 2 patients of group A (types 1 and 12 respectively). None of the haemolytic streptococci isolated were resistant to penicillin.

Change of treatment to topical chlorhexidine has not influenced the course. The average duration in patients treated solely with chlorhexidine was 101 days.

Circumscript cellulitis was seen in 4 out of 17 patients with t-r streptococci—not more often than in other patients with leg sores (17 out of 128 patients). Nose and throat swabs from the staff did not result in growth of haemolytic streptococci.

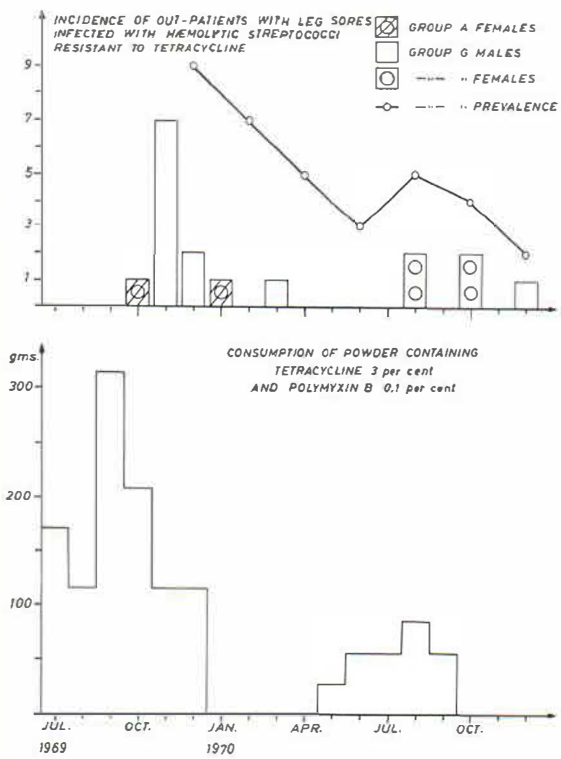

Fig. 1.

Table III. *Bacterial strains isolated from leg ulcers*

I. 46 T–P[a] treated patients without T-resistant streptococci
II. 12 T–P treated patients with T-resistant streptococci
III. 5 patients not treated with T–P but with T-resistant streptococci.

	I	II	III
Staphylococcus aureus	33	10	4
Other Micrococci	14	1	2
Haemolytic streptococci			
Group A	—	1	1
Group B	1	—	—
Group G	—	11	4
Streptococcus faecalis	11	3	1
Klebsiella pneumoniae	3	1	—
Enterobacter cloacae	2	—	—
Proteus mirabilis	2	1	1
Proteus vulgaris	1	1	—
Proteus morgani	2	—	—
Proteus rettgeri	1	1	—
Serratia marcescens	—	5	—
Pseudomonas aeruginosa	—	3	3

[a] T, tetracycline; P, polymyxin B.

DISCUSSION

None of the patients harboured t-r group G streptococci in their ulcers on admittance and streptococci were first isolated after approximately 2 months.

Spread of the t-r streptococci was rapid at the start, but ceased when the use of terramycin-polymyxin B powder was discontinued (Fig. 1). However, a few patients were infected when the powder was used accidentally.

That t-r streptococci of group G did dominate in the clinic is surprising as they were not common in the rest of the hospital (Table I), and as it was t-r streptococci of group A that were first isolated in the clinic. Perhaps the spread occurred in the male ward accidentally starting from a patient with group G t-r streptococci. This would explain the predominance in men (Table II, Fig. 1).

Pulverer (5) found that approximately 10% of 73 randomly chosen t-r strains belonged to group G. We found in the dermatological department 69–92% but for the rest of the hospital frequencies similar to Pulverer's (Table I). Three per cent of the streptococci of group A isolated were resistant to tetracycline, which is considerably lower than the figures quoted in Anglo-saxon literature (1, 3, 4, 6).

Treatment of patients with t-r streptococci was

twice as long as that of patients without these streptococci. The streptococci may have contributed to the longer duration of the ulcers, or ulcers of long duration were more apt to be infected as the patients had many visits to the clinic. The anaerobic conditions in deep ulcers may have favoured the streptococci and *Serratia marcescens* as well, explaining the coincidence of these two species in 5 patients out of 12 (Table III). This coincidence cannot be a random result of the powder containing tetracycline and polymyxin B as seen from comparison of columns I and II in Table III ($t = 4.6$, $f = 58$, $P < 0.001$).

CONCLUSION

Our results show that the use of a powder containing tetracycline in a milieu where streptococci are prevalent will promote the spread of t-r streptococci with consequent risk of infection of other patients.

The topical use of chlorhexidine, which is a compound with minimal risk of sensitization and with no influence on the sensitivity pattern of micro-organisms, has not changed the length of treatment. Furthermore, no increase has been seen in the incidence of bacterial complications following the use of this compound.

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