SENSITIVITY OF *Neisseria gonorrhoeae* TO PENICILLIN AND OTHER ANTIBIOTICS*

STUDIES CARRIED OUT IN TORONTO DURING THE PERIOD 1961 TO 1968

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For many years the Provincial Public Health Laboratory at Toronto has attempted to maintain an efficient service for the laboratory diagnosis of gonorrhoea. In the early years of its formation the Gonococcus Diagnosis Unit processed only a few hundred specimens by cultural methods, the main task being the microscopic examination of smears submitted by private physicians and hospital clinics. The work has continued to increase until at the present time the number of genital exudate specimens examined each month by cultural methods exceeds 3,000, more than 200 strains of *N. gonorrhoeae* being isolated. The majority of these specimens are leucorrhoeal discharges not caused by gonococci: this explains the low percentage of isolations. Each strain isolated is tested for sensitivity to penicillin, sulphadiazine, tetracycline, and chloramphenicol. In addition, several of the newer antibiotics recommended for the treatment of gonorrhoea have been investigated *in vitro*. The considerable amount of information thus collected has been analysed and the results are here presented. The value of this study would have been greatly increased if it had been possible to include clinical data and results of treatment. Unfortunately, this was not possible because the specimens were usually submitted with no information except the name of the physician and his patient. No follow-up was attempted.

It should be borne in mind that these findings refer only to strains isolated during a certain period of time from patients living in one metropolitan area. In another city such as Windsor, Ontario, which differs from Toronto in its topographical and

sociological characteristics, the incidence and spread of the disease are not the same; and the sensitivity to antibiotics of gonococci presently circulating in the two populations is known to be different.*

The introduction of exotic strains of gonococci (for example, directly or indirectly from South-East Asia) into a large urban population is a matter of great importance because these may have a different antibiotic sensitivity pattern to that of established strains. The recognition of such 'new' strains is one of the main reasons why surveillance studies of this kind must be continued.

Methods

Specimens of genital discharge were sent to the laboratory in a modified Stuart's transport medium (Amies, 1967a) in which the viability of the gonococcus is maintained for a period of 2 to 3 days. Smears of exudate were submitted at the same time. Cultivation was carried out on a highly selective serum—yeast extract agar medium containing antibiotics (Amies and Garabedian, 1967) with incubation at 37°C. in an atmosphere containing 4 per cent. CO₂. Confirmation was obtained by the fluorescent antibody method, using F A gonococcus antiserum prepared by the Difco Laboratories.

Antibiotic sensitivity tests were performed by streaking a pure culture of each isolate on Mueller Hinton agar (Difco) containing 5 per cent. ox serum and sufficient antibiotic solution to provide the required concentration. In the case of penicillin G, a series of five different concentrations was prepared: 0.03, 0.1, 0.3, 1.0, and 3.0 units per ml., equivalent to 0.018, 0.06, 0.18, 0.62, and 1.86 µg./ml. It may be objected that a considerable amount of the penicillin is fixed by the serum component of the medium. This is so, but in performing tests of this nature it is essential to employ a culture medium which supports good growth of the organism.

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Furthermore, in clinical practice, the drug is required to act in the presence of the patient's plasma proteins, so the test *in vitro* should attempt to approximate the same conditions. The culture plates were used within the week following their preparation. A disc technique is not satisfactory for determining the sensitivity of the gonococcus to antibiotics.

A suspension of each strain to be tested was prepared by adding one full 2 mm.-loopful of growth to 0.4 ml. thioglycollate broth. An even dispersion was obtained by rapidly rotating a cotton or rayon-tipped swab in the broth. One 2 mm.-loopful of this suspension (opacity approximately No. 10 on the McFarland scale) was then spread over a quadrant of the antibiotic-containing medium. Ten or more strains could be accommodated on each plate. They were incubated in a humid atmosphere with 4 per cent. CO₂ for 48 hours before the results were recorded.

A similar procedure was adopted in the case of other antibiotics. Precisely assayed samples of each drug were obtained through the courtesy of the various manufacturers. Stock 1 per cent. sterile solutions were prepared and dispensed into small vials for storage in the frozen state. A fresh vial was opened for each batch of medium.

Results

The results of growth-inhibition tests are usually expressed as minimum inhibitory concentrations (MIC), that is, the smallest concentration of antibiotic required to inhibit growth completely. For some purposes, however, it is more instructive to indicate the lowest concentration to which the organism is resistant. A diagram illustrating the gradual development of resistance to an antibiotic is a more direct demonstration than a curve indicating decreasing sensitivity. This method is followed here in the case of penicillin G. The procedure followed with the other drugs was first to test a series of strains at several concentrations likely to be attained in the blood plasma. With the experience so obtained it was then possible to select a single limiting concentration. Sensitivity to this concentration was then accepted as evidence that the drug, given in normal therapeutic doses, would probably be effective, whereas resistance to this concentration suggested that unsatisfactory clinical results would be obtained.

Penicillin

The results of a 6-year study of the development of resistance to penicillin have already been published (Amies, 1967b). The figure presented in that communication has now been re-drawn and brought up to date, so as to include all the strains tested during the years 1966, 1967, and the first half of 1968. The new graph (Figure) shows that the

rate of increase of resistance to penicillin was not maintained during 1967. This was perhaps the result of fewer treatment failures after giving much larger doses of penicillin than was formerly believed necessary. Another factor is the increasing use of newer antibiotics, particularly the tetracyclines, by physicians who have had experience with clinical relapses after penicillin treatment. Penicillin resistant strains are thus eliminated by treatment with another antibiotic. A summary of the results obtained in 1967 is given in Table I.

TABLE I
SENSITIVITY OF 1,976 STRAINS OF *N. GONORRHOEA* TO PENICILLIN G IN THE YEAR 1967

MIC (units/ml.)	No. of Strains	Percentage of Total	Cumulative Percentage
0.03	689	34.9	—
0.1	374	19.0	53.9
0.3	545	27.5	81.4
1.0	334	16.9	98.3
3.0	34	1.7	100.0

During the first half of 1968 the upward trend of resistant strains was resumed (Figure). There is reason to believe that many of the highly resistant strains isolated during that period had been recently introduced into the Toronto area. In a few cases at least the physician had noted on the data sheet that the patient had contracted the disease while on holiday abroad. The evidence, however, is mainly based on the fact that the antibiotic sensitivity pattern of these new strains was different from that of strains isolated locally in previous years. Further reference to this subject will be made in the sections dealing with tetracycline and chloramphenicol.

*January 1 to June 30 only.

FIGURE.—Resistance of gonococci to penicillin, 1959-1968.

It may be inferred from a study of Table I that many treatment failures will occur unless a concentration of 1 unit penicillin per ml. plasma is reached and maintained for a sufficient length of time to bring the infection under control. The clinical implications of this finding will be discussed later.

Ampicillin

The range of sensitivity to this broad-spectrum penicillin was determined in a series of 137 strains isolated in January, 1967. The results are given in Table II.

TABLE II
SENSITIVITY OF 137 STRAINS OF *N. GONORRHOEAE*
TO AMPICILLIN IN JANUARY, 1967

MIC ($\mu\text{g./ml.}$)	No. of Strains	Percentage of Total	Cumulative Percentage
0.03	52	37.9	—
0.1	52	37.9	75.8
0.3	28	20.4	96.2
1.0	2	1.5	97.7
3.0	3	2.2	100.0

Routine testing of all isolates was carried out from February to October, 1967, using two concentrations only: 0.1 $\mu\text{g./ml.}$ and 1.0 $\mu\text{g./ml.}$ The results are summarized below:

Total number of strains tested	1,230
Sensitive to 0.1 $\mu\text{g./ml.}$	993 (80.1 per cent.)
Sensitive to 1.0 $\mu\text{g./ml.}$	231 (18.7 per cent.)
Resistant to 1.0 $\mu\text{g./ml.}$	6 (1.2 per cent.)

In comparing the results obtained with penicillin and ampicillin allowance must be made for the fact that one international unit of penicillin G is equivalent to only 0.62 $\mu\text{g.}$ of the pure substance. Sensitivity to these two antibiotics was, in fact, very similar.

Hetacillin

Hetacillin (Versapen, Bristol), a derivative of 6-aminopenicillanic acid, has been recommended for the treatment of gonococcal infections on account of

the high concentration of drug obtainable in the urine and tissues of the urinary tract. The bactericidal effect of this drug on the gonococcus was studied in a series of 327 fresh isolates. Table III summarizes the results and includes a comparison with the sensitivity of these same strains to penicillin G.

Resistance to penicillin is correlated with resistance to hetacillin, and the minimal inhibitory concentrations of the two drugs are similar. Any advantages that hetacillin may possess over penicillin are thus not demonstrable by the *in vitro* tests employed here.

Cephaloridine

Oller (1967a, 1967b) has reported his findings in two clinical studies supported by antibiotic disc sensitivity tests. Strains of gonococci that showed a reduced sensitivity to penicillin also showed some degree of resistance to cephaloridine; and, in general, the response to treatment was correlated with the degree of sensitivity to the drug *in vitro*. Cephaloridine has one very considerable advantage; it may be safely used in patients who have become sensitized to penicillin. Other clinical studies have recently been reported by McLone, Scotti, Mackey, and Hackney (1968) and by Jouhar and Fowler (1968).

The present studies include 369 freshly isolated strains tested on cephaloridine-containing medium. The results are set out in Table IV.

TABLE IV
SENSITIVITY OF 369 STRAINS OF *N. GONORRHOEAE*
TO CEPHALORIDINE, OCTOBER TO DECEMBER, 1967

MIC ($\mu\text{g./ml.}$)	No. of Strains	Percentage of Total	Cumulative Percentage
1.0	110	29.8	29.8
3.0	130	35.2	65.0
10.0	126	34.1	99.1
> 10.0	3	0.9	100.0

A comparison of the sensitivity of these same 369 strains to penicillin and cephaloridine is given in Table V.

TABLE III
COMPARISON OF SENSITIVITY OF 327 STRAINS OF *N. GONORRHOEAE* TO PENICILLIN G AND HETACILLIN

MIC ($\mu\text{g./ml.}$)	Penicillin G			MIC	Hetacillin		
	Number of Strains	Per cent. Sensitive	Cumulative Percentage		Number of Strains	Per cent. Sensitive	Cumulative Percentage
0.018	89	27.2	—	—	—	—	—
0.06	64	19.5	46.7	0.1	181	55.3	—
0.18	77	23.5	70.2	0.3	137	41.9	97.2
0.62	97	29.6	100.0	1.0	9	2.7	100.0

TABLE V

COMPARISON OF SENSITIVITY OF 369 STRAINS OF *N. GONORRHOEAE* TO PENICILLIN AND CEPHALORIDINE

PENICILLIN		CEPHALORIDINE			
MIC (units/ml.)	No. of Strains	MIC Number of Strains Sensitive to—(μg./ml.)			
		1	3	10	> 10
0.03	142	96	45	1	0
0.1	79	14	58	7	0
0.3	92	0	25	67	0
1.0	53	0	2	51	0
> 1.0	3	0	0	0	3

These figures indicate that cephaloridine is unlikely to be of value in the treatment of penicillin-resistant cases of gonorrhoea. They thus confirm the work of Oller cited above.

Erythromycin

This antibiotic was included in the investigation because some authorities regard it as the drug of choice for the treatment of gonorrhoea. A small series of 175 strains was tested during July and August, 1967, with the results shown in Table VI.

TABLE VI

SENSITIVITY OF 175 STRAINS OF *N. GONORRHOEAE* TO ERYTHROMYCIN IN THE YEAR 1967

MIC (μg./ml.)	No. of Strains	Percentage of Total	Cumulative Percentage
0.1	49	28.0	—
0.3	75	42.8	70.8
1.0	45	25.7	96.5
3.0	6	3.5	100.0

The results obtained with erythromycin were then compared with the corresponding figures for penicillin. The analysis presented in Table VII lends no support to the belief that erythromycin is a valuable alternative to penicillin in the treatment of gonorrhoea. In general, sensitivity to these two antibiotics runs a parallel course, and only occasionally do the results suggest that an infection with a penicillin-resistant strain might respond to treatment with erythromycin.

TABLE VII

COMPARISON OF SENSITIVITY OF 175 STRAINS OF *N. GONORRHOEAE* TO PENICILLIN AND ERYTHROMYCIN

PENICILLIN		ERYTHROMYCIN			
MIC (units/ml.)	No. of Strains	MIC No. of Strains Sensitive to—(μg./ml.)			
		0.1	0.3	1.0	3.0
0.03	53	24	26	2	1
0.1	36	13	17	4	2
0.3	55	4	26	24	1
1.0	30	8	6	15	1
3.0	1	—	—	—	1

Spiramycin

Spiramycin (Rovamycin, Poulenc) has a lower activity *in vitro* than erythromycin to which it is chemically closely related. However, it is said to persist longer in the tissues and is concentrated 5-fold in the kidney. For these reasons its use in the treatment of gonorrhoea has been suggested, and clinical reports by Willcox (1956), Siboulet and Durel (1961), and others have been favourable.

Sensitivity to spiramycin *in vitro* was determined in a series of 181 strains isolated in April and May, 1967. The results are recorded briefly in Table VIII. Comparison with the erythromycin results

TABLE VIII

SENSITIVITY OF 181 STRAINS OF *N. GONORRHOEAE* TO SPIRAMYCIN IN THE YEAR 1967

MIC (μg./ml.)	No. of Strains	Percentage of Total	Cumulative Percentage
0.3	12	6.6	—
1.0	104	57.5	64.1
3.0	54	29.8	93.9
≥ 5.0	11	6.1	100.0

(Table VI) confirms the statement, made above, that the latter has a higher activity *in vitro*. A separate analysis showed a close correlation between the degrees of resistance to penicillin and spiramycin.

Tetracycline

The range of sensitivity to tetracycline was first established in March, 1966, by determining the minimum inhibitory concentrations of a series of 292 recently isolated unselected strains of *N. gonorrhoeae*. The results are presented in Table IX.

TABLE IX

SENSITIVITY OF 292 STRAINS OF *N. GONORRHOEAE* TO TETRACYCLINE IN THE YEAR 1967

MIC (μg./ml.)	No. of Strains	Percentage of Total	Cumulative Percentage
0.1	18	6.2	—
0.3	152	52.1	58.3
1.0	110	37.6	95.9
3.0	12	4.1	100.0

On the evidence of these findings it was decided to test all isolates for sensitivity to tetracycline at the 1.0 μg./ml. level only. This concentration is readily attained in the blood plasma by administering the drug in the usual dosage of 250 mg. 6-hrly. The results obtained in the years 1966, 1967, and the first 6 months of 1968 are set out below:

Period of Time	Mar.—Dec., 1966	Jan.—Dec., 1967	Jan.—June, 1968
No. of strains tested	1,445	1,976	1,538
Sensitive to 1.0 μg. tetracycline/ml.	95.3 per cent.	95.5 per cent.	91.2 per cent.
Resistant to 1.0 μg. tetracycline/ml.	4.7 per cent.	4.5 per cent.	8.8 per cent.

It may be said, therefore, that the strains of *N. gonorrhoeae* presently circulating in the Toronto area are usually sensitive to tetracycline and that, up to the close of 1967, this sensitivity showed no signs of decreasing in spite of the fact that this drug was being used to an increasing extent for the treatment of penicillin-resistant cases. The figures for 1968, however, are less reassuring. During the first 6 months of this year, 136 tetracycline-resistant strains were found among 1,538 tested (8.8 per cent.) All of these showed a high resistance to penicillin (minimum inhibitory concentrations 1 unit/ml.). This may be the first evidence of the establishment of new highly-resistant strains in this area.

Correlation of resistance to penicillin and tetracycline

Further analysis of the data shows that resistance to tetracycline is strongly correlated with resistance to penicillin. Of the total of 155 tetracycline-resistant strains isolated in 1966 and 1967, all except seven (3 per cent.) were resistant to 0.1 unit or more of penicillin. The converse, however, is not true, for many penicillin-resistant strains were found to be sensitive to tetracycline. This statement is borne out by the following analysis of the figures obtained during 1966-67:

Sensitive to tetracycline 1 µg./ml.:	} 641 strains
Resistant to penicillin 0.1 unit (MIC 0.3 unit)	
Sensitive to tetracycline 1 µg./ml.:	} 437 strains
Resistant to penicillin 0.3 unit (MIC 1.0 unit)	
Sensitive to tetracycline 1 µg./ml.:	} 56 strains
Resistant to penicillin 1 unit (MIC 3 units)	

In the complete series of 3,421 strains examined between March, 1966, and December, 1967, there were 1,134 (33 per cent.) which showed an appreciable resistance to penicillin but were sensitive to an easily obtainable concentration of tetracycline.

Chloramphenicol

Preliminary experiments to determine the range of sensitivity to chloramphenicol were carried out in September, 1966. The results are summarized in Table X.

TABLE X

SENSITIVITY OF 130 STRAINS OF *N. GONORRHOEA* TO CHLORAMPHENICOL IN SEPTEMBER, 1966

MIC (µg./ml.)	No. of Strains	Percentage of Total	Cumulative Percentage
0.3	27	20.7	—
1.0	90	69.2	89.9
3.0	9	6.9	96.8
10.0	3	2.3	99.1
> 10.0	1	0.8	100.0

It was accordingly decided to test all isolates for sensitivity at the 3 µg./ml. level. This is three times the concentration chosen for tetracycline to allow for the higher level reached in the blood and tissue fluids when chloramphenicol is given by intramuscular injection. The results obtained were as follows:

Year	No. Tested	Resistant to 3 µg./ml.	
		Number	Per cent.
1966 (Nov.-Dec.)	252	11	4.3
1967	1,976	104	5.2
1968 (Jan.-June)	1,529	221	14.4

Once again it is disappointing to note the trend towards resistance, indicated by the figure for the first 6 months of 1968. If this increase in the percentage of resistant strains is maintained, it may be necessary to modify our present belief that chloramphenicol is a useful alternative to penicillin. Nevertheless, it should be noted that, among the 136 tetracycline-resistant strains isolated in 1968, there were 28 (20.5 per cent.) that were sensitive to chloramphenicol at a concentration of 3 µg./ml.

Kanamycin

It seems worth while to place on record the results of some less extensive investigations of antibiotics which have been recommended for the treatment of gonorrhoea. The first to be studied was kanamycin, a drug successfully used by Hirsch and Finland (1960), Wilkinson, Race, and Curtis (1967), and Fischnaller, Pedersen, Ronald, Bonin, and Tronca (1968). It has nephrotoxic and ototoxic properties which make it necessary to administer it with considerable caution.

The minimal inhibitory concentration was determined for a small series of 118 strains of *N. gonorrhoeae* isolated in March, 1967. The results are given in Table XI.

TABLE XI

SENSITIVITY OF 118 STRAINS OF *N. GONORRHOEA* TO KANAMYCIN IN MARCH, 1967

MIC (µg./ml.)	No. of Strains	Percentage of Total	Cumulative Percentage
2	4	3.3	3.3
4	30	25.4	28.7
8	55	46.6	75.3
16	29	24.7	100.0

According to Garrod and O'Grady (1968), a single intramuscular injection of 0.5 g. kanamycin

results in blood levels between 10 and 20 $\mu\text{g./ml.}$ one hour later, thereafter decreasing exponentially with time. As toxic effects may follow a dosage of 1 g. daily it will be appreciated that the therapeutic and toxic levels are not far apart. Another disadvantage of kanamycin is the pain and discomfort produced by intramuscular injection.

Sensitivity of the *Gonococcus* to Sulphadiazine

During the first 7 years of this study, sensitivity to sulphadiazine was determined at three levels: 3, 10, and 30 mg./100 ml. culture medium. Throughout this period the percentage of strains with a minimum inhibitory concentration of 10 mg. per cent. or less remained stable at about 80. In the year 1967, however, resistant strains were rarely encountered, no less than 96 per cent. being sensitive to this concentration of the drug. The figures for the first half of the year 1968 are not significantly different. Resistance to sulphonamide and to the antibiotics is completely unrelated. It seems likely, therefore, that the sulphonamides could once again play an important though limited role in the treatment of gonorrhoea. They should properly be restricted to the treatment of patients infected with sensitive strains which have been found resistant to the commonly used antibiotics. Their widespread use would, of course, soon result in the return of sulphonamide-resistant strains.

Comment

This study emphasizes the important part that should be played by the bacteriological laboratory in the diagnosis and treatment of gonorrhoea. The era of the methylene blue-stained smear is past. Isolation of the infecting organism and determination of its sensitivity to at least four antibiotics should be performed in every case. With this information adequate treatment can be given; and this should be followed by further bacteriological examination to establish the fact that a cure has been obtained. If the physician adopts this procedure he will contribute greatly to the control of this increasingly prevalent disease. (In Ontario the physician is required by law to notify the case to the Health Department so that other control measures may be initiated.) Unfortunately, relatively few physicians enjoy the advantage of a complete laboratory service. If this is not available and only moderate doses of penicillin are administered, relapses will be frequent and the number of resistant strains in circulation will increase. On the other hand, the giving of very large doses of penicillin also gives rise to problems. The official recommendation in the

United States of America is a single intramuscular injection of aqueous procaine penicillin G, 2.4 million units, for the treatment of gonorrhoea in males (USPHS, 1965). For women a total dosage of 4.8 million units given intramuscularly has been recommended by Thayer, Samuels, Martin, and Lucas (1965), and Thayer and Garson (1965). Cost of the drug then becomes a serious consideration; and the volume of the drug that has to be injected intramuscularly makes patient acceptance difficult. Commercially available preparations of penicillin G seldom exceed 600,000 units per ml. It is not surprising, therefore, that some venereologists (Willcox, 1967; McLone, Kiley, and Hackney, 1967; Holmes, Johnson, and Floyd, 1967) are recommending the use of tetracyclines. The figures published in the present report mainly support this method of treatment. Nevertheless, warnings of the development of tetracycline-resistant strains resulting from widespread use of the drug have been issued by Thayer and his colleagues (1965) and by Amies (1967b). These warnings are likely to be justified by future experience.

It is outside the scope of this article to discuss in detail the relative merits of penicillin and other antibiotics from the clinical aspect. This subject is well reviewed in recent textbooks by King (1964) and Willcox (1964).

Finally, in view of the evidence here presented, it seems justifiable to enter a plea for further trial of chloramphenicol in penicillin-resistant cases. This antibiotic has the advantage of being injectable intramuscularly (as chloramphenicol succinate) with very little discomfort to the patient. If it were given as a single or once repeated injection of 1 to 1.5 g., the danger of toxicity to the bone marrow would seem to be remote.

Summary

In the year 1959 in Toronto, only 3 per cent. of the currently circulating strains of *Neisseria gonorrhoeae* were resistant to 0.1 unit penicillin. This figure has gradually increased until it now stands at 50 per cent. At present 30 per cent. of strains are resistant to 0.3 units penicillin. This drug will soon be useless for the treatment of gonorrhoea. It is now advisable to isolate the infecting organism in every case and to determine its sensitivity not only to penicillin but also to tetracycline, chloramphenicol, and sulphonamide. In this way a choice of treatment becomes possible. Resistance to penicillin is never absolute; only a few strains are insensitive to a concentration of 1 unit. To obtain this concentration in the body, however, a heavy dosage (variously

estimated at a total of 2 to 10 million units) must be administered intramuscularly.

The results of sensitivity tests *in vitro* with ten different antibiotics are presented in detail. Tetracycline appears to be a satisfactory drug at present, but resistance to it will eventually develop if it is widely used, particularly if treatment is inadequate. The possibility of using chloramphenicol succinate, administered intramuscularly, is suggested.

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Sensibilité de *Neisseria gonorrhoeae* à la pénicilline et à d'autres antibiotiques Etudes effectuées à Toronto pendant la période 1961-1968

RÉSUMÉ

Pendant l'année 1959, 3 pour cent seulement des souches de *Neisseria gonorrhoeae* couramment rencontrées étaient résistantes à 0,1 unité de pénicilline. Ce chiffre s'est accru graduellement pour être maintenant à 50 pour cent. A présent, 30 pour cent des souches sont résistantes à 0,3 unités de pénicilline. Ce médicament sera bientôt sans valeur pour le traitement de la gonococcie. Il est maintenant recommandable d'isoler l'agent infectant dans chaque cas et de déterminer sa sensibilité, non seulement pour la pénicilline, mais aussi pour tétracycline, chloramphénicol et sulfamide. De cette façon, il est possible de choisir le traitement. La résistance à la pénicilline n'est jamais absolue: seules quelques souches sont insensibles à la concentration d'une unité. Cependant, pour atteindre cette concentration dans le corps, une posologie forte (2 à 10 millions d'unités selon les diverses estimations) doit être prescrite, par voie intramusculaire.

Les résultats d'études de sensibilité *in vitro* vis-à-vis de 10 antibiotiques sont présentés en détail. La tétracycline apparaît actuellement satisfaisante mais la résistance pourra éventuellement apparaître si elle est largement employée, surtout si le traitement n'est pas approprié. On suggère la possibilité d'employer, par voie intramusculaire, le succinate de chloramphénicol.