

Prolonged use of the Greenland method of treatment of gonorrhoea

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SUMMARY Of 1081 patients with gonorrhoea treated with probenecid 1 g orally and benzyl penicillin 5 megaunits intramuscularly, 96.7% were cured and no complications were encountered. This treatment regimen was associated with a pronounced reduction in the proportion of gonococcal strains showing diminished sensitivity to penicillin, from 51% to between 4% and 14% over a period of four years. When this treatment method was abandoned, however, the percentage of less sensitive strains rose to 33% over the following 18 months.

Introduction

By 1971 we were becoming seriously worried because 43% of gonococci isolated in Plymouth showed diminished sensitivity to penicillin *in vitro* (a zone of inhibition corresponding to a minimum inhibitory concentration (MIC) $\leq 0.1 \mu\text{g/ml}$). In 1969 and 1970 our routine treatment for uncomplicated gonorrhoea in men and women had been with co-trimoxazole tablets *BP* (4 tablets initially and then 2 tablets twice daily for five days).

Olsen and Lomholt¹ reported in 1969 from Greenland that when probenecid 1 g and benzyl penicillin 5 megaunits had been introduced as the routine treatment for gonorrhoea the proportion of strains less sensitive to penicillin had fallen noticeably and had remained low. Gray *et al*² suggested that the use of this regimen nationally might result in a substantial reduction in the prevalence of less sensitive strains.

In the hope of achieving a similar reduction in these less sensitive strains we adopted Olsen's and Lomholt's¹ method of treatment, which we have called the Greenland method. From February 1971 to May 1977 this was the standard treatment for gonorrhoea in the clinic at Plymouth. For the next six months alternate cases were treated with either cefuroxime (1 g *i.m.* and 1 g probenecid orally) or the Greenland method. Throughout 1978 all cases were treated with cefuroxime (either 1.5 g *i.m.* or 0.75 g plus 1 g probenecid).

The results with this regimen, particularly the changes in the sensitivity pattern of the gonococci isolated, are reported here.

Patients and methods

STUDY POPULATION

Between February 1971 and May 1977, 1925 cases of gonorrhoea (1227 men and 698 women) were treated with the Greenland method. Only patients who were hypersensitive to penicillin, those with disseminated gonococcal infection or salpingitis, and the rare patient who refused injection were excluded from the series.

The age and racial distribution of the patients remained the same throughout each year of the series. The only discernible change over the period was that the male-to-female ratio changed from 1.7 : 1 to 1.4 : 1.

Of the initial 1925 patients, 844 (632 men and 212 women) were withdrawn from the series or else defaulted or were transferred elsewhere without follow up. The chief reason for withdrawal was because the patient had been given tetracycline for post-gonococcal urethritis during the follow-up period. As a result the withdrawal/default rate is much higher in men (51%) than in women (30%). There remained therefore 1081 cases (595 men and 486 women) for assessment.

DIAGNOSIS

Gonorrhoea was diagnosed on the finding of intracellular Gram-negative reniform diplococci in stained smears, or on the isolation of *Neisseria gonorrhoeae* on culture, or on both. Of the 1925 initial cases, gonococci were found in both Gram-

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stained smears and cultures in 1539 (80%)—that is, in 84% of men and 74% of women. In 297 (15%) cases the diagnosis was made on the basis of positive results to Gram-stained smears only (190 men and 107 women) and in 89 (5%) cases by culture only—13 (1%) men and 76 (11%) women.

Specimens for Gram-stain and culture were taken from the urethra in men and from the urethra and cervix in women and from the rectum in all male homosexuals. Throat swabs for culture were taken from all patients who admitted to orogenital contact, from all male homosexuals, and from any patient who was a known contact of gonorrhoea but from whom we had failed to isolate gonococci from other sites.

CULTURE AND SENSITIVITY TESTING

Culture and sensitivity testing methods and the criteria for distinguishing sensitive from less sensitive strains were as previously reported.³ To ensure that these criteria had not changed during the period of this report, the MIC of benzyl penicillin (determined by plate diffusion) for 12 strains was compared with the zone of inhibition around a 1.5 unit disc (Oxoid). No change was shown to have occurred.

TREATMENT

All patients with gonorrhoea were treated with probenecid 1 g by mouth followed after about 15 minutes by a single intramuscular injection of benzyl penicillin 5 megaunits dissolved in 6.5 ml of 0.5% xylocaine to make a final volume of 8 ml (the Greenland method).

Patients were instructed to refrain from sexual intercourse for two weeks after treatment.

FOLLOW UP

Patients were seen at seven and 14 days after treatment. If any urethral discharge was found at either follow-up attendance in men who had had gonococcal urethritis, urethral smears and cultures were made. If no discharge was present, a two-glass urine specimen was examined and a smear made of any threads in the urine. At each attendance, specimens for Gram stain and culture were taken from the urethra and cervix in women, from the rectum in patients with gonococcal proctitis, and from the throat in patients with gonococcal pharyngitis.

If gonococci were found at any time within two weeks of treatment, and the patient denied further sexual intercourse, treatment was then considered to have failed. If gonococci were found after two weeks then reinfection was assumed to have occurred. No method of assessing which cases relapsed and which were reinfected is infallible; the method used here was suggested 20 years ago by Dallas.⁴

Results

Of the 1081 cases (595 men and 486 women) treated with the Greenland method and followed up at seven and 14 days, gonococci were isolated on culture during the follow-up period from 34 (20 men and 14 women) and two more had positive results only on Gram stain, making 36 failures in all. The cure rate was 96.7% (men 96.5%, women 97%). Of the men, 27 had gonococcal proctitis and two of them were not cured. Five patients had gonococcal pharyngitis and treatment failure occurred in one.

The failure rate was significantly higher ($\chi^2 = 5.878$, $P < 0.02$) in patients infected with strains of gonococci with reduced sensitivity to penicillin. Of 919 cases followed up, and from whom strains of gonococci which were fully sensitive to penicillin were isolated, 25 were considered to be treatment failures, giving a failure rate of 2.7%, whereas of 162 cases followed up who had strains showing reduced sensitivity to penicillin 11 were treatment failures, giving a failure rate of 6.8%.

TABLE *Penicillin sensitivity of gonococci isolated between 1971 and 1977*

Sensitivity to penicillin	Men		Women		Total	
	No	%	No	%	No	%
Fully sensitive	831	84	490	87	1321	85
Diminished	162	16	74	13	236	15
Total	993		564		1557	

ANTIBIOTIC SENSITIVITIES

In 1628 cases gonococci were cultured from at least one site. In 71 cases the isolate died on subculture and antibiotic sensitivity could not therefore be assessed. Results of sensitivity testing to penicillin in the remaining 1557 cases (993 men and 564 women) are given in the Table. This shows that during the six years when the Greenland method was the routine treatment for gonorrhoea 15% of the isolates showed diminished sensitivity to penicillin. No β -lactamase-producing strains were found.

Since 1969 we have followed the variations in the percentage of strains of gonococci which showed diminished sensitivity to penicillin. These variations are shown for each six-month period in the Figure, together with the 95% confidence limits for a proportion calculated with a correction for continuity thus:

$$\hat{p} \mp \{1.96\sqrt{(\hat{p}\hat{q}/n) + \frac{1}{4}n}\}$$

There is a highly significant difference ($\chi^2 = 67.734$, $P < 0.001$) in the proportion of resistant strains between the three different treatment methods.

From mid-1969 to the beginning of 1971, while co-trimoxazole was the routine treatment, the percentage of less sensitive strains rose from 34 to 43%.

However the difference between the six-month periods is not significant ($\chi^2_1 = 1.386$, $P=0.5$). For the first six-month period after the introduction of the Greenland method there was a further rise in the proportion of less sensitive strains to 51% (Figure); thereafter there was a rapid fall over the next two years to 5% in 1973. Use of the Greenland method was continued until mid-1977 and during that time the proportion remained low, within the limits of 3.5% to 12.4%. Thus there is a pronounced heterogeneity between these 13 samples, which is highly significant ($\chi^2_{12} = 197.251$, $P<0.001$).

During the six-month period when alternate patients were treated by the Greenland method or with cefuroxime the proportion of less sensitive strains remained low (6%) (figure). During 1978, when cefuroxime alone was the routine treatment, the proportion of less sensitive strains rose to 25%

and then to 33%. The difference between samples during this 18-month period is also significant ($\chi^2_2 = 36.447$, $P<0.001$).

There has been one other change in the sensitivity pattern. Of all the strains of gonococci isolated in 1971 10% were resistant to streptomycin, and all the strains in that year which showed reduced sensitivity to penicillin were also resistant to streptomycin. Over the years the combination of reduced sensitivity to penicillin and resistance to streptomycin has become rare. Only two (0.8%) strains in 1978 showed resistance to streptomycin.

Discussion

The satisfactory results obtained with the Greenland method of treatment (a cure rate of 96.7%) is in keeping with the findings of the originators¹ of this

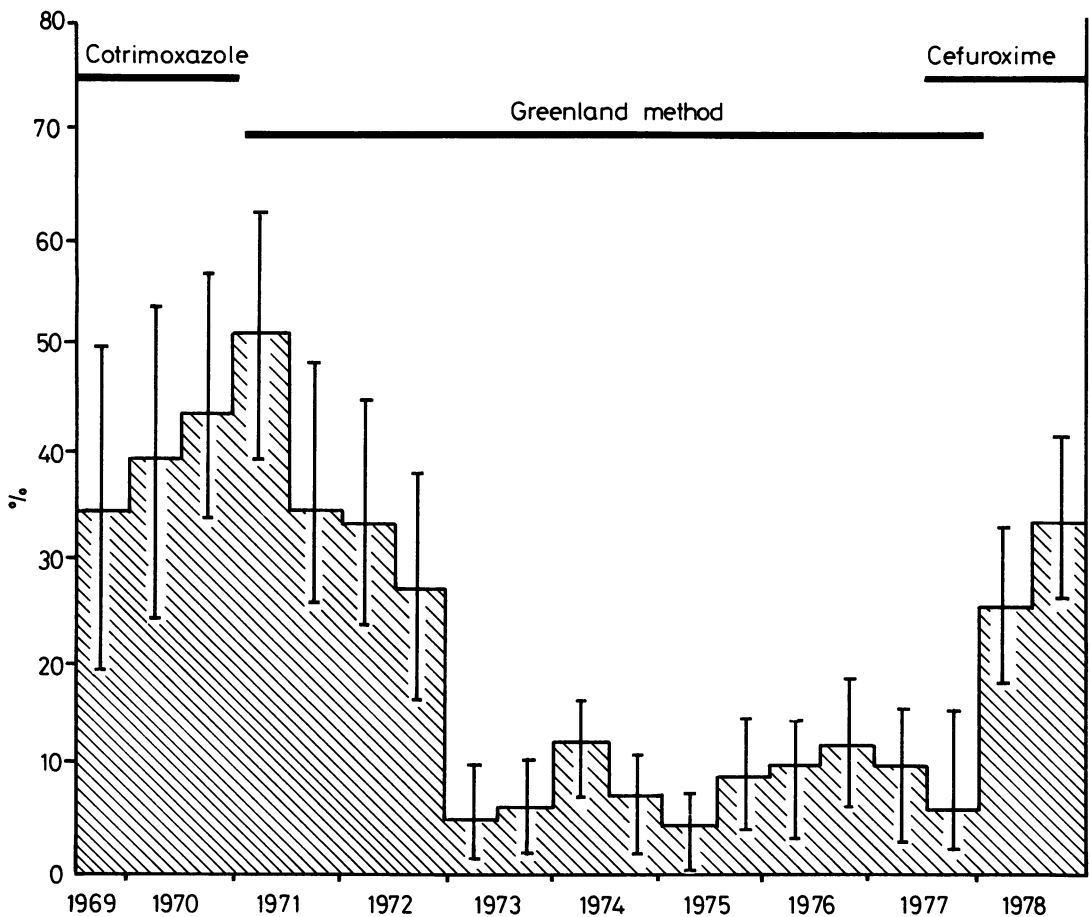


FIG Variation in percentage of strains of gonococci less sensitive to penicillin with different treatment regimens (1969-78) and showing 95% confidence limits with correction for continuity

routine and of others.² Wigfield *et al*⁵ suggested that the large volume (8ml) of the injection might be disadvantageous. This has not been our experience and we have not recorded any difficulties or major complications with its use.

Olsen and Lomholt¹ reported a pronounced reduction in Greenland in the proportion of strains of gonococci which were less sensitive to penicillin when their method of treatment was introduced. This improvement continued throughout the 3½ years covered by their report. Our results from Plymouth confirm these findings, although our series continued for longer (over six years).

What has not previously been reported is that on discontinuing treatment by the Greenland method the proportion of less sensitive strains rises sharply again.

It is difficult to see any reason for these changes. Wigfield *et al*⁵ pointed out that the reduction in less sensitive strains could not be attributed to the efficiency of the method, since this would eliminate sensitive and less sensitive strains equally well, and so the proportion of less sensitive strains would remain the same.

There have been many reports of a wide variation in the prevalence of less sensitive strains in different centres, and at the same centres at different times.⁶⁻⁸ The statistical analysis however shows that our results are most unlikely to be due to chance and that, whatever the reason, the use of the Greenland method of treatment is associated with a diminution of strains which are less sensitive to penicillin. We know of no other reports associating the therapeutic regimen with variation in the sensitivity pattern of the gonococci isolated.

The near disappearance of streptomycin-resistant strains is surprising. However, streptomycin is now never used for the treatment of gonorrhoea and this may explain the decrease in the number of streptomycin-resistant strains. A similar reduction in streptomycin-resistant strains has been reported from Denmark.⁹

Patients infected with strains of gonococci of reduced sensitivity to penicillin have a higher failure rate when treated with penicillin than do patients infected with fully sensitive strains.^{6-8 10-12} Similar results have been obtained in the present series. Prolonged use of the Greenland method is associated with a reduction in less sensitive strains and should

therefore result in a lower failure rate. This theoretical advantage is so great that we have now reverted to the use of the Greenland method as our standard treatment for gonorrhoea in Plymouth. It will be interesting to see if this is again associated with a reduction in the numbers of less sensitive strains of gonococci.

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Addendum

Use of the Greenland method throughout 1979 has been associated with a fall in the proportion of strains less sensitive to penicillin from 33% to 22%.

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