Review

Epidemiological treatment and tests of cure in gonococcal infection: evidence for value

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Objectives: To evaluate the evidence for value of using epidemiological treatment and of using tests of cure in the management of gonococcal infections.

Methods: Medline was used to search the literature for well-conducted studies that had a bearing on the evaluation of these issues.

Conclusions: Epidemiological treatment is treatment given to named contacts of patients after a history of exposure to disease but without or in advance of confirmatory pathological findings. It may be given when the clinician considers that the risk to the patient of unnecessary treatment is outweighed by the risk of complications of the infection or the probability of transmission of the infection to other contacts. It may be appropriate where detection by microscopy is relatively unreliable such as when infection of the cervix, rectum, or pharynx is suspected. If epidemiological treatment is given, then it does not obviate the need for confirmatory tests to be sent, tests of cure to be done, or for contact tracing. At least one test of cure is mandatory following treatment of gonorrhoea. The test of cure in women should include a blind rectal swab. For infection of the pharynx and rectum the chances of a false negative test of cure are higher and, therefore, more than one test of cure is required. An additional test of cure is also necessary in patients with salpingitis or disseminated gonococcal infection. This paper is a discussion of two interrelated issues in the management of gonorrhoea. It is based on two presentations by the author at a workshop organised by Dr Mark Fitzgerald entitled *Development of audit measures and guidelines for good practice in the management of gonorrhoea* and held at the Royal College of Physicians, London, in May 1995. The conclusions reached are based on the consensus view of the participants. For simplicity the two issues are dealt with consecutively.

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Epidemiological treatment

Introduction Various definitions of epidemiological treatment exist. The broader definition refers to "administration of antibiotics when the diagnosis is considered likely".¹ For the purposes of this paper the following, narrower, definition is used, that is, "treatment given to named contacts of patients after a history of exposure to disease but without or in advance of confirmatory pathological findings".² The rationale of using epidemiological treatment is "that the limitations of the available diagnostic procedures and the delays arising therefrom or due to attempting repeated tests, may nullify or reduce the value of the treatment ultimately given".³

In this paper three approaches are used to examine the evidence for the value of epidemiological treatment. Firstly, international comparisons; secondly, an evaluation of the major factors influencing the decision for and against epidemiological treatment; and lastly, a summary of two studies which have provided data for its direct evaluation. With one or two notable exceptions most of the studies which provide evaluable data to contribute to the debate were done at least ten years ago. The author does not believe that the implications of the studies would be different were they to be repeated today. Much useful information has been provided by the National Audit Development Project in Sexual Health. Nevertheless, further up-to-date well-

conducted studies would provide a more secure foundation on which to base decisions on management.

International Comparisons It is unwise to give too much weight to international comparisons when evaluating epidemiological treatment. Many other factors such as the nature of the health care system and the level of resources available are important in the control of sexually transmitted diseases. However, the experience in Sweden suggests that the appropriate use of epidemiological treatment can contribute to lowering the incidence of gonorrhoea.

Different countries have adopted the practice of epidemiological treatment with differing enthusiasm. Before 1970 Swedish venereologists and other physicians generally considered that because of legislation, treatment of gonorrhoea could not be started unless gonococci had been demonstrated by direct microscopy and/or by culture. From 1970 onwards the Swedish public health authorities also recommended treatment based on epidemiological information. According to Danielsson "the measures were certainly of importance to prevent further spread of gonococcal infections".⁴ The incidence of gonorrhoea in Sweden fell from 487 cases per 100 000 in 1970 to 31 cases per 100 000 in 1987.⁵

In the USA the Centers for Disease Control has recommended since 1950 that female con-

tacts of men with gonorrhoea receive epidemiological treatment, and in 1972 this policy was extended to include male contacts of culture-positive women.⁶ Gonorrhoea morbidity rates reached a peak in 1946 in the USA, decreased until 1957 and increased again for nearly two decades, peaking at 473 per 100 000 in 1975.⁵

A survey of gonorrhoea practices in Great Britain was conducted by the British Co-operative Clinical Group in 1968. This found that 69% of clinics treated females with epidemiological treatment at least in some cases, but only 19% of clinics did so for males.⁷ Data discussed later in this paper provide an explanation for this greater tendency to use epidemiological treatment for females than for males. The incidence of gonorrhoea in England has remained below 120 per 100 000 for the past 30 years and more. It decreased to 30 per 100 000 in 1995.⁸

Factors for and against epidemiological treatment Prevention of morbidity in the patient. The higher the risk of morbidity arising in the contact the greater the argument for epidemiological treatment. The prevalence of gonorrhoea among female contacts of infected men ranges from 36% to 92% and in most studies usually runs between 45% and 60%. The prevalence of gonorrhoea in the male sexual partners of infected women ranges from about 40% to 90%.⁹ A nationwide survey in the UK in early 1995 found that the prevalence rates of gonorrhoea among female and male contacts were 60% and 74% respectively. (Fitzgerald M, Bedford C for the Central Audit Group in Genitourinary Medicine: The Clinical Management of Gonorrhoea. Results from the National Audit Development Project in Sexual Health. 1996). Pelvic inflammatory disease (PID) has been found to occur in 25/570 (4.4%)¹⁰ to 61/606 (10.6%)¹¹ of cases in UK studies. Delay in treatment appears to be important. It has been estimated (though no data are shown) that 15% of women with gonorrhoea will develop PID during the first month of their infection.⁹ One study found that of 124 female patients with gonorrhoea who were not treated at the initial visit and who required treatment at the second visit (at a mean interval of seven days, range 2 to 83 days), nine (7.3%) developed pelvic inflammatory disease during the interval between visits.¹² Disseminated gonococcal infection is far less common and has been estimated to occur in about 1% of cases.¹³

Patient default rate A retrospective sample of female cases of gonorrhoea treated in clinics in England and Wales during 1978 found that "six per cent of contacts who had negative smear results at their initial visit, were not treated epidemiologically, but were subsequently proved to be infected by culture defaulted before treatment. Among patients who attended with a contact slip, however, the default rate was only 2% compared with 14% among those who gave a verbal history of exposure to gonorrhoea".¹⁴

Diagnostic difficulties: microscopy Epidemiological treatment is more likely to be used when there are difficulties in making the diag-

nosis at the initial visit. This may apply particularly to developing countries.¹⁵ In the UK the ability to diagnose by microscopy varies according to the site being tested. Gonococcal urethritis in men is relatively easily diagnosed on microscopy, being found in 94.5% of cases.¹⁶ In contrast, women infected at the cervix or urethra or both, were only diagnosed on microscopy in 61.8% of cases in one study¹⁶ and 53.4% in another.¹⁰ A recent audit at one large London clinic showed that the sensitivity of cervical gram stained smears was only 29%.¹⁷ Earlier work showed that rectal gonorrhoea in men was diagnosed by microscopy in 58% of cases.¹⁸ In 1995 the Central Audit Group in Genitourinary Medicine found that while 681/762 (89%) of male urethral gonorrhoea was diagnosed on microscopy, only 152/407 (37%) of gonorrhoea in females, and 20/49 (41%) of rectal gonorrhoea in male homosexuals was diagnosed in this way. Rates of diagnosis by microscopy may, however, be higher when the patient is a known contact of gonorrhoea.

Diagnostic difficulties: culture If a single culture is a relatively insensitive means of diagnosing gonorrhoea at a specific site, clinicians may be more inclined to use epidemiological treatment. A combination of microscopy and culture performed on one occasion in a woman with gonorrhoea will miss the diagnosis in 3–9% of cases.^{19 20} About 7% of men with rectal gonorrhoea may be missed by culture on only one occasion, and at least 25% with pharyngeal gonorrhoea will be missed on a single culture.¹⁸

Other issues which need to be considered concern the cost of the unnecessary treatment of uninfected contacts and the side effects caused. There may also be medico-legal problems arising from treating someone for a condition which they do not have. Furthermore, there may be a risk of lax standards developing where epidemiological treatment is used frequently.

Studies providing data for the direct evaluation of epidemiological treatment In a study of 604 cases of gonorrhoea in women 16 patients who were microscopy negative but culture positive with the first set of tests failed to return and were not treated. Only four of these 16 patients were contacts of men with gonorrhoea. The authors estimate that epidemiological treatment would have resulted in the unnecessary treatment of 142 patients, and in the treatment of the four infected contacts who defaulted but not the 12 patients in whom there was no reason to suspect gonorrhoea.¹⁰

In Belsey's study of practices in STD clinics in England and Wales in 1978, a sample of 2933 cases diagnosed, treated or returned as gonorrhoea was obtained. Exactly one-third of patients were not named contacts and thus could not have been given epidemiological treatment. Of the remaining patients who provided some evidence of a history of exposure to the disease, 24% were treated epidemiologically. Thirty-five per cent of cases treated epidemiologically were later proved to be true cases of gonorrhoea.¹⁴ It is worth bearing in

mind, however, the insensitivity of a single culture. Belsey's figure of 35% being proved to be true cases may hide a further small number of true cases. Nevertheless, it appears that nearly two-thirds of patients treated epidemiologically did not, in fact, have gonorrhoea.

Conclusions Epidemiological treatment has advantages for the patient in cutting the risk of complications. On the other hand, it reduces the proportion of true cases of gonorrhoea in whom the diagnosis is confirmed because a single microscopy plus a single culture will miss some cases. If such cases are not used as index cases for contact tracing this will tend to mitigate against good control of gonorrhoea in the community. It is, therefore, advisable that contact tracing is conducted on all patients treated epidemiologically. If epidemiological treatment is to be employed the disadvantages are less when the contacts are truly untraceable. The case for epidemiological treatment is strengthened when microscopy and culture are insensitive or unreliable. There is, therefore, a stronger case for using epidemiological treatment when the patient is at risk of having infection at the pharynx, cervix or rectum because diagnostic techniques are less sensitive at these sites than at the urethra. Diagnostic techniques may, in general, be less reliable in parts of the developing world and, in the UK, when taken outside of genitourinary medicine clinics. Epidemiological treatment may, therefore, be more justifiable in these settings provided that it does not lead to the development of lax standards. In conclusion, epidemiological treatment may be given when the clinician considers that the risk to the patient of unnecessary treatment is outweighed by the risk of complications of the infection or the probability of transmission of the infection to other contacts. If epidemiological treatment is given, then it does not obviate the need for confirmatory tests to be sent, tests of cure to be done, or for contact tracing.²¹

Tests of cure

Introduction The rationale given for tests of cure is two-fold. Firstly, to prevent complications in the index case and, secondly, to minimise the risk of subsequent transmission of infection from the index case. Tests of cure may at times inadvertently pick up new infections which have been acquired since successful treatment of the initial episode. In such instances the same benefits accrue. This paper examines the evidence which may be used to assess the value of tests of cure under the following headings: biological factors; difficulties in diagnosis and treatment; and finally, studies attempting a direct evaluation.

Biological factors Prevention of complications and of transmission may be particularly important for strains of gonococci which have been shown to carry a risk of greater morbidity. The gonococci causing salpingitis are likely to have the following characteristics: non-Arg⁻ Hyx⁻ Ura⁻, higher-molecular weight protein I's and the WII serotype.²² Similarly, there are markers associated with gonococci which are prone to cause disseminated gono-

coccal infection.²² There is a greater need for tests of cure for patients with these conditions.

Antibiotic-resistant strains of gonorrhoea pose a threat to the public health, especially if they show multiple resistance. For this reason there is an increased need for tests of cure for penicillinase producing *Neisseria gonorrhoeae* (PPNG).

Difficulties in diagnosis and treatment If treatment is known to carry a high risk of failure at a particular anatomic site, there is a greater need for tests of cure. If diagnostic techniques are insensitive at making the initial diagnosis of gonococcal infection at a particular site those same techniques will again be insensitive when used as tests of cure.

Anatomic site of infection has been shown to be important when treating gonococcal infections.²³ In a systematic review of published therapeutic trials of various antimicrobial regimens for the biological cure of uncomplicated mucosal *Neisseria gonorrhoeae* infections, the cure rates were calculated by anatomic site for 16,737 infections. The cure rates were as follows: female urethra, 98.4%; male urethra, 96.4%; cervix, 98%; female pharynx, 83.7%; male pharynx, 79.2%; female rectum, 97.9%; and male rectum, 95.3%. The figures obtained by the Central Audit Group in the UK in early 1995 in a survey of 843 gonococcal infections were as follows: female urethra, 97%; male urethra, 96%; cervix, 97%; female pharynx 8/9 (89%); male pharynx, 91%; female rectum, 95%; male rectum 93%. It may be argued, therefore, that the need for tests of cure is greatest for gonococcal infections of the pharynx.

Diagnosis of gonococcal infections may be insensitive in men infected at the pharynx or rectum. At least 25% of pharyngeal gonorrhoea in homosexual men will be missed on a single culture and about 7% of rectal gonorrhoea.¹⁹ Three to nine percent of cases of gonorrhoea in women may be missed by one set of tests (microscopy and culture).^{20 21}

Studies to evaluate tests of cure A large study in the USA attempted to evaluate the need for post-treatment cultures in men with gonococcal urethritis.²⁴ Because the large majority of men with gonorrhoea respond to antimicrobial therapy it was hypothesised that a symptomatic response would predict successful treatment. The records of 4897 men with gonorrhoea were studied. One hundred and eighty three (3.7%) were treatment failures on days 3-7 after treatment. The clinical response to therapy was correlated with microbiological outcome. Before therapy, 4662 men (95.2%) had dysuria and/or urethral discharge. Of the 582 men who remained symptomatic, 103 (17.7%) had a positive culture after treatment, as compared with only 78 (1.9%) of 4080 men who became asymptomatic ($p < 0.01$). The conclusion was that men who are initially symptomatic and become asymptomatic after therapy have a small chance (one in 50) of being infected at the post-treatment visit. However, almost half (78 of 183, 42.6%) of treatment failures in men with gonococcal urethritis are asymptomatic. Therefore, a policy

of confining post-treatment cultures to those who remain symptomatic would miss 42.6% of treatment failures and this would have implications for the risk of developing complications and particularly for greater transmission of gonorrhoea. The authors concluded that "If resources allow, all patients with gonorrhoea should have a post-treatment culture". However, the cost implications are considerable. In 1976 Judson and Wolf calculated the cost of detecting a positive post-treatment culture. Using a calculated average cost per follow-up visit of \$12.75, they worked out that it cost \$427 to detect a patient (male or female) with a positive culture.²⁵ A later paper from the USA compared four alternative strategies for the management of men with acute urethritis. They calculated that test-of-cure cultures for patients who were asymptomatic after treatment for gonorrhoea required the expenditure of from \$4 900 to \$109 800 for each case of asymptomatic, persistent gonorrhoea discovered and cured.²⁶

An American paper specifically evaluated rectal culture without the use of an "anoscope" as a test of cure of gonorrhoea in the female.²⁷ The rectal and cervical sites were compared as a test of cure in 908 female patients who had gonorrhoea. After treatment, positive cervical or rectal cultures (or cultures of both sites) were found in 10.6% of the patients. Thirty per cent of the therapeutic failures would have been missed if only the cervical site had been tested. It was also found that antibiotic therapy is more likely to fail if *Neisseria gonorrhoea* infects both the cervix and the rectum.

Conclusions If tests of cure are not performed routinely on men treated for gonococcal urethritis, almost half (42.6%) of treatment failures will be missed with important consequences for subsequent transmission. The case for tests of cure is even stronger for infection in men at other anatomic sites and infection in women. There is also a strong case for performing a blind rectal swab as a test of cure in women with gonorrhoea. For infection of the pharynx and rectum the chances of a false negative test of cure are higher and, therefore, more than one test of cure is required. An additional test of cure is also necessary in patients with salpingitis or disseminated gonococcal infection as they are likely to carry strains which are prone to cause these complications. The cost of performing tests of cure is high but this must be balanced against the costs generated by less effective control of

gonorrhoea in the community. An up-to-date cost-benefit analysis would be useful.

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