Survival of treponemes after treatment: comments, clinical conclusions, and recommendations

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SUMMARY Treponemes may persist after treatment that has been accepted as effective; the reasons for this are discussed. Nevertheless, the epidemic of syphilis after the second world war was not followed by an epidemic of late syphilis, and the results of treatment with penicillin are excellent.

Neurological signs may progress in some treated patients, and the standard doses of soluble penicillin and any dose of benzathine penicillin (even with added probenecid by mouth) cannot be relied on to achieve treponemicidal concentrations in the cerebrospinal fluid (CSF). There are no large scale studies of CSF findings after treatment of early syphilis with benzathine penicillin.

Standard dosage, such as procaine penicillin G 600 000 international units (IU) by intramuscular injection for 10 days, is the treatment of choice for the patient suffering from uncomplicated early syphilis; this should be preferred to benzathine penicillin, which should only be used when standard treatment as above cannot be given.

Treponemicidal concentrations of penicillin should be achieved in the CSF of patients suffering from neurosyphilis by schedules of probenecid by mouth and procaine penicillin by single daily intramuscular injections; treatment should last for 17 to 21 days. Benzathine penicillin should not be used for the treatment of patients suffering from neurosyphilis or from the iritis of late syphilis including that accompanying interstitial keratitis. Treatment for interstitial keratitis should initially be as for neurosyphilis, but in recurrent cases it may have to be prolonged to eradicate *Treponema pallidum* that is dividing slowly.

Doxycycline 300 mg by mouth daily for 21 days provides a supervisable outpatient schedule for patients allergic to penicillin. Cephaloridine (and probably cefuroxime and the new cephalosporins) may be useful for patients who are allergic to penicillin but have not developed anaphylactic allergy.

If erythromycin is used for treating syphilis in pregnant women who are allergic to penicillin, then the newborn babies should be treated with penicillin.

Introduction

Treponemes may survive what has been considered to be adequate treatment of syphilis. Virulent *Treponema pallidum* has been recovered from cerebrospinal fluid (CSF) or the eye from some patients who had been treated for early syphilis with penicillin (including benzathine penicillin). What

have been generally accepted as adequate regimens of penicillin (including all dosage levels of benzathine penicillin) demonstrably do not achieve treponemicidal levels of penicillin in the CSF. The progression of neurosyphilis after "adequate" treatment has been noted. These findings are considered, and some conclusions are drawn.

Late syphilis after early syphilis treated with penicillin

Nearly 40 years have elapsed since the immediate postwar epidemic of early syphilis was treated with penicillin. If treponemes commonly survive such

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treatment in forms able to cause lesions of late syphilis there would now be a high incidence of such manifestations. That this has not happened (figure)^{1 2} is one of the major benefits of penicillin.

FIGURE Syphilis in England and Wales 1939-82.

Results of treatment of early syphilis were excellent;^{2 3} most patients who were treated again had probably been reinfected.³ Thus in most cases of early syphilis treated with conventional courses of penicillin the treponemes were destroyed or, if they survived, they did so in forms that did not produce disease in man.

The decline in late syphilis, including general paralysis of the insane (GPI),⁴ has continued (figure). Results of treatment of late syphilis with penicillin were good.² Prognosis depends on the lack of tissue damage at the start of treatment. The earlier the treatment was started the better was the prognosis.

Penicillin by itself was the drug of choice for the treatment of neurosyphilis,⁵ including asymptomatic neurosyphilis⁶ and GPI.⁷ Nevertheless, clinical follow up for 10 years or more by Wilner and Brody of 64 patients with paresis who had been treated with penicillin showed new clinical signs of neurological involvement in 25.⁸ Thus long term follow up suggested that in some cases of late syphilis treponemes might survive after treatment with penicillin, although in general results were good.

Laboratory evidence of survival of treponemes after treatment

This has been obtained by two methods: the direct detection of treponemal forms by microscopy of body fluids or tissues, or by the infection (shown by microscopy) of experimental animals, usually rabbits, after their inoculation with body fluids or tissues.

The characteristic morphology and motility of *T pallidum* may be shown by dark field microscopy of wet preparations. The examination of fixed specimens has the disadvantages of distortion of tissue and loss of treponemal motility. The organism may be stained with silver (and many dyes), which may give variable and unpredictable results,⁹ or the background may be stained. Alternatively, the more specific fluorescent antibody staining may be used for smears and tissues.

PERSISTING TREPONEMES DETECTED BY MICROSCOPY

Studies were reported initially by Collart *et al* in France in 1962¹⁰ and reviewed in 1964¹¹ and then by workers in the United States of America, the United Kingdom, and India. Tests gave low yields of positive findings so that in one series only 42 (19%) of 223 patients with treated or untreated syphilis gave positive results.¹²

Some organisms were artefacts,^{13 14} whereas *T pallidum* could be transferred to previously blank slides during fluorescent staining and washing.¹⁵ In the absence of proved infection of an experimental animal a treponeme like form in man cannot be accepted with certainty as being pathogenic *T pallidum*.

INFECTION OF EXPERIMENTAL ANIMALS

Six groups of workers infected animals with syphilis by inoculation with material from patients who might have persisting treponemes,^{10 11 16-20} but one of these groups found positive infectivity test results only after "inadequate" treatment.¹⁹ Turner *et al* stressed the importance of the positive infectivity test in rabbits.²¹ Such inoculation is insensitive, however, even in early syphilis, so only eight of 15 transfers of infectious material from patients with primary or secondary syphilis resulted in infection.²²

How does *T pallidum* survive?

Some factors to be considered are:

STAGE OF DISEASE

In late compared with early syphilis the infection is relatively inactive, and organisms are presumably dividing at a much slower rate than the 30 to 33 hour division time of *T pallidum* in early syphilis of experimentally infected rabbits.^{23 24}

As the organism replicates, penicillin links with transpeptidase catalases forming an inactive complex, so that the treponemal cell wall is not synthesised or repaired. Thus some organisms that are not dividing during treatment may survive. Collart *et al* incubated virulent *T pallidum* for 15 hours in Nelson-Mayer medium, in which they do not replicate, with penicillin 1 000 IU/ml to 10 000

IU/ml.²⁵ After the penicillin had been destroyed by penicillinase the treponemes still caused syphilitic orchitis in rabbits.

Magnuson and Eagle showed that incubating syphilis in rabbits could be cured or aborted by only 1/32 of the curative dose if given within three days of inoculation.²⁶ The dose required in early syphilis increased with the duration of infection and the number of spirochaetes present. The smaller the inoculum and the earlier the penicillin was administered the greater was its suppressive effect.

Late latent syphilis in rabbits is more resistant to treatment than early syphilis as measured by positive lymph node transfers and seroconversion in recipient animals.²⁷ Because *T pallidum* divides slowly in late syphilis, recurrences may be reduced by prolonging the duration of treponemicidal concentrations of penicillin in eyes affected by interstitial keratitis. The organism recovered by Hardy *et al*, however, was obtained after treating a newborn baby for early congenital syphilis (see special sites of infection—eye).¹⁸

MICROBIAL PERSISTENCE

McDermott used this term for the fact that some organisms survive attack by antibiotics to which they are fully sensitive.²⁸ Thus if *T pallidum* behaves like other organisms, occasional treatment failure without obvious cause is to be expected.

SPECIAL SITES OF INFECTION

Central nervous system

Smith *et al* reported a cumulative failure rate of 21% 18 months after treating patients for asymptomatic neurosyphilis with injections of benzathine penicillin G 2.4 MIU or 2.5 MIU, compared with 10.5% for other preparations of penicillin.²⁹ Increasing the dose of benzathine penicillin to 4.8 MIU given in two injections of 2.4 MIU seven to 10 days apart did not reduce the failure rate, which was 33% (8/24 followed up), if CSF cell counts of over 5/mm³ after six months or more are accepted as abnormal.³⁰ Thus even 4.8 MIU of benzathine penicillin is an inefficient preparation for treating neurosyphilis.

T pallidum has been detected in CSF from a patient three weeks after treatment with 10.8 MIU of benzathine penicillin G for neurosyphilis.²⁰ Failure to achieve treponemicidal concentrations in CSF has been reported with intramuscular injections of benzathine penicillin G³¹⁻³⁴ even after a total dose as high as 14.4 MIU (4.8 MIU weekly for three weeks) in all of nine cases,³³ in four of six given this dose and probenecid by mouth,³³ and in 12 of 13 given 3.6 MIU weekly for four weeks.³¹

In newborn babies intramuscular injections of benzathine penicillin G 100 000 IU/kg produced CSF concentrations of 0.012 to 0.21 (mean 0.06)

mg/l for up to 24 hours after injection. Five out of 10 specimens of CSF did not contain treponemicidal concentrations at 48 hours, and no penicillin was detected in the five specimens tested at 120 hours.³⁵ Intramuscular injections of procaine penicillin G 50 000 IU/kg daily without accompanying probenecid produced treponemicidal CSF concentrations in newborn babies.³⁶

Procaine penicillin G alone or with 2% aluminium monostearate (PAM) 600 000 IU daily by intramuscular injection achieved treponemicidal concentrations in the blood but not the CSF.³⁷⁻⁴² Procaine penicillin 600 000 IU gave such a concentration in the CSF of one out of six patients, 1.2 MIU in two out of seven, 1.8 MIU in one out of two, and 2.4 MIU in two out of three.⁴¹ The cumulative concentration of penicillin after intramuscular injection of procaine penicillin 600 000 IU daily for 14 to 21 days was treponemicidal in the serum but not the CSF of 10 patients.⁴⁰ The addition of probenecid by mouth produced treponemicidal CSF concentrations in six out of 11.⁴⁰

The addition of probenecid 500 mg by mouth every six hours to various regimens produced treponemicidal CSF concentrations as follows: procaine penicillin G 600 000 IU daily by intramuscular injection in two out of three patients,³⁸ procaine penicillin 1.2 MIU daily in four out of five patients,³⁸ benzyl penicillin 500 000 IU every six hours in all of 31 patients,³⁸ procaine penicillin 2.4 MIU once daily in all of 38 patients,⁴² and procaine penicillin 1.8 MIU once daily in all of 12 patients.⁴² The last regimen is practical for outpatients.⁴³ It produced CSF penicillin concentrations of 0.06-1.8 mg/l. A wide margin above the treponemicidal concentration of 0.018 mg/l is probably desirable to allow for error in the method of estimation and because in animals the penicillin concentration in the brain may be about one tenth of that in the CSF,⁴⁴ and probenecid increases brain concentrations less than it increases CSF concentrations.⁴⁵

Oral administration of amoxycillin 1 g six times a day with probenecid 2 g a day produced treponemicidal amoxycillin concentrations (>0.42 mg/l) three and nine hours after the last dose.⁴⁶ This suggests that a 3 g sachet of amoxycillin twice a day (possibly once a day) with probenecid would produce even higher CSF concentrations, which would be maintained by probenecid. This is under review. Such a schedule might be used for the supervised treatment of outpatients suffering from neurosyphilis.

Eye

Drugs sparingly soluble in lipids, such as the penicillins,^{47 48} achieve low concentrations in the

ocular compartments.⁴⁸ Ampicillin penetrates aqueous humour more effectively than penicillin G.⁴⁹⁻⁵¹ Concentrations of the penicillins in the eye are increased from about 6% to 50% of the serum concentrations by inflammation⁴⁸ and by probenecid. Concentrations of penicillin achieved in the vitreous humour and lens of animals are about one third to one fifth of those in the aqueous humour.⁴⁸

Acute iritis occurs in almost 5% of patients with early secondary syphilis and in just over 9% of recurrent cases.⁵² It responds promptly to conventional antisyphilitic treatment, as does subclinical iritis in secondary syphilis diagnosed by slit lamp microscopy.⁵³ Severe inflammation that aids the penetration of antibiotics may not be a prominent feature of syphilitic infection of the eye or CNS. Because *T pallidum* has been isolated from normal CSF, CSF changes clearly understate the incidence of neurological involvement.⁵⁴

Virulent *T pallidum* fully sensitive to penicillin was isolated by the inoculation of rabbits with aqueous humour and eye tissue (but not liver) from a baby infected with congenital syphilis who died aged 22 days.¹⁸ The mother had been treated for secondary syphilis before pregnancy with an unknown amount of tetracycline and in the seventh month of pregnancy with benzathine penicillin G 2.4 MU intramuscularly. The baby was delivered 10 days later, and a treponemicidal concentration of penicillin was present in the cord blood. The baby then received benzyl penicillin 50 000 IU/kg/day intramuscularly for 17 days. At autopsy a non-motile treponeme was present in the aqueous humour, and a similar one had been found in the CSF on the 10th day of life.

UNCHANGED INTRACELLULAR FORMS OF *T PALLIDUM*

T pallidum may be found within the cytoplasm and nuclei of cells by electron microscopy.⁵⁵⁻⁶⁰ Treponemes are taken up by macrophages and polymorphonuclear leucocytes, where they are destroyed. Virulent *T pallidum* may enter cells that are incapable of complete phagocytosis, such as fibroblasts, where they remain unchanged, or virtually unchanged (as in plasma cells). Penetration of cells in tissue culture is rapid and may occur within 30 minutes of inoculation.⁶¹ This intracellular position may be important because it may play a part in the development of the host's immune response, may protect *T pallidum* from the action of penicillin in extracellular fluid, and because the superoxide dismutase in host cells may protect *T pallidum* against high tissue concentrations of oxygen.⁶²

With the exception of rifampicin, which has no action against *T pallidum*, short courses of antibiotics do not enter living mammalian cells. If

they are administered for about seven days, however, they do enter some mammalian cells.⁶³

"ZONE PHENOMENON" OF EAGLE

Penicillin acts upon growing organisms. Tipper and Strominger showed that low concentrations of penicillin acting upon *Staphylococcus aureus* caused the production of cell walls that were deficient in peptide cross linkages and the accumulation in the cells of nascent peptidoglycan units.⁶⁴ High concentrations of penicillin rapidly inhibit growth of the organisms so that defective cell walls are not produced and nascent peptidoglycan units do not collect. This may explain the fact that the killing rate of low concentrations of penicillin for *Staph aureus* was higher than that of high concentrations (the "zone phenomenon" of Eagle). It is unknown whether this applies to *T pallidum*. The baby reported by Hardy *et al*¹⁸ had received low level benzathine penicillin in utero and high level penicillin G by injection after birth. Despite this, virulent *T pallidum* gave a positive infectivity test result.

Biology of *T pallidum* related to treatment^{63 65}

STRUCTURE OF *T PALLIDUM*

Treponemes contain ribosomes, which are presumably acted on by erythromycin and tetracyclines, and have cell walls. In summary, penicillin acts by interfering with the synthesis of cell walls. It is only active against organisms that synthesise their cell walls in growth and division.

TREPONEMAL REPRODUCTION

A sexual reproductive phase, which could serve as a means of transmission of resistance to antibiotics as it does in Gram negative bacteria, has been postulated.

The 30 to 33 hour division time for *T pallidum*^{23 24} is for organisms from lesions of early syphilis. If the treponemes in a patient suffering from late syphilis are dividing more slowly or not dividing at all, the requirements for their elimination may well be different from those of treponemes in early syphilis. If a treponemicidal concentration of penicillin is present but the organisms are not dividing, they remain viable, virulent, and unaffected by the drug.²⁵

If the intervals between doses are too great they will allow treponemal recovery between doses. Thus in early syphilis short intervals between doses are appropriate if a soluble penicillin is used, and a dose that produces a treponemicidal concentration for an appreciable proportion of the life of each generation will be required. In early syphilis it seems that treatment should be for no less than seven and a half days, or six generations. In late syphilis very long lasting penicillinaemia may occasionally be required.

DOSE AND DURATION OF TREPONEMICIDAL CONCENTRATIONS

Motility and virulence of *T pallidum* are not synonymous. Organisms that still remain motile after in vitro incubation with penicillin may be unable to infect rabbits,^{66 67} but infection cannot be caused by treponemes that have been immobilised by penicillin.

Raising the concentration of penicillin increases its effect until an optimum concentration has been attained; higher concentrations do not increase the effect. This applies to Reiter treponemes,⁶⁸ to the immobilisation of virulent *T pallidum* after an initial lag phase of four hours with pure penicillin,⁶⁹ to syphilitic orchitis in rabbits,⁷⁰ and to the time taken for chancres to become negative on dark field microscopy.⁷¹ The dose of any antimicrobial agent must have a sufficient margin to provide treponemidal concentrations for the required time. This must allow for microbial variations and differences in absorption due to the size, age, and activity of the patient and the preparation used.⁷²

In man a treponemidal serum concentration of 0.03 IU/ml (0.018 mg/l) lasts for seven days after intramuscular administration of benzathine penicillin G 300 000 IU, nine days after 600 000 IU, and about 21 to 24 days after 2.4 to 3 MIU. Treponemidal CSF concentrations, however, are generally not achieved by this preparation (see above).

If short acting penicillins are used, the duration of effective penicillinaemia increases with increasing dosage. A sequence of large doses may be more effective than even larger infrequent doses because it avoids appreciable gaps and (particularly if given with probenecid by mouth) may produce effective concentrations in the CSF and eye. Intramuscular injections of benzyl penicillin G 500 000 IU every six hours, or procaine penicillin G 1.8 MIU daily, with probenecid by mouth can be relied on to produce treponemidal CSF penicillin concentrations (see above).

Studies of treatment of early experimental syphilis in rabbits with penicillin suggest that very high doses of aqueous penicillin are wasteful and that about eight days is the optimum duration of treatment. In each experiment the amount of penicillin required to cure 50% or 100% of the rabbits was less if it was given in the form of depot injections. If the duration of treatment was fixed at eight days, then aqueous penicillin given twice a day was as effective as a single depot injection daily.⁶³

ENCYSTMENT OF *T PALLIDUM*

Treponemes in chancres in man may be encysted.⁵⁶ They may be motile⁷³ within a variable enclosing wall that is thought to represent a protective early⁷³ or degenerative⁷⁴ reaction to noxious stimuli.

"CAPSULE"

A clear zone⁷⁵ or extracellular layer⁷⁶ surrounds *T pallidum* in syphilitic lesions. This might reduce phagocytosis and be a barrier to low concentrations of antibiotics.⁷⁶

RESISTANCE OF *T PALLIDUM* TO PENICILLIN

There is some evidence of reduced sensitivity to penicillin of *T pallidum* after its passage in rabbits that were treated subcuratively.⁷⁷⁻⁷⁹ Collart and Poitevin, however, could not produce true penicillin resistance after repeated passages in and subcurative treatment of rabbits for seven years.⁸⁰ Apparently, strains of *T pallidum* consisted of heterogeneous groups with different multiplication times.

Treatment failure has never been shown to be due to resistance of *T pallidum* to penicillin.¹⁸

WEAK PENICILLIN

This has not been a factor since penicillin was standardised as penicillin G.

ORAL TREATMENT OF PATIENTS WITH SYPHILIS

Moore stated that, because of poor patient compliance, treatment of syphilis should be by injection.⁸¹ Because high concentrations of amoxycillin can probably now be achieved reliably by doses once or twice daily together with probenecid by mouth, the objections to oral treatment with the penicillins are less applicable. For patients who are allergic to penicillin, doxycycline 300 mg once daily may be given under supervision.

PROBENECID WITH PENICILLINS AND AMPICILLIN

Fishman showed that the effect of probenecid on CSF penicillin concentrations was to raise blood concentrations, to inhibit excretion of penicillin from the CSF, and to bind serum protein so that diffusable penicillin was released. The concentration in the brain was also increased, but to a lesser extent than in the CSF.⁴⁵ In patients being treated for neurosyphilis, probenecid increased the CSF penicillin concentration by a factor of 6 and the CSF ampicillin concentration by a factor of 3.⁸² Probenecid raised the concentrations of ampicillin^{50 83} and penicillin⁵⁰ in the eye.

Antitreponemal drugs other than penicillin G

AMPICILLIN

Ampicillin 500 mg four times a day for 10 days provides effective treatment for early syphilis if the antibiotic is taken as ordered and diarrhoea does not develop. The peak blood concentration is 2 to 2.5 mg/l, and the half life two hours. Probenecid

extends the half life and increases the penetration of the eye and the CSF. Talampicillin, which is metabolised to ampicillin, causes less gastrointestinal disturbance and fewer sensitivity rashes.

AMOXYCILLIN

Amoxycillin promises to be even more useful. The antitreponemal equivalent of 0.018 mg/l of penicillin is 0.42 mg/l of amoxycillin, which is easily reached and maintained, even in the CSF, with probenecid.⁴⁶ It is better absorbed than ampicillin, and causes fewer sensitivity reactions and less gastrointestinal disturbance.

CEPHALOSPORINS

Cephaloridine

Cephaloridine has treponemicidal activity about one tenth that of penicillin, so it is more effective than the tetracyclines or chloramphenicol.

If a patient has developed non-anaphylactic allergy to penicillin treatment and has normal renal function, closely supervised treatment with cephaloridine 1 g intramuscularly twice daily for 15 days (for uncomplicated early syphilis) or for 21 days (for complicated syphilis) is effective. Cross sensitivity to cephaloridine may be present or will develop in less than 10% of patients. For this reason cephalosporins are absolutely contraindicated in patients who have had an anaphylactic reaction to penicillin.

Cephalexin

Cephalexin has a half life of about 40 minutes, so would require administration by mouth four times a day. The problems posed by patient non-compliance make it an unsuitable preparation for the treatment of syphilis.

Cefuroxime

Cefuroxime has been shown to have considerable effect against *T pallidum* in vitro, as the minimum immobilising concentration is about 10 times greater than that of penicillin G.⁸⁴ Cefuroxime enters the CSF in meningitis in man.⁸⁵

CHLORAMPHENICOL

Chloramphenicol has weak antitreponemal activity but penetrates the CSF and eye well because it is lipophilic and has a small molecule. It causes dose independent or dose related aplastic anaemia, so should not be used for treating syphilis.

ERYTHROMYCIN

The estolate produces high blood concentrations and probably more hepatitis than other preparations. Although this has been denied,⁸⁶ the drug is best

avoided at present. The antitreponemal action of erythromycin approximates to that of the tetracyclines, but absorption is variable and the drug does not enter the CSF or eye or cross the placenta effectively.^{87 88} At least five cases have been reported of erythromycin apparently curing early syphilis in pregnant women who subsequently gave birth to children affected by active congenital syphilis.⁸⁹⁻⁹² Erythromycin should not be used for treating neurosyphilis.

LINCOMYCIN, CLINDAMYCIN, METRONIDAZOLE, AND VANCOMYCIN

These four drugs have some action against *T pallidum* but insufficient for therapeutic use. The aminoglycosides have very little effect so that, with the possible exception of spectinomycin, they can be used to treat gonorrhoea without invalidating a diagnosis of early syphilis.

TETRACYCLINES

Doxycycline and methacycline are usually either as effective as tetracycline or 10 times more effective against cultivable treponemes.^{93 94} The tetracyclines are considerably less effective than penicillin G in vitro and in vivo. Positive infectivity test results have followed the administration of an unknown amount of tetracycline¹⁸ and tetracycline hydrochloride 2 g a day for 10 days.²⁰

Tetracycline hydrochloride 500 mg by mouth yields a serum concentration of 3.5 mg/l with a half life of six to nine hours. Doxycycline 200 mg yields the same concentration with a half life of 17 to 20 hours.⁹⁵ Doxycycline and minocycline are well absorbed from the gut and enter the eye and CSF more effectively than tetracycline.⁹⁶ Absorption is not impaired by milk or milk products. Tetracyclines stain teeth and cause embryopathy and are therefore contraindicated in pregnant women and young children. Doxycycline particularly causes photosensitivity, so direct sunshine should be avoided during and for three days after the course of treatment.

Clinical conclusions and recommendations

The standard treatment of early syphilis with procaine penicillin 600 000 IU, with or without 2% aluminium monostearate, by daily intramuscular injection for 10 days has proved to be highly effective and is the treatment of choice.

The value of depot injections of benzathine penicillin is less certain for early syphilis, and no large scale studies include CSF findings. There is no evidence that results are improved by intramuscular injections of 2.4 MU for adults at intervals of two

weeks to a total of 2, 3, or 4 injections.⁹⁷ Even this dose cannot be relied on to eliminate treponemes from the CSF.

It is logical to maintain a treponemicidal CSF penicillin concentration (0.018 mg/l) in treating neurosyphilis by intramuscular injections of benzyl penicillin G 500 000 IU every six hours together with probenecid 500 mg by mouth for 17-21 days. Alternatively, procaine penicillin 1.8 MIU intramuscularly and probenecid by mouth daily for 17-21 days is suitable for outpatients.

IRITIS OF LATE SYPHILIS, EITHER CONGENITAL (WITH INTERSTITIAL KERATITIS) OR ACQUIRED Treatment should be at least as intensive as for neurosyphilis, and in a patient suffering from recurrent interstitial keratitis may have to be prolonged (using, say, talampicillin or amoxycillin with probenecid) to eradicate infrequently dividing organisms.

TREATMENT WITH ANTIBIOTICS OTHER THAN PENICILLIN

Doxycycline is the tetracycline of choice. It can be administered daily in a single supervised 300 mg dose (with milk after eating) for 15 days to treat early uncomplicated syphilis or for 21 days to treat complicated or late syphilis.

Cephalexin 1 g twice a day intramuscularly is useful for patients who have had a non-anaphylactic allergic reaction to penicillin. It may be given for 15 days to treat early uncomplicated syphilis or for 21 days to treat complicated or late syphilis.

Erythromycin 500 mg (with milk after eating) four times a day for 21 days may be used for patients who cannot tolerate penicillin or doxycycline. It crosses natural barriers poorly and therefore hardly enters the eye, CSF, or fetus. If it is used for pregnant women, the newborn babies should be treated with procaine penicillin 300 000 IU a day intramuscularly for 10 days. The mother's CSF should then be examined, and her treatment should be completed with doxycycline as required after breast feeding has stopped.

FURTHER INFORMATION

A regular computer search should be made to collect and assess further information on treatment with doxycycline, minocycline, and other tetracyclines; erythromycin; cephalexin; the new cephalosporins; and amoxycillin. Finally the use of benzathine penicillin should be fully assessed.

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