MEDICAL PRACTICE

Occasional Review

Recognition and management of genital chlamydial infection

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Chlamydia trachomatis is widely prevalent. It is an obligate intracellular bacterial parasite whose genital strains (genital chlamydiae) are immunologically and epidemiologically distinct from the ocular strains that cause classical trachoma.[1] These are transmitted from eye to eye in hot, dry climates, particularly when standards of hygiene are low, but genital chlamydiae are sexually transmitted, and can often be isolated from patients attending venereal disease (VD) clinics in Western countries. Although the conjunctivae may be infected by genital chlamydiae both in neonates, who acquire the infection during parturition, and in adults, through the accidental transfer of infected material to the eye, eye-to-eye infections are rare.

"Non-specific" genital infection—that is, non-gonococcal urethritis (NGU) in men, and the various syndromes in both sexes associated with it—is now a major health problem in Western society.[2] The role of genital chlamydiae in the pathogenesis of these diseases has now been recognised,[3] and the development of sensitive and reliable cell-culture methods for isolating them[4-9] has led to intensive research into their epidemiology and pathogenicity in the human genital tract. As a result, groups particularly prone to infection have been identified.

This knowledge has produced a dilemma for both the venereologist and the medical microbiologist, partly because the isolation technique, though feasible in specialist centres, is time-consuming and labour-intensive, and therefore unsuitable for widespread screening of patients attending VD clinics. Nevertheless, genital chlamydiae have been implicated as an important cause of "non-specific" genital infections which should therefore be identified and treated in the interests of patients and the community as a whole.

Although much still needs to be learnt about these infections, enough information is available to allow us to try to define where available diagnostic facilities should be concentrated, and also to rationalise the management and treatment of these infections. We also aimed at highlighting particular difficulties in management and treatment.

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Incidence of chlamydial infection

Genital chlamydiae are commonly found in the genital tract in promiscuous populations. When the incidence of these organisms in groups of women was compared with the incidence of other recognised sexually transmitted pathogens (*Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and herpes simplex virus, type 2), chlamydiae were usually the most frequently isolated organism.[10-15]

SEXUAL TRANSMISSION

Epidemiological evidence for the sexual transmission of genital chlamydiae was provided by showing that the chlamydial isolation rate in different groups of sexually active women was highest in women attending VD clinics.[10 15] Several studies of chlamydial isolation rates in sexual partners have also shown that partners of patients from whom chlamydiae were isolated (chlamydia-positive patients) were also usually chlamydia-positive, whereas consorts of patients from whom chlamydiae were not recovered (chlamydia-negative patients) were generally chlamydia-negative.[11 16-18]

GENITAL CHLAMYDIAE IN MEN

Chlamydiae are associated with and are probably causal agents in up to half of unselected cases of NGU in men attending VD clinics.[16 17 19–21] Chlamydiae are also found in 19-32% of men with gonococcal urethritis,[16 19 21 22] and these chlamydia-positive men with gonorrhoea are liable to be left with a residual abacterial urethritis, so-called postgonococcal urethritis (PGU) after successful treatment of gonorrhoea by antibacterials such as gentamicin, penicillin, ampicillin, or spectinomycin.[16 19 22] Chlamydiae may also cause epididymitis,[23] and they are associated with some cases of Reiter's syndrome.[24] Nevertheless, chlamydiae cannot be implicated in all cases of NGU or PGU.

GENITAL CHLAMYDIAE IN WOMEN

Chlamydiae can be isolated from 20-30% of unselected women attending VD clinics.[10 11 15 25] The organisms are recovered from 30-60% of women with gonorrhoea,[10–12 15] from 30-35% of women who are sexual contacts of men with NGU,[10–12] and from 2-17% of other women attending VD clinics whose contact history is unknown.[10–12 25] By contrast, the isolation rate in other clinics, such as family-planning or "well-women" clinics, is appreciably lower (2-7%).[10 13 15] Cervical infections with *C trachomatis* are often asymptomatic, but the organisms are frequently associated with a cervical syndrome termed variously "cervicitis",[13] "hypertrophic erosion,"[26] or "cervical discontinuity,"[27] and with the presence of purulent material in the endocervical canal. Chlamydiae may also cause salpingitis in women after childbirth[26] and in other groups.[28]

OCULAR INFECTIONS

In Western society ocular infection by genital chlamydiae is sporadic. A broad range of ocular disease occurs.[29] The most common syndrome in adults is inclusion conjunctivitis, a chronic follicular conjunctivitis of acute or subacute onset. Neonatal ocular disease ("inclusion blennorrhoea"), however, usually presents as an acute papillary mucopurulent conjunctivitis.[30] Colonisation of the respiratory tract by chlamydiae may also cause a distinctive pneumonia syndrome in neonates.[31] Ocular infections seldom occur in adults with chlamydial infections arising in the genital tract,[19] but babies of chlamydia-positive women risk acquiring chlamydial ophthalmia at birth.[32]

Diagnosis and treatment

Definitive diagnosis can be made at present only by isolating the organism from the genital tract (usually the urethra in men and the cervix in women). Direct demonstration of chlamydial inclusions in infected epithelial cells obtained from the patient, a method used to diagnose ocular chlamydial infections,[33] is not satisfactory in genital infections, and serological techniques do not at present provide a suitable alternative.[34]

Genital chlamydial infections are treated to alleviate local symptoms and prevent local complications such as epididymitis and salpingitis; to prevent chlamydial ophthalmia in the newborn; and to minimise the transfer of organisms to uninfected people and thus reduce the reservoir of genital chlamydial infections in the community. Adequate antimicrobial treatment is available, and in-vitro systems for assaying antibacterials against *C trachomatis* have been developed.[35–37] Eradication (assessed by repeated failure to reisolate the organism after treatment) can be achieved both in the genital tract and in the eye by treatment with tetracyclines or erythromycin.[38]

A regimen of tetracycline or oxytetracycline 1 g daily in divided doses for 14 days seems to be adequate for genital infections.[39] Erythromycin stearate 250 mg six-hourly for two weeks is an adequate alternative for those who are intolerant of tetracycline. Systemic treatment should be combined with topical tetracycline applications to the eye (1% chlortetracycline eye ointment *BPC* applied four-hourly) in oculogenital infections in adults. In neonatal ophthalmia local tetracycline applications combined with systemic erythromycin (see below) is advisable, since ocular infection is not always eradicated by local treatment alone.[40] Systemic erythromycin should also be used as an alternative to tetracyclines when treating pregnant women.

Management of genital chlamydial infections in men

NON-GONOCOCCAL URETHRITIS

Routine isolation of chlamydiae in men presenting with NGU is not needed, since tetracyclines are the treatment of choice, and will be prescribed whether or not the patient is chlamydia-positive. Moreover, "blind" tetracycline treatment in these patients has the added advantage that the genital mycoplasmas, which may also be causally associated with some cases of NGU, normally respond to tetracyclines.[18] Nevertheless, tetracycline treatment must be adequate, and a course of treatment of less than two weeks is probably suboptimal. A true relapse of urethral chlamydial infection in men after treatment is rare, but may occur after both oxytetracycline and erythromycin treatment.[38 39] Relapse may be due to lack of patient compliance or irregular absorption rather than to the existence of antibiotic-resistant strains.

GONORRHOEA

Diagnostic isolation facilities, if available, should be concentrated on identifying men with chlamydia-positive gonorrhoea by screening for chlamydiae at each patient's initial attendance. Gonorrhoea is normally treated with procaine penicillin injections or oral ampicillin, usually combined with oral probenecid, or with spectinomycin injections. After such treatment patients yielding chlamydiae should receive a full course of tetracycline or oxytetracycline as above, since penicillin and other regimens used for treating gonorrhoea do not eradicate chlamydial infections,[41] and these men are therefore susceptible to chlamydial PGU after successful treatment of their gonorrhoea.

When screening facilities are not available all men with gonorrhoea should be encouraged to attend for follow-up examination for not less than two weeks so that cure of the gonococcal infection may be confirmed and PGU detected by microscopy of Gram-stained urethral specimens or first-catch urine for appreciable numbers of polymorphonuclear leucocytes. Adequate treatment with tetracycline or oxytetracycline as above should then be instituted. Reducing the number of men who default from VD clinics without follow-up examination is probably at least as important a method of reducing the incidence of persistent chlamydial infections in these patients as actually identifying chlamydial infections by isolation. In a population who are particularly likely to default after treatment for gonorrhoea there seem to be sound arguments for a routine course of a tetracycline after specific treatment for the gonococcus.

Management of genital chlamydial infections in women

Chlamydial infections in women are difficult to identify clinically because they are generally "silent." Untreated, these infections tend to persist, often with excretion of infectious organisms, but also perhaps as latent infections that may be reactivated and become a source of future infections.

FEMALE CONSORTS OF MEN WITH NON-GONOCOCCAL URETHRITIS

There is no general agreement at present on how these patients should be managed. No evidence has yet been produced to show that treating female partners of men with NGU with tetracycline prevents NGU recurring in the men.[42] Nevertheless, many clinicians think that the evidence that NGU is basically a sexually transmitted condition, probably caused by several different infectious agents including genital chlamydiae, is sufficiently strong to justify vigorously tracing female contacts of men with NGU. After investigation to exclude associated infections these women are treated with the same tetracycline regimen as men with NGU receive. In centres with this policy of tracing and treating all female consorts of men with NGU attempted isolation of chlamydiae is not necessary. In clinics where this is not routine practice screening to identify and treat those who are chlamydia-positive is probably advisable.

GONORRHOEA

Management of women with gonorrhoea poses considerable problems; for chlamydiae can be recovered from 30-60% of such patients, and they probably represent an important reservoir of active chlamydial infection in the community. If treating chlamydia-positive consorts of men with NGU is accepted as desirable then logically chlamydia-positive women with gonorrhoea should also be identified and treated. If isolation facilities are not available all women with gonorrhoea should perhaps be given antichlamydial treatment after eradication of the gonococcus, since chlamydial infections are so common in these patients. A two-week course of tetracycline or oxytetracycline should be given, but if the patient is pregnant erythromycin is substituted. Adequate treatment of pregnant women is particularly important in preventing chlamydial ophthalmia neonatorum.

OTHER WOMEN ATTENDING VD CLINICS

Since it is not feasible at present to screen all women attending VD clinics for chlamydiae, attention should be concentrated on patients with cervical disease—that is, cervical discontinuity and a purulent cervical discharge.[27] Isolation should be attempted if facilities are available; if not, a therapeutic trial of tetracyclines is probably justified in women with this syndrome. Identifying other genital tract pathogens, such as *T vaginalis*, *Candida albicans*, and herpes simplex virus, does not exclude the possibility of a concomitant chlamydial infection, since these women are often simultaneously infected with several species of organism.[14 43] Nevertheless, by restricting investigations to women attending VD clinics with symptoms or signs of "cervicitis," a proportion of cervical chlamydial infections will be unrecognised and untreated.

Management of eye infections caused by genital chlamydiae

Definitive diagnosis of these infections by isolating chlamydiae is important in both adults and neonates, since this allows adequate treatment to be instituted and shortens the course of an otherwise persistent conjunctivitis that occasionally leads to severe long-term sequelae similar to those of classical trachoma.[1 44] Chlamydial ophthalmia should be considered in all babies in whom mucopurulent conjunctivitis develops four or more days after birth. If isolation facilities are available this diagnosis can then be made or excluded. Without these facilities chlamydial infection may be considered if the conjunctivitis fails to respond to the standard treatment with topical chloramphenicol or neomycin; under these circumstances a therapeutic trial of antichlamydial treatment is probably indicated.

If chlamydial ophthalmia is diagnosed or strongly suspected, treatment is by application of chlortetracycline eye ointment 1% four-hourly, combined with oral erythromycin stearate, 6 mg/kg body weight six-hourly, treatment being continued for at least two weeks. If *C trachomatis* has been recovered from the infant's eye it is advisable to examine and treat both parents. The gonococcus should be excluded as a cause of neonatal ophthalmia, though these infections may occur together in the eyes of neonates.

Other considerations

Under some circumstances latent chlamydial infections may persist in infected patients, with no excretion of infectious organisms. Nevertheless, these infections are potentially capable of reactivation, and fresh contacts may be infected.[45 46] If such latent infections occur even vigorous identification and treatment of active chlamydial infections will not eradicate genital chlamydiae. In particular, the important association of chlamydiae with gonorrhoea, especially in women, suggests that a gonococcal infection itself may act as a potent chlamydial reactivator. Vigorous measures to control gonorrhoea may thus be one of the most effective ways of controlling chlamydial infections in the community.

Conclusions

Genital chlamydiae, long recognised in Britain as sporadic pathogens in the eye, are now becoming widely accepted as an important cause of genital infections. While chlamydial infection in men is a problem for the venereologist, infection in women also concerns the gynaecologist; and in this respect *C trachomatis* resembles *N gonorrhoeae*, with which, indeed, it is often associated.

Widespread screening of patients for chlamydiae, comparable with that performed in VD clinics and elsewhere for *N gonorrhoeae*, is not yet feasible. At present existing diagnostic services should probably be concentrated on patients who are unlikely to receive tetracycline treatment, and we have indicated some of these groups above; additional groups, particularly in gynaecological practice, could no doubt be defined. Increasing awareness of the association between genital chlamydiae and gonorrhoea is needed, since patients with gonorrhoea do not at present routinely receive antichlamydial treatment. A single antimicrobial agent effective in treating both chlamydiae and gonorrhoea has yet to be discovered, and so follow-up examination of men with gonorrhoea is important in recognising and treating PGU. The policy to be adopted towards women with gonorrhoea is particularly difficult, since up to two-thirds of them may also have a chlamydial infection, which usually remains untreated. Such patients therefore constitute an important reservoir of active chlamydial infections in the community.

How valuable to the clinician are facilities for isolating chlamydiae? For precise diagnosis leading to rational treatment they are probably most important in eye infections, particularly in neonates. In men, these facilities are probably less important except possibly, as argued above, in those with gonorrhoea. They are valuable, however, in both venereological and gynaecological practice for elucidating the causes of inflammatory cervical disease and salpingitis and thereby avoiding "blind" and sometimes unsuccessful antibacterial treatment.

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MATERIA NON MEDICA

The plague at Prato

Remaindered books almost always represent excellent value. But at 40p Carlo Cipolla's *Cristofano and the Plague* is almost literally and metaphorically priceless. This short book, which satisfies an evening's reading to perfection, is a masterpiece of the medical historian's art; and Cipolla is not a medical man, but an economic historian. His hero, however, Cristofano di Giulio Ceffini, Provedditore della Sanità of the tiny Tuscan town of Prato, was not a physician or surgeon either, but an accountant and administrator.

In 1629 a German army entered Italy through the St Gotthard Pass and brought with it the deadlier enemy of the plague. In eight months the disease spread down into the Po valley, and then south towards Florence. Medical treatment was known to be useless, and public health measures were the only possible way of keeping the disease at bay. The motto of the Sicilian physician, Giovan Filippo Ingrassia, for his treatise on the disease, was *Ignis, Furca, Aurum sunt Medicina Mali*: fire to destroy infected items, the gallows to deter the populace from breaking health regulations, and gold for the expense of it all. But it was gold that Prato did not have. The plague bankrupted the town for years afterwards and compromised all of its countermeasures. Infected beds were too valuable to be burnt, and merchants could not afford to discontinue trading, thereby breaking the slender defence of quarantine.

Cristofano's facility with numbers converted him into an epidemiologist before the word was invented. His accountant's mind carefully chronicled the carnage; and it is these invaluable statistics that Cipolla has used to reconstruct so accurately the impact of the plague on a late Renaissance town; the bills of mortality, the ever-increasing wages of the ever-decreasing number of grave diggers, and the cost of the staple diet of bread, wine, and salad. Cristofano's task was not only to fight the plague; a sharp letter had to be sent to the hospital administrators reminding them that it was their duty "to tend and succour the poor even if it means some inconvenience," and not "to try to increase the receipts of suchlike pious place." At times he was even reduced to "begging" for sheets and blankets.

Cristofano was successful by the standards of his time. Only 1500 of the population of 6000 had died in 10 months; in Genoa in 1657 55 000 out of 73 000 were to die. Cipolla's success is in recreating, by scrupulous scholarship in the State Archives of Florence and Prato, the horror, the impotence born from ignorance, and above all the constraints of pre-industrial poverty in fighting the plague. Cristofano was "lost in the darkness of an absurd fight against an invisible enemy."—I C MCMANUS (research student, Cambridge).

Closed-circuit soccer

On 25 June I had my first opportunity to watch a world cup final on closed-circuit television. As an expatriot weaned on maximal doses of *Match of the Day*, I approached the occasion with some trepidation and the discomfort of having to pay for something that I had been raised to believe was an inherited if not conjugal right. The afternoon turned out to be a most enjoyable oone.

About 2000 people were present, 95% of whom were, I am sure, permanent residents of the United States. Large blue and white flags, smaller stature, and Spanish accents identified the supporters of one side. Small red, white, and blue flags, cycling caps, and orange T-shirts characterised the supporters of the other side. Both factions maintained a noise level throughout the match which, if not equal to that of the River Plate Stadium, was at least comparable to a Concorde take-off that even British Airways would have been ashamed of. That passions should flow so liberally throughout the afternoon was most intriguing and added to the enjoyment of the occasion.

One very interesting aspect of the afternoon was the reaction of the American audience to the time-wasting tactics of the winning team. Seeing players collapse in agony normally associated with the fracture of a long bone or the severing of a limb each time they were touched by an opponent produced a reaction of utter disgust. This increasingly prevalent aspect of the game is absent in all American sports, even to the point where the participants deliberately conceal any reaction that may be construed as a sign of weakness. The absence of yellow cards for deliberate handling offences also surprised the audience.

While soccer in this country may not yet have reached puberty, the increasing enthusiasm for and participation in the sport would suggest that the entry of the United States into the world game is not far off. Its contribution may well be in helping to eliminate some of the trivial and time-wasting tactics rather than the unnecessary alteration of some of the laws. Look west, young men, your future opponents may well have the adapted styles of a Pele, Beckenbauer, Best, Ball, or Marsh.—J V NIXON (cardiologist, Dallas, Texas).