CHLAMYDIAL INFECTIONS 
OF THE FEMALE UROGENITAL TRACT

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SUMMARY

Bacteria in the genus *Chlamydia* comprise four species, namely *C. trachomatis*, *C. psittaci*, *C. pecorum* and *C. pneumoniae*. *C. trachomatis* infection is common, varying in prevalence up to 37%, in women. In the United States and perhaps elsewhere the overall prevalence rate among women is estimated to be about 5%. Pregnancy may predispose to an increased chance of infection with *C. trachomatis* through physiological immunosuppression and/or cervical ectopy.

The cervix, not the vagina, is the primary target for *C. trachomatis* infection which is often asymptomatic. Urethritis frequently accompanies cervical infection, but the main complications come from spread to the upper genital tract which leads to endometritis, salpingitis, perihepatitis and periappendicitis. The eventual outcome may be ectopic pregnancy, tubal infertility and chronic pelvic pain. Much of the pathology seems to be mediated immunologically. Fibrosis and scarring are a feature and it is possible that cytokines, particularly those that stimulate fibroblast activity (interleukin I and tumour necrosis factor), participate in the pathogenesis.

In pregnancy, *C. trachomatis* has been associated with premature rupture of the membranes, stillbirth and low birth-weight infants. The incidence of vertical transmission of chlamydiae from mother to baby varies; if the mother is untreated, 20%-50% of the new-borns will develop conjunctivitis and 10%-20% will develop pneumonia.

*C. psittaci* infection in pregnancy is rare but it can cause abortion, particularly in women who come into contact with infected sheep during the lambing season.

Accurate diagnosis of *C. trachomatis* infection has improved considerably with the advent of molecular techniques for amplifying chlamydial DNA. This, together with the ability to detect *C. trachomatis* in urine and vaginal swabs, is proving helpful in the promotion of screening programmes. Tetracyclines, usually doxycycline, and erythromycin and azithromycin form the mainstay of treatment.

INTRODUCTION

Chlamydial infection has been recognised since antiquity in the form of conjunctival blindness. However, it is only relatively recently, at the turn of this century, that the genital manifestations of non-gonococcal infection were
recognised in some individuals as being chlamydial. Isolation of *Chlamydia trachomatis*, one of the four *Chlamydia* species, was achieved initially by using the yolk sac of embryonated hens’ eggs and in the 1960s by using cell cultures, which were more sensitive. However, the slow delivery of a result often rendered the procedure of limited clinical value. The development of antigen detection tests improved diagnosis somewhat, but not as much as the most recent tests based on DNA amplification. *C. trachomatis* was and probably still is the most common cause of pelvic inflammatory disease in the western world, and the consequent high rate of tubal damage makes this microorganism the most common cause of tubal infertility. *C. trachomatis* infection has an incubation period of 10-14 days, but latent asymptomatic infection may last for months or even years. In this review chlamydial infections in women are highlighted and the effect on pregnancy and the new-born are discussed, as are laboratory diagnosis and approaches to treatment.

**MICROBIOLOGICAL BACKGROUND**

Taxonomically, chlamydiae are placed in their own order (Chlamydiales) and the family, Chlamydiaceae, contains a single genus, *Chlamydia*, which comprises four species. (*Chlamydia trachomatis* contains 15 serovars; serovars A-C cause the chronic cicatrizing eye disease, trachoma and, rarely, sexually related infection (*Mabey* and *Whittle*, 1982); serovars D-K do not seem to be associated with trachoma, but cause paratrachoma and a variety of genital tract diseases. Serovars L1-L3 are responsible for lymphogranuloma venereum (LGV). *C. psittaci* causes disease in birds and animals and respiratory disease (*psittacosis*) and occasionally abortion in humans. *C. pecorum* causes pneumonia, arthritis and diarrhoea in cattle and sheep. *C. pneumoniae* is the recent binomial designation for strains which hitherto were termed TWAR. It causes human respiratory disease and has been associated with atherosclerosis.

Chlamydiae are recognised as bacteria because they possess peptidoglycan cell wall material, contain RNA and DNA and are sensitive to a wide variety of broad-spectrum antibiotics. However, the size of the infectious particles (elementary bodies: EBs) is similar to that of the large viruses (300 nm) and, like viruses, they have an obligate intracellular existence. This is probably due to their inability to generate adenosine triphosphate and the need to acquire it from the host cell to drive their own metabolic processes. The intracellular reproductive cycle comprises several well recognised phases (*Ward*, 1988), that is attachment of the metabolically inactive EB to the host cell surface, presumably through specific receptors and adhesins, and phagocytosis; conversion to a metabolically active reticulate body (RB) after about 8 hours; increase in the number of RBs by binary fission (cytoplasmic 'inclusion' formed); reorganisation of RBs to new EBs (larger inclusion) after 24-30 hours and, finally, release of the infectious EBs from the cell.

Recognition of late inclusions by staining with vital dyes or immunocytochemical techniques forms the basis of chlamydial detection in cell culture. Inclusions produced by *C. trachomatis* contain glycogen and, therefore, stain with iodine whereas those of the other chlamydial species do not. The EBs of many, but not all, *C. pneumoniae* strains are pear-shaped and have large periplasmic spaces. This distinguishes
them, by electron microscopy, from those of the other species which are round and have barely discernible spaces.

EPIDEMIOLOGY

*C. trachomatis* genital tract infection is common; prevalence rates varying from 2% to 37% have been reported for asymptomatic women in the United States (*Hammerschlag* et al., 1979; *Hardy* et al., 1984). Studies of pregnant women have revealed prevalence rates of chlamydial infection similar to those for non-pregnant women. In general, in both pregnant and non-pregnant groups, higher prevalence rates are found among indigent populations in urban areas, but overall it has been estimated that the prevalence rate in the United States is about 5% (*Schachter* et al., 1986). Studies based on gynaecological clinics and general practice in the United Kingdom have provided prevalence rates ranging from 3% to 12% (*Ridgway* et al., 1983; *Smith* et al., 1991).

The main demographic factors associated with high *C. trachomatis* prevalence rates in non-pregnant women are young age (24 years or less), low socio-economic class, single marital status, use of oral contraceptives or no contraception, intercourse with a new partner in the preceding two months, and living in an urban area (*Handsfield* et al., 1986). Risk factors for chlamydial cervical infection occurring in pregnant women are similar but also include the presence of mucopurulent cervicitis, abacteriuric pyuria and late antenatal clinic booking (*Sweet* and *Gibbs*, 1990). It is not clear whether oral contraceptive usage prior to pregnancy affects the rate of infection with *C. trachomatis* in pregnancy.

*C. trachomatis* has been detected in up to about 50% of women with gonococcal infection attending sexually transmitted disease (STD) clinics. Chlamydial infection prevalence rates usually parallel those for gonococcal infection, but in most populations chlamydial genital infections are three to four times more common than gonorrhoea (*Eager* et al., 1985), a ratio which may be higher in pregnancy.

DISEASE IN WOMEN (Table 1)

Bartholin's gland abscess

It seems that purulent infection of Bartholin's ducts may be due to chlamydial infection (*Davies* et al., 1978), either alone or with concurrent gonococcal infection. However, apart from a single further report (*Saul* and *Grossman*, 1988) of chlamydiae occurring in an abscess, little has been done to establish a causal relation.

Cervicitis

The cervix would seem to be the primary target for *C. trachomatis* infection, but its removal by hysterectomy does not necessarily mean that chlamydiae will not be found in the vagina (*Barton* et al., 1985), although their ability to cause vaginitis in the adult is unlikely. Infection of the cervix by *C. trachomatis* is often asymptomatic (*Leclerc* et al., 1988; *Cates* and *Wasserheit*, 1991). *Rahm* et al. (1988) noted that one-sixth of asymptomatic infected adolescents developed symptoms within 3 months. Indeed, chlamydiae are well-known to cause mucopurulent/follicular cervicitis, a condition that has been ex-
Table 1: Assessment of the extent to which *C. trachomatis* is involved in various oculogenital and associated diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Evidence that <em>C. trachomatis</em> is a cause*</th>
<th>Proportion of disease due to <em>C. trachomatis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In women:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethritis</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Bartholinitis</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>++++</td>
<td>About 50%</td>
</tr>
<tr>
<td>Cervical dysplasia</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Endometritis</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Salpingitis</td>
<td>++++</td>
<td>40-60%</td>
</tr>
<tr>
<td>Periappendicitis</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Perihepatitis</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Infertility</td>
<td>+++</td>
<td>≥8% due to chlamydial salpingitis</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Abortion</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td><strong>In men or women:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++++</td>
<td>?</td>
</tr>
<tr>
<td>Otitis media</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Arthritis (Reiter's syndrome)</td>
<td>+++</td>
<td>About 40%</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Proctitis</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Lymphogranuloma venereum</td>
<td>++++</td>
<td>100% (by definition)</td>
</tr>
<tr>
<td><strong>In infants:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++++</td>
<td>Up to 50%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>++++</td>
<td>30%?</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>-</td>
<td>?</td>
</tr>
</tbody>
</table>

*: ++++ = overwhelming; +++ = good; ++ = moderate; + = weak; - = none

Amended in detail (Dunlop et al., 1989). Nevertheless, it is not clear how common chlamydial cervical infection is because the proportion of asymptomatic infections is unknown. It is assumed that many are, but this notion may be warped because studies have involved predominantly STD clinic populations where most chlamydial infections are detected in sexual contacts of men with non-gonococcal urethritis or gonorrhoea, that is in women who have attended the clinic because of their contact history and not because of symptoms. Asymptomatic infections may abound in the community at large, but it is noteworthy that the majority of infected women in a general practice setting had symptoms (Longhurst et al., 1987). Factors influencing the initial acquisition of chlamydiae are numerous and must include age, frequency of exposure, use of contraceptives, the role of which has been debated (Edelman, 1988), and
spermicides (Ehret and Judson, 1988). In addition, the hormonal status and the presence of ectopy and host defences influence acquisition. The mix is so complex and doubtless variable that in an individual case it would probably be unrewarding and perhaps impossible to determine the relative contribution of each, although certain risk-factors have been outlined (Magder et al., 1988). Although postmenopausal chlamydial cervicitis has been purported to occur (Nagashima, 1987), patients under 25 years old, those who use oral contraceptives and those who have signs of cervicitis are more likely to have a chlamydial infection, although these factors are not always predictive (Kent et al., 1988). One would also like to think that host defences, in terms of both cell-mediated immunity and pre-existing antibody, have an important role in determining acquisition because it may be possible to enhance any protective influence they have. Of course, knowing who is most likely to be infected based on a multiplicity of historical and clinical characteristics is helpful in deciding who should be screened. Selection may be required because routine testing may only be cost-effective if the prevalence of chlamydial infection is relatively high (Phillips et al., 1987).

Meijer et al. (1989) found a correlation between C. trachomatis infection and inflammatory, but not neoplastic, changes of cervical cells. However, Paavonen et al. (1998) have provided serological evidence that C. trachomatis infection increases the risk of subsequent development of invasive squamous cell carcinoma of the uterine cervix.

Women with chlamydial cervicitis often have an associated and frequently asymptomatic urethritis (Horner et al., 1995) but the main complications of cervical infection derive from spread of chlamydiae to the upper genital tract.

**Pelvic inflammatory disease (PID)**

Canalicular spread of chlamydiae to the upper genital tract, which may be completely asymptomatic (Stacey et al., 1990; Tait et al., 1997), leads to endometritis, often plasma-cell associated (Paavonen et al., 1985) and sometimes intensely lymphoid in reaction (Thomas, 1986). Further spread causes salpingitis, perihepatitis, sometimes confused with acute cholecystitis in young women (Shanahan et al., 1988), in addition to peri-appendicitis and other abdominal complaints (Duffy et al., 1985), although the organisms are not always found in the cervix when these conditions are recognised (Moller et al., 1986). Factors contributing to the spread of the organisms are the time in the menstrual cycle during which acquisition occurs, serovar and infecting dose, duration of infection, presence of associated infections, absence of antibody, hormonal status and also the integrity of the genital tract. The most important of these in an individual case may be impossible to identify, although the trauma of surgery, for example termination of pregnancy (Heisterberg et al., 1985), or insertion or removal of an intrauterine contraceptive device, are obvious predisposing factors. So too is chorionic villus sampling, but routine screening before sampling is not cost-effective unless the procedure is being undertaken in a high-risk population (Moncada et al., 1987).

Chlamydial infection has been the major cause of salpingitis in Scandinavia (Mårdh, 1986) but it is unknown exactly how common chlamydial salpingitis is in most countries, because laparoscopy required for clinical diagnosis and for obtaining specimens to distinguish accurately between upper and lower genital tract infection is not undertaken routinely. Whether it will be possible to undertake laparoscopy more often and/or develop non-invasive pro-
procedures of sufficient sensitivity and specificity to be helpful still remains to be seen.

The eventual outcome of PID may be tubal infertility, for which there is direct isolation evidence (Brunham et al., 1988) and indirect serological evidence (Robertson et al., 1987) to link it with chlamydial infection; it seems that this often may be asymptomatic (Cates et al., 1994). Other consequences are ectopic pregnancy, which also may arise as a result of a subclinical chlamydial tubal infection and for which a serological association with chlamydiae has been seen (Cates and Wasserheit, 1991), and chronic pelvic pain. What factors determine precisely the development of such sequelae in chlamydial PID are unclear, although there is evidence from the Scandinavian studies that the number and severity of the infections influence subsequent fertility rates (Westrom et al., 1992). Infertility could be due to endometritis, or blocked or damaged tubes resulting from cellular infiltrates, or perhaps abnormalities of ovum transportation, as suggested by the results of work on a mouse model (Tuffrey et al., 1986).

THE EFFECT OF PREGNANCY ON CHLAMYDIA TRACHOMATIS INFECTIONS

Rates of isolation of *C. trachomatis* from the cervix have been reported to be higher in the second and third trimester than in the first (Brunham et al., 1990). However, it is not known whether pregnancy increases the degree of shedding of chlamydiae from the cervix, because the data were derived from patients who were examined only at ante-natal booking and may merely reflect the increased risk of *C. trachomatis* infection in those booking in the third trimester. Nevertheless, chlamydial infection is associated with cervical ectopy, a physiological condition predisposed to by an increased serum concentration of oestrogen, and it is plausible that the ectopy associated with pregnancy predisposes to increased shedding of, and/or risk of infection with *C. trachomatis*.

Pregnancy is physiologically immunosuppressive and cell-mediated immune responses are reduced progressively with advancing gestation to a nadir at 32 weeks gestation, recovery occurring by term in the absence of any superimposed immunosuppression. However, whether this suppression affects replication and shedding of *C. trachomatis* is unknown.

Maternal IgG antibody produced in response to *C. trachomatis* infection begins to cross the placenta after 5-6 weeks of gestation and is transferred at a more or less constant rate up to 17 weeks of gestation, after which there is an increase with increasing gestational age. However, up to two-thirds of babies born to mothers with genital *C. trachomatis* infection become infected, so that this passive maternofetal immunisation is, if at all, only partially protective. Specific antibodies are found also in breast milk, but the protective value to the new-born is unknown (Brunham et al., 1990).

THE EFFECT OF CHLAMYDIA TRACHOMATIS ON PREGNANCY

Infection with *C. trachomatis* can occur at any time throughout pregnancy and in the postpartum period; the manifestations of infection depend on the trimester in which it occurs.
Infection in the first trimester of pregnancy

Surgical termination of pregnancy in a woman with chlamydial cervicitis may cause PID with endometritis and/or salpingitis. Approximately 20% of patients with *C. trachomatis* infection prior to termination have developed salpingitis (Giertz et al., 1987). Many authors have advocated screening for *C. trachomatis* to avoid this iatrogenically induced pathology. Prophylactic use of erythromycin has been shown to reduce the incidence of postabortal PID, but it is debatable whether prophylaxis in the absence of screening is of value (Sorensen et al., 1992).

It is not known whether infection with *C. trachomatis* predisposes to spontaneous abortion, since the high background rate of both *C. trachomatis* and spontaneous abortion makes causation difficult to either prove or refute.

Infection in the second and third trimesters of pregnancy

Chorioamnionitis, premature labour and rupture of the membranes have all been associated with *C. trachomatis* infection, but whether the infection is a cause needs to be looked at more closely. Early prospective studies in pregnant women failed to show an association of chlamydial infection with prematurity (Schachter et al., 1979), but most of the women in these studies were enrolled in the third trimester; when enrolment occurred earlier, at 19 weeks of gestation, a highly significant association was found between infection with *C. trachomatis* and stillbirth, premature birth and perinatal death from prematurity (Martin et al., 1982). In another study, Harrison et al. (1983) showed no association overall between *C. trachomatis* infection and spontaneous abortion, stillbirth, premature labour or rupture of membranes. However, in a subgroup of women in whom *C. trachomatis* infection was detected by culture and by having IgM chlamydial antibody (24% of those infected with *C. trachomatis*), the infection was associated with low birth-weight infants and with premature rupture of membranes. This led to the hypothesis that recent exposure to *C. trachomatis* was important in its pathogenic effect on the chorioamnion.

Postpartum infection

The existence of postpartum chlamydial endometritis in mothers of children born with inclusion conjunctivitis was confirmed in a prospective study by Rees et al. (1977). Endometritis may be asymptomatic or patients may present with secondary postpartum haemorrhage, fever, lower abdominal and/or vaginal discharge. Postpartum endometritis may be subdivided into early (within the first 48 hours after birth) or late (3 days to 6 weeks after birth). Chlamydial postpartum endometritis tends to fall into the late category and usually develops 2 to 6 weeks after birth. Late postpartum endometritis occurred in 22% of women with antepartum *C. trachomatis* infection and in 5% of those who were uninfected (Wager et al., 1980) and tended to be associated with vaginal delivery. In another study of women with late postpartum endometritis after vaginal delivery (Hoyme et al., 1986), 23% had *C. trachomatis* detected in the endometrium and a further 37% had the microorganism detectable in the cervix, but the majority of patients were afebrile and not seriously ill.

THE EFFECT OF CHLAMYDIA PSITTACI ON PREGNANCY

This review highlights *C. trachomatis*, but it is necessary to consider *C. psittaci* because of its known effects on pregnancy. There is no evidence for any
effect of *C. pneumoniae* on pregnancy, but *C. psittaci* organisms may be transmitted from various birds and mammals to humans and such infections occasionally command attention. Thus, it is known that in the United Kingdom and France, pregnant women have aborted after exposure to *Chlamydia*-infected sheep during the lambing season (*Giroud* et al., 1956; *McKinlay* et al., 1985). *C. psittaci* strains of ovine origin have been isolated from placental samples of women, usually sheep farmers' wives, who have been in contact with aborting ewes. The women also exhibited antibody responses.

Although the exact mechanism of placental involvement and abortion is unknown, the pathological features suggest the likely course of events. *C. psittaci*, acquired presumably through the respiratory rather than the genital route, escape into the maternal circulation and invade the placenta because of a predilection for the human trophoblast. There they multiply rapidly, are released into the intervillosus spaces and spread to other chorionic villi, inducing an intense acute inflammatory response. Free EBs in the intervillosus spaces, augmented by others released from degenerating trophoblast tissue, are phagocytised by inflammatory cells. While those in the trophoblast invade deeper into the placenta, producing a foetal stem vasculitis. The considerable tissue damage causes placental insufficiency and foetal anoxic death. The maternal disseminated intravascular coagulation/shock syndrome is probably due to the destruction of trophoblast tissue, releasing large amounts of thromboplastic material and/or chlamydial endotoxin into the maternal circulation.

Studies of the prevalence of *C. psittaci* antibodies in sera collected from workers on farms in northern England where chlamydial ovine abortion occurred (*Hobson* and *Morgan-Capner*, 1988) indicated that human infection with ovine *C. psittaci* strains was uncommon. Antibody was detected no more frequently in farmers and their wives than in the non-farming adult community. Indeed, as indicated above, only a few cases of human abortion arising in the way described have been recorded. Nevertheless, it is clearly prudent to advise pregnant women to avoid contact with sheep, especially in the lambing season.

THE EFFECT OF *CHLAMYDIA TRACHOMATIS* ON THE NEW-BORN

Chlamydial infection of infants delivered by caesarian section and/or those who have signs at birth (*Attenburrow* and *Baker*, 1985) indicates that intrauterine infection can occur. However, the major risk to the infant of acquiring a chlamydial infection, which may manifest as conjunctivitis and/or pneumonia, is from passing through an infected cervix. Whether or not chlamydial infections of the new-born constitute a problem will depend on the prevalence rate of cervical infection which, as indicated previously, varies widely.

**Conjunctivitis**

Various studies have shown that between one-fifth and one-half of infants exposed to *C. trachomatis* infecting the cervix will develop conjunctivitis. The disease occurs usually from 5 to 19 days after birth and is characterised by a mucopurulent discharge and occasionally by pseudomembrane formation. Although it might be quite severe, corneal ulceration and follicle formation are rare and the disease is usually self-limited and resolution occurs without visual impairment; if complications
arise, they tend to be in infants that have not been treated.

**Respiratory tract infection**

The realisation that *C. trachomatis* could cause neonatal pneumonia lagged behind its recognition as a cause of conjunctivitis. The association with pneumonia was brought into focus by Beem and Saxon (1977) who described a series of cases. Overall, about 10-20% of exposed infants develop pneumonia (Schachter, 1988), that is about half of those that develop conjunctivitis. However, pneumonia is not always preceded by conjunctivitis. Chlamydial pneumonia occurs usually between the fourth and eleventh weeks of life, preceded by upper respiratory symptoms. A history of recent conjunctivitis and bulging eardrums is found in about half the cases. The disease is characterised by an a-febrile protracted course in which there is tachypnoea and a prominent staccatto-type cough. Generalised hyperinflation with bilateral, diffuse and symmetrical interstitial infiltration with scattered areas of atelectasis are the radiographic findings.

The exact way in which pneumonia develops is unknown, although a relative eosinophilia in some cases has suggested the possibility of a hypersensitivity mechanism. However, whatever the mechanism, there is evidence that the disease can lead to permanent lung damage. Thus, children who have experienced chlamydial infection during infancy are more likely to develop obstructive lung disease and asthma than are those who have had pneumonia due to other causes or healthy controls (Weiss et al., 1986).

**INFORMATION FROM ANIMAL MODELS**

It is easier to draw conclusions about the ability of chlamydiae to cause human disease if the animal model is a subhuman primate. The more distant the phylogenetic relationship, the more difficult it is to make inferences. Despite this, small animal models have had and still have a lot to offer, particularly in relation to mechanisms of pathogenicity. For example, because of their short reproductive cycle, mice provide an excellent model for investigating mechanisms of *C. trachomatis* induced infertility (Tuffrey et al., 1986). Such infertility appears to be due to failure in transportation of ova to the oviduct even when the tubes are not occluded. This could account for ectopic pregnancies associated with chlamydial infection in women. The mouse model has been used also to investigate the effects of *C. trachomatis* infection on pregnancy outcome (Tuffrey et al., 1987). When mice were inoculated intraperitoneally, or both intravenously and intravaginally, chlamydiae were isolated from at least one placental disc in about a quarter of the mice, but never from foetal tissue even when there was heavy placental colonisation. Thus, unlike *C. psittaci*, *C. trachomatis* did not cross the placenta. This is consistent with the fact that the pregnancy outcome in these mice was unaffected (Gale et al., 1986).

**PATHOGENESIS AND IMMUNE RESPONSE**

The immune response to chlamydial infections may be protective or damaging, and contribute to the pathogenesis of disease (Monnickendam, 1988; Taylor-Robinson and Ward, 1989; Witkin, 1995). The hallmark of
chlamydial infection, whatever the anatomical site, is the lymphoid follicle. Follicles contain typical germinal centres consisting predominantly of B lymphocytes, with T cells, mostly CD8 cells, in the parafollicular region. Between follicles the inflammatory infiltrate contains plasma cells, dendritic cells, macrophages, and polymorphonuclear leukocytes, in addition to T and B lymphocytes. The late stage of chlamydial infection is characterised by fibrosis, seen typically in trachoma and PID. T lymphocytes are also present and outnumber B cells and macrophages. Biopsies taken from patients with cicatricial trachoma and persisting inflammatory changes show a predominance of CD4 cells, but those from patients in whom inflammation has subsided contain mainly CD8 cells.

Experiments using oviduct organ cultures suggest that direct cell damage is unlikely to account for chlamydial pathology. However, in view of the histopathological features that have been mentioned, the fact that chlamydiae cause immense damage to oviducts in the intact host and that vaccination has sometimes caused more damage than protection, it is reasonable to suppose that much of the pathology might be mediated immunologically. Longitudinal studies of trachoma have shown that certain individuals appear predisposed to persistent severe inflammatory disease, perhaps reflecting genetically determined differences in the immune response to sensitising chlamydial antigens. Evidence for the existence of sensitising chlamydial antigens is seen from the fact that repeated ocular infection by chlamydiae induces progressively worse disease with a diminished ability to isolate the organisms, features noted both naturally and experimentally. Also, primary inoculation of the oviducts of pig-tailed macaques with C. trachomatis has produced a self-limiting salpingitis with minimal damage, whereas repeated tubal inoculation has caused hydrosalpinx formation and adnexal adhesions. An exaggerated inflammatory response also has been induced by the ocular instillation of Triton X-100 extract of surface antigens of the guinea pig inclusion conjunctivitis agent in previously infected, but not in naive, guinea pigs, the time course and histopathology of the response showing it to be due to delayed hypersensitivity. In a cynomolgus monkey model, a similar phenomenon was effected by a genus-specific protein of 57 kDa that has sequence homology with the GroEL heat-shock protein of Escherichia coli. However, while there seems no doubt about the importance of this antigen, its exact role in chronic non-gonococcal urethritis and PID is unknown. So too is the pathogenesis of fibrosis or scarring which occurs as a late sequel of chlamydial infection, typically in trachoma and PID. It is possible that interferon-γ may be responsible and feasible that other cytokines, particularly those that stimulate fibroblast activity, such as interleukin I and tumour necrosis factor-β, may participate in the pathogenesis of scarring.

LABORATORY DIAGNOSIS

The diagnosis of chlamydial infection, reviewed in detail recently (Taylor-Robinson, 1997), depends on detection of organisms or their antigens or DNA and to a much lesser extent on serology. It is worth emphasising that male and female 'first-catch' urine specimens, ignored for years because they were not suitable for chlamydial culture, are valuable samples, as are vaginal swabs, provided that the centrifuged deposits are tested by molecular methods.
Detection methods

Culture of *C. trachomatis* involves the centrifugation of specimens (not required for *C. psittaci*) usually on to cycloheximide-treated McCoy cell monolayers, and less often on to HeLa 229 cells treated with diethylaminoethyl (DEAE)-dextran. LGV strains are more likely to grow in cells that have not been treated with DEAE-dextran than are other *C. trachomatis* serovars. Isolation of *C. pneumoniae* is particularly difficult and may be facilitated by using a line of human lung cells. Inoculation of any of the cell cultures is followed by incubation and staining with fluorescent monoclonal antibody or with a vital dye, usually Giemsa, to detect inclusions; one blind passage may increase sensitivity. However, culture for *C. trachomatis*, despite its force in cases of litigation, is not practised often because it lacks sensitivity and is labour intensive and slow. The latter is not a feature of direct staining of specimens with species-specific fluorescent monoclonal antibodies, a technique that in competent hands allows detection of a few elementary bodies, even one. The method is most suited to laboratories dealing with a small number of specimens and for confirming positive results obtained by other tests.

The popularity of enzyme immunoassays that detect chlamydial antigens is due to their ease of use, but it is rarely possible to detect small numbers of organisms (<10) of whatever chlamydial species. Thus, since at least 30% of genital specimens contain such small numbers, many *Chlamydia*-positive patients are misdiagnosed.

However, molecular techniques, that is those involving polymerase chain and ligase chain reactions, by enabling enormous amplification of a DNA sequence specific to the chlamydial species, have overcome the problem of poor sensitivity. Unquestionably, they have a place in research and in routine diagnosis and their existence is helping to promote screening programmes (Boag and Kelly, 1998).

Serological tests

A good correlation has been found between IgG and/or IgA antibody, measured by micro-immunofluorescence, in tears and the isolation of *C. trachomatis* from the conjunctivae of subjects with endemic trachoma or adult ocular parachlomma. In genital infections, serum antibodies occur frequently in the absence of a current chlamydial infection of the cervix so that reliance cannot be put on a single serum or local IgA specific antibody titre to denote a current infection. In PID, pre-existing antibody or a delay in clinical diagnosis usually prevents confirmation on the basis of a rising antibody titre, but titres tend to be higher, especially in the Curtis Fitz-Hugh syndrome, than in uncomplicated cervical infections. A very high IgG antibody titre, for example 1:512 or greater, is suggestive of an aetiological association in pelvic disease, but high levels do not always correlate with detection of chlamydiae and are associated more with chronic or recurrent disease. In distinct contrast, the detection of specific *C. trachomatis* IgM antibody in babies with pneumonia is pathognomonic of *Chlamydia*-induced disease.

**TREATMENT OF CHLAMYDIAL INFECTIONS**

Up-to-date guidelines for the treatment of sexually transmitted diseases, including *Chlamydia*-induced disease, have been published recently (MMWR, 1998). Chlamydiae are particularly sensitive to drugs that interfere with protein synthesis, for example tetracyclines and macrolides, but are sensitive
Table 2: Susceptibility of *Chlamydia trachomatis* to various antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Minimum inhibitory concentration (MIC) (µg/ml)</th>
<th>Minimum bactericidal concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>0.005 - 0.25</td>
<td>0.015 - 0.25</td>
</tr>
<tr>
<td>Rosaramicin</td>
<td>0.015 - 0.25</td>
<td>0.05 - 0.25</td>
</tr>
<tr>
<td>Minocycline</td>
<td>0.015 - 0.5</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.02 - 0.5</td>
<td>0.02 - 2.0</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>0.025 - 0.5</td>
<td></td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>0.03 - 0.25</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.03 - 0.5</td>
<td>0.1 - 4.0</td>
</tr>
<tr>
<td>Josamycin</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Miocamycin</td>
<td>0.06 - 0.125</td>
<td></td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>0.125 - 2.5</td>
<td>0.125 - 2.5</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.25 - 2.0</td>
<td></td>
</tr>
<tr>
<td>Spiramycin</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5 - 1.0</td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1.0 - 2.0</td>
<td>1.0 - 2.0</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>0.25 - 50</td>
<td>1.0 &gt; 100</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.25 - 50</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Sulphamethoxazole</td>
<td>0.5 - 50</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1.0 - 10</td>
<td>&gt; 8 - 10</td>
</tr>
<tr>
<td>Augmentin</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>2.0 - 4</td>
<td></td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>2.0 - &gt; 4</td>
<td></td>
</tr>
<tr>
<td>Rosoxacin</td>
<td>4 - 8</td>
<td>4 - 8</td>
</tr>
<tr>
<td>Sulphisoxazole</td>
<td>2.0 - 200</td>
<td>2.0 - 500</td>
</tr>
</tbody>
</table>

*: In addition, the following antibiotics with MIC values of >8 µg/ml have been tested and are shown more or less in order of increasing MIC value: amifloxacin, enoxacin, pefloxacin, trospectomycin, sulphamethiazole, cloxacillin, norfloxacin, cephaloridine, trimethoprim, spectinomycin, flumequine, novobiocin, nalidixic acid, kanamycin, lincomycin, colistin, gentamicin, vancomycin, metronidazole, streptomycin.

also to other drugs. The minimum inhibitory concentrations of a wide range of antibiotics are presented in Table 2 in which the antibiotics are listed in order of diminishing *in vitro* activity. Antibiotics with a minimum inhibitory concentration of 2.0 or more µg/ml are of no therapeutic value. The exact order in which the antibiotics are placed is arguable but the overall pattern is likely to be correct. The rifampicins are probably more active than the tetracyclines *in vitro* but are reserved usually for mycobacterial infections. Tetracyclines remain the drugs given most widely for chlamydial infections and resistance, if it occurs, does not seem to have accounted for the occasional anecdotal report of failure to respond to tetracyclines. Nevertheless, vigilance should be kept for tetracycline-resistant strains that could jeopardise clinical practice, as the use of non-cultural diagnostic procedures has made their detection less easy. Of the macrolides, erythromycin is used most often and is chosen for chlamydial infections in infants, young children and pregnant and lactating women. Azithromycin in a single dose remains expensive but is gaining favour...
because it is effective and enhances compliance. Alternatives, such as some of the quinolones, particularly ofloxacin, are effective but have not found regular use.

In complicated genital-tract infections, such as PID, treatment will almost certainly be needed before a microbiological diagnosis can be established, following which additional broad-spectrum antibiotic cover may be required. In the case of *C. pneumoniae* and *C. psittaci* infections, treatment follows the same principles as for *C. trachomatis* infections, as they are susceptible to the same types of antibiotic. Finally, treatment is likely to be most effective when given over a long rather than a short time, sub-optimal doses are avoided, compliance is strict, and in the case of genital tract infections, partners of patients are also treated.

LITERATURE


