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Ureaplasma — Are you sitting comfortably?

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Summary The role of *Ureaplasma* spp. in human disease has been controversial, as these bacteria are commonly isolated as part of the normal genital tract flora. Ureaplasma has been shown to have a causal role in urogenital infections and is associated with significant foetal and neonatal morbidity and mortality when infection occurs during the perinatal period. Although rare, invasive Ureaplasma infection (meningitis, renal abscess, mediastinitis and arthritis) has also been reported in both adults and children. This review outlines the unique microbiological features and various clinical presentations of Ureaplasma infection. It also discusses the treatment options, which in the neonatal period can be particularly challenging.

Background

Ureaplasma was initially discovered in 1954 as a pathogen causing non-gonococcal urethritis in men. This bacterium is commonly isolated in humans as part of the normal flora.[1] Two species have been found to cause human infection — *Ureaplasma parvum* and *Ureaplasma urealyticum*. *U. parvum* has four serovars (1, 3, 6, and 14) and *U. urealyticum* has 10 serovars (2, 4, 5, and 7—13).[2] While *U. parvum* is more commonly implicated in clinical disease[3] *U. urealyticum* is more frequently seen in urogenital infection.[4]

Microbiological diagnosis

Ureaplasma spp. do not have a cell wall and therefore cannot be seen on Gram stain. The absence of a cell wall makes them susceptible to drying and other environmental conditions.[5] Ureaplasma do not grow on routine culture media but can grow in two to five days on mycoplasma-specific transport media,[6] in particular A8 agar and 10B arginine broth.[7] Ureaplasma isolates were previously named 'T-mycoplasmas' because of the 'tiny' 15—60 μm brown granular colonies they form.[5] Detection of Ureaplasma infection therefore depends on specimens being cultured on

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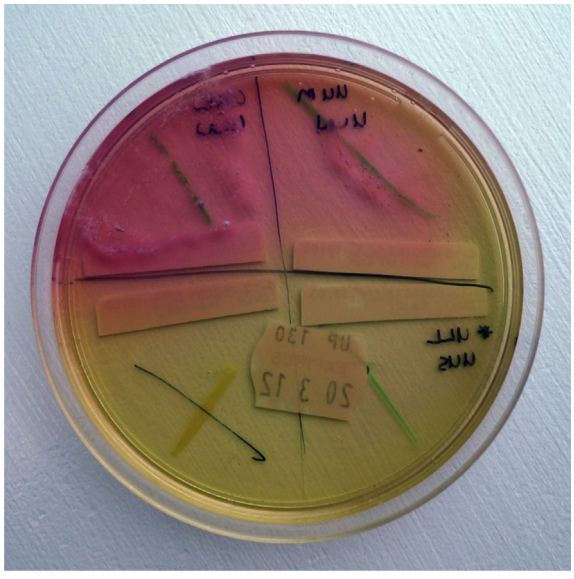
appropriate media. In some laboratories, cerebrospinal fluid (CSF) samples from neonates are not routinely cultured on mycoplasma-specific transport media and may need to be specifically requested when Ureaplasma infection is considered to be a possibility.

Ureaplasma produces urease which hydrolyses urea to generate ATP which, on Shepard's 10B arginine broth results in a rise in pH in turn causing the phenol indicator to change from yellow to pink[8] (Fig. 1). It depletes the urea in 10B arginine broth quickly and therefore needs to be subcultured on A8 agar to prevent organism death.[1] PCR assays for the detection of *Ureaplasma* multiple-banded antigen (*mba*) or urease genes may be more sensitive than culture and are used to distinguish between species.[9] The *mba* gene is thought to be a species-specific virulence factor.[10] Serology has only been used in research settings.[11]

Epidemiology and transmission

Ureaplasma is detected in the vaginal flora of 40—80% of sexually active women. Risk factors for colonisation include multiple sexual partners, low socioeconomic status and oral contraception.[1] Horizontal transmission is by sexual contact and genital infection is usually asymptomatic. Nosocomial transmission has not been described.[7] Although *U. urealyticum* has been isolated from public toilets and has been found to survive for up to 2 h on the toilet rim, transmission by this route has not been reported.[12]

The vertical transmission rate varies from 18 to 88% in different studies. Babies can be infected by intrauterine infection or intrapartum transmission.[5] The colonisation rate in term and preterm infants has been reported as 45—66% and 58% respectively.[7] However, the rate of colonisation from vertical transmission is higher in low birth weight babies; 54% in infants with a birth weight 1000 g or higher and 89% in extremely low birth weight (less than 1000 g) babies in one study.[13] Common sites of neonatal colonisation include the respiratory and urogenital tract due to adhesion of Ureaplasma to epithelial cells. Respiratory tract colonisation rate increases with the duration of rupture of membranes suggesting that ascending infection is important. However, notably, in a quarter of neonates in whom Ureaplasma is cultured from blood or CSF, the duration of membrane rupture is less than one hour, suggesting intrauterine infection also plays an important role.[14]



Courtesy of Dr Andrew Daley

Figure 1 Ureaplasma cultured on A8 agar. The pink discolouration indicates an alkaline change in the media resulting from urease production by *Ureaplasma* spp.

Clinical presentation

The role of *Ureaplasma* spp. in human disease is contentious as it is frequently isolated in healthy individuals as part of the normal flora.[8]

Spectrum of disease in adults

Ureaplasma is the most common bacterium found in urogenital infections. It has been shown to have a causal role in up to 30% of individuals with non-gonococcal urethritis and cystitis.[8] Urinary tract infections with urease-producing organisms predispose to renal stones containing ammonium magnesium phosphate and calcium phosphate.[15] In animal models, *U. urealyticum* results in crystallisation of urine. It has been suggested that urease inhibitors may prevent the formation of stones but the efficacy of this approach requires further research.[16] In men, although genital tract infection is usually asymptomatic, *U. urealyticum* is one of the most common pathogens associated with male infertility and is isolated in 76% of infertile men compared with 19% of fertile men.[17] The mechanism underlying this association is unknown but infection is believed to diminish sperm quality.[18] Female genital tract colonisation may result in bacterial vaginosis and salpingitis. Ureaplasma may also have a role in female infertility but this association remains unproven.[3,19]

Infections outside the genital tract in adults are rare with case reports of *Ureaplasma* spp. causing sternal wound infections,[20] mediastinitis, aortic graft infection[21] and a renal abscess in a transplanted kidney.[22] There has been one report of Ureaplasma meningitis in an adult renal transplant patient who responded successfully within 48 h to treatment with chloramphenicol.[23]

Ureaplasma has become increasingly recognised as an important pathogen in pregnancy and has been associated with chorioamnionitis, spontaneous abortion and stillbirth.[7] A prospective cohort study found that genital colonisation with *U. parvum* was associated with late abortion and preterm birth (OR 3.0; 95% CI 1.1—8.5).[24] It has been proposed that heavy colonisation with Ureaplasma in the genital tract is associated with premature labour.[25] However, prospective studies have not confirmed a true association.[26] A recent Cochrane review found no significant difference in low birth weight births (less than 2500 g) when women