

OppA (oligopeptide binding protein A), the periplasmic component of another uptake transporter, appears to cooperate with the Sap transporter for LL37 uptake. For beta-defensin resistance, *H. ducreyi* utilises the MTR efflux transporter. MTR is a member of the resistance-nodulation-division family of multidrug resistance transporters that pump hydrophobic agents from the periplasm and cytoplasm out of the cell. Our data demonstrate that the *H. ducreyi* MTR transporter confers resistance to both LL37 and beta-defensins. Interestingly, we also found that the MTR transporter affects activation of CpxRA, which globally regulates virulence factors in *H. ducreyi*. The role of MTR in human virulence is under investigation. Together, these studies highlight the significance of AP resistance mechanisms to pathogen survival in the human host.

S07.4 IDENTIFICATION OF DETERMINANTS TRIGGERING ANTIGENIC VARIATION IN *MYCOPLASMA GENITALIUM*

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Mycoplasma genitalium (MG) is an emerging sexually transmitted pathogen associated with reproductive tract disease in men and women. Despite the development of a robust antibody response, MG can persist for months to years, potentially increasing the risk for sexual transmission and serious upper reproductive tract infection in women. The molecular basis of MG pathogenesis is poorly understood, in part due to its fastidious nature, extremely small genome lacking known virulence genes, and the limited genetic tools available for molecular investigations. Nevertheless, previous studies have linked MG virulence to its unique terminal organelle, a complex structure that mediates adherence, motility, and cell division. The terminal organelle is composed of a complex array of unique proteins, including MgpB and MgpC which serve as major adhesins and are required for terminal organelle biogenesis. Remarkably, these two surface-exposed proteins also undergo phase and antigenic variation through a unique process of segmental recombination between discrete variable regions within *mgpB* and *mgpC* and multiple homologous archived sequences, termed MgPa repeats (MgPar). Our goal is to identify the molecular factors required to promote this genetic diversity, a mechanism which likely contributes to the ability of MG to adapt to different host conditions and maintain persistent infections. Recently, we have shown that RecA is required for *mgpB/C* gene variation and that this protein is expressed in several isoforms. We have now expanded these studies by showing that these RecA isoforms originate from different translational start sites and that specific *recA* upstream sequences regulate the expression ratio of these isoforms and *mgpB/C*-MgPar recombination. Together, these studies suggest the presence of novel regulatory mechanisms that may allow this genetically challenged organism to cause disease, evade the host immune response, and persist in infected individuals.

S07.5 UNDERSTANDING DISSEMINATION OF *TREPONEMA PALLIDUM* WITHIN THE HOST - IS THERE HOPE FOR A SYPHILIS VACCINE?

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Treponema pallidum is a highly invasive spirochete that disseminates to organ sites distal to the site of primary infection and is able to cross both the blood-brain and placental barriers during the course of infection. The corkscrew motility used by *T. pallidum* undoubtedly contributes to its invasive nature. However, this signature motility is shared with other spirochetes and thus the factors responsible for the widespread dissemination capability that is

unique to *T. pallidum* remain unknown. We have identified the treponemal-specific, surface-localised protein pallilysin as a dual functioning adhesin/metalloprotease that exhibits specific attachment to, and degradation of, multiple extracellular matrix components. Pallilysin is produced as an inactive proprotease that can be activated via either autocatalytic cleavage or host-originating thrombin cleavage. Purified recombinant pallilysin, as well as a non-invasive model treponeme heterologously expressing pallilysin on its surface, exhibit specific degradation of fibrin clots. Pallilysin immunisation alters the course of *T. pallidum* dissemination following challenge within the rabbit model of syphilis infection, with immunised rabbits exhibiting a reduced bacterial burden within organs distal to the site of challenge compared to unimmunized control rabbits. Further, rabbit infectivity tests (RIT) showed that rabbits receiving lymph nodes from challenged, unimmunized rabbits seroconverted and developed orchitis by 30 days post-transfer, while 66% of RIT rabbits receiving lymph nodes from challenged, pallilysin-immunised rabbits remained seronegative and had no signs of orchitis at the termination of the experiment (day 185 post-transfer). Collectively these studies identify pallilysin as a *T. pallidum*-specific metalloprotease that (1) exploits the host coagulation cascade to facilitate protease activation, (2) plays a central role in treponemal dissemination and (3) shows promise as a novel syphilis vaccine candidate.

S.08 - STI/HIV treatment guidelines: Important areas of clinical uncertainty

S08.1 TREATMENT OF GONORRHOEA IN AN ERA OF EMERGING CEPHALOSPORIN RESISTANCE AND RESULTS OF A RANDOMISED TRIAL OF NEW POTENTIAL TREATMENT OPTIONS

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Background Cephalosporins are the mainstay of recommended gonorrhoea treatment, and there is an urgent need for treatment options for cephalosporin-allergic patients or infections with suspected cephalosporin resistance. We evaluated the efficacy and tolerability of two novel combinations of existing antimicrobials for treatment of uncomplicated urogenital gonorrhoea.

Methods We conducted a non-comparative trial, randomising patients with urogenital gonorrhoea to one of two regimens: gentamicin 240 mg intramuscularly plus azithromycin 2 g orally (GENT/AZI), or gemifloxacin 320 mg orally plus azithromycin 2 g orally (GEMI/AZI). The primary outcome was microbiologic cure of urogenital infections (negative follow-up culture) at 10–17 days post-treatment. All participants who returned for follow-up and had evaluable follow-up cultures were included in this per protocol analysis.

Results For 401 evaluable participants (GENT/AZI-202; GEMI/AZI-199), the mean age of both groups was 30 years. Most participants were heterosexual men (GENT/AZI, 57%; GEMI/AZI, 51%), followed by men who have sex with men (GENT/AZI, 33%; GEMI/AZI, 39%), and women (GENT/AZI, 9%; GEMI/AZI, 11%). Microbiological cure was achieved by 100% (lower one-sided 95% confidence interval, 98.5%) of GENT/AZI participants, and 99.5% (lower one-sided 95% confidence interval, 97.6%) of GEMI/AZI participants. GENT/AZI cured 10/10 pharyngeal and 1/1 rectal infections; GEMI/AZI cured 15/15 pharyngeal and 5/5 rectal infections. In the GENT/AZI arm, the most common adverse events (AEs) were mild-moderate nausea (27% of participants), diarrhoea (19%), abdominal discomfort/pain and vomiting (both 7%). In the GEMI/AZI arm, the most common AEs were nausea (37% [8% moderate-severe]), diarrhoea (23%), and abdominal discomfort/pain (11%).

Conclusions Both study regimens were highly effective. Gastrointestinal AEs, especially nausea and diarrhoea, were common. These results provide alternative gonorrhoea treatment options for patients who cannot be treated with cephalosporins.

S08.2 IS AZITHROMYCIN THE BEST TREATMENT FOR CHLAMYDIA?

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Azithromycin has been widely used for many years as first-line therapy for chlamydial infection (or as equal first-line with doxycycline). However, there are now several reasons to reconsider its position.

Firstly, although earlier trials showed azithromycin to have cure rates which were high and equivalent to those of doxycycline, more recent studies have found it to have lower, and inadequate, levels of success in women with cervical infection, men with urethral infection, and for rectal infection in both men and women.

Secondly, the increasing recognition of the importance of *Mycoplasma genitalium* as a pathogen, especially as an important cause of urethritis in men. In the absence of a readily available test for *M. genitalium*, men with non-gonococcal urethritis are often treated with a single dose of azithromycin, which is known to be a less effective treatment for *M. genitalium* than is doxycycline. As a result many such men have persistent symptoms following such treatment, requiring repeat visits and further antibiotic therapy. Their sexual partners may also require further treatment. Additionally, there is evidence that single-dose azithromycin therapy (as against longer courses) can induce resistance in *M. genitalium*.

Thirdly, the widespread use of azithromycin is probably leading to increasing resistance to this agent in other infections where it has a place; especially in gonorrhoea where it is now widely recommended as an adjunct to ceftriaxone in the belief that this will reduce the likelihood of resistance to ceftriaxone developing, but also in the treatment of syphilis where azithromycin has a role as a second-line agent e.g. in cases of allergy to penicillins.

S08.3 MYCOPLASMA GENITALIUM AND CHLAMYDIA TRACHOMATIS IN LAPAROSCOPICALLY DIAGNOSED PELVIC INFLAMMATORY DISEASE

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Introduction Pelvic inflammatory disease (PID) is a well known complication of infection with *Chlamydia trachomatis* (*C. trachomatis*). The knowledge of *Mycoplasma genitalium* (*M. genitalium*) and its role in PID is relatively limited. In this study we report on the proportions of *C. trachomatis* and *M. genitalium* attributable to PID from an ongoing study of laparoscopically diagnosed cases of PID.

Method Women seeking care at the emergency service at the Department of Obstetrics and Gynaecology at Malmo University Hospital in Sweden from 2004 through the mid of 2012 with clinically suspected PID, who underwent diagnostic laparoscopy, were eligible. Specimens from the cervix/and or vagina together with abdominal fluid were collected and analysed for pathogens such as *C. trachomatis* and *M. genitalium*.

Results In all, 208 women were included and 123 (59.1%) were diagnosed with PID at laparoscopy. *C. trachomatis* was present in cervix and/or abdominal fluid in 29/123 (23.6%) of these cases. *M. genitalium* was present in cervix and/or abdominal fluid in 5/123 (4.1%) cases of PID. In three of these cases *M. genitalium* was positive only in cervix and there was a dual infection with *C. trachomatis* positive in the abdominal fluid. Two PID cases were *M. genitalium*

positive only, (2/123, 1.6%). A significantly declining trend for *C. trachomatis* PID was observed (42.8% - 11.5% $p < 0.001$). The prevalence of *C. trachomatis* and *M. genitalium* was 2.8% and 2.1% respectively in 5519 women tested from 2003 to 2008 in the same clinic.

Conclusion The over all proportion of PID attributable to *C. trachomatis* was 23.6% but over the study period a significantly declining trend was seen. The proportion of PID attributable to *M. genitalium* (1.6%) was significantly lower considering the prevalence to be in the same range as for *C. trachomatis*, suggesting that *M. genitalium* was a less aggressive pathogen in terms of clinical manifestations of PID.

S08.4 MYCOPLASMA GENITALIUM: IMPLICATIONS FOR DISEASE, TREATMENT AND THE PUBLIC HEALTH

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M. genitalium is an established cause of sexually transmitted urethritis and cervicitis, and may cause upper tract disease in women. Detection by nucleic acid amplification tests is currently the only diagnostic method available, but no FDA approved assays are currently available, and the CE marked tests suffer from limited clinical evaluation.

In most settings, *M. genitalium* infections explain 15–25% of symptomatic non-gonococcal urethritis, but as diagnosis of the infection is not routinely carried out, treatment will usually be syndromic. However, only a few randomised trials have evaluated treatment of *M. genitalium*, and compared only doxycycline 200 mg daily for 7 days with a 1 g single dose of azithromycin. Together with results from open trials, it is obvious that doxycycline is inefficient in eradicating *M. genitalium* showing eradication rates around 35%. The eradication rate after azithromycin 1 g single dose is significantly better, but differs greatly between studies. Thus, older studies appear to have higher eradication rates than recent ones and a lower eradication rate is reported in studies from centres where azithromycin has been used as the primary treatment for chlamydial and idiopathic urethritis and cervicitis.

At present, the only second line antibiotic that has been shown to have a high activity against macrolide resistant *M. genitalium* is moxifloxacin. However, this drug is significantly more expensive and has a less favourable safety profile than macrolides, and multi-drug resistant infections have emerged, primarily in patients with contact to South East Asia. Consequently, there is an urgent need for clinical trials with possible alternative drugs. Such trials should preferably also address the treatment efficacy in chlamydial and idiopathic urethritis and cervicitis as a single treatment covering these conditions would be advantageous.

S.09 - Molecular mechanisms of antimicrobial resistance

S09.1 MOLECULAR DETECTION OF ANTIMICROBIAL RESISTANCE IN STI PATHOGENS

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