

**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 Malmö 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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The emergence of antimicrobial resistance (AMR) among sexually transmitted infections (STI) is a cause for global concern, and is epitomised by the fact we are now running out of treatment options for gonorrhoea. The role of AMR surveillance is now more important than ever. Ideally, AMR surveillance should be fast, easy, inexpensive, accessible, reproducible across testing methods, and provide clinically meaningful information to inform treatment strategies. In reality this is not the case, with AMR surveillance activities for STIs typically weak or non-existent in many parts of the world. Molecular methods have the potential to enhance AMR surveillance, particularly for organisms that cannot easily or readily be characterised phenotypically; which is the case for most STIs. The challenges for molecular surveillance are however many and include factors such as; the mechanisms of resistance may be many or otherwise unknown, they may miss novel mutations, the technology can be expensive, they need specialised laboratories and trained staff, and that their specificity can be undermined where target sequences are shared across different species. Despite these challenges, such methods are being developed and are now finding their way into routine settings. Advances in molecular technology and expanding knowledge of resistance mechanisms continue to pave new directions in this important area.

### S09.2 **NEISSERIA GONORRHOEA: ARE WE EXERTING THE SELECTIVE PRESSURE?**

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Treatment of gonorrhoea has historically been delivered by a single dose of a highly effective antimicrobial agent, to which resistance is not documented, to aid compliance and break transmission. Resistance in *Neisseria gonorrhoeae* compromises this approach and occurs both by acquisition of plasmids or chromosomal DNA from other bacteria or *Neisseria* spp or by selection of mutants resulting from misuse or overuse of antimicrobial agents, such as long term use of a single agent.

Resistance to ciprofloxacin, a fluoroquinolone, illustrates the effect of both misuse of earlier generations of quinolones and of suboptimal doses, as well as overuse. Quinolones target the DNA gyrase and topoisomerase enzymes that are responsible for DNA supercoiling and any interference with this process is bactericidal. Ciprofloxacin was widely used, often at low doses because of its high efficacy, but resistance emerged quickly resulting from selection of mutants, altering the target site and giving increasing drifts to resistance. Azithromycin, a macrolide which binds to 23S rRNA component of the 50S ribosome and interferes with protein synthesis, is effective against multiple STIs and therefore the selective pressure for resistance has been considerable. Although low-level resistance emerged quickly, high-level resistance in *N. gonorrhoeae*, resulting from a single point mutation in the peptidyltransferase loop of domain V of the 23S rRNA gene, was only reported in recent years and threatens to compromise its use. Sporadic use of spectinomycin selected for high-level resistance in a single step, which appears clonal and has not spread widely. Limited use of the aminoglycoside, gentamicin, for which the efficacy data is weak, appears to remain clinically active.

In this era of multi-drug resistant gonorrhoea it is imperative that the selective pressure exerted by continual use of a single agent is understood and clinical practise modified, where necessary, to prevent gonorrhoea becoming untreatable.

### S09.3 **HERPES SIMPLEX VIRUS**

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The more and more frequent and widespread use of acyclovir (ACV), but also the increasing number of immunocompromised patients might induce an increase in HSV (Herpes Simplex Virus) resistance. HSV resistance to ACV is mainly associated with mutations in the thymidine kinase (TK) gene although mutations in the DNA polymerase can be observed. Up to now, resistance of HSV to ACV was a major concern for immunocompromised patients with a frequency between 2.5 and 10%. This study aimed to reassess HSV resistance to ACV, during a ten year period, in immunocompetent and in immunocompromised patients (bone marrow transplant patients, solid organ transplant, HIV positive patients, cancer patients). From 2002 to 2011, 1538 patients positive for HSV were tested for the susceptibility of their virus to ACV (1044 immunocompetent and 494 immunocompromised). In immunocompetent patients, prevalence of resistance remains under 0.5%, whatever the period studies. In immunocompromised patients, a significant increase can be observed, from 4.3% during 2002–2006 (11/255 patients) to 13.4% during 2007–2011 (32/239) ( $p = 0.0002$ ). This significant increase is mainly observed among bone marrow transplant patients in which the prevalence is 10% (5/52) during 2002–2006 and 38% (30/79) during 2007–2011 ( $p = 0.0002$ ), whereas other types of immune deficiencies do not show an increase (1.3% versus 2.9%,  $p = 0.2$ ). New chemotherapy protocols (FLAMSA) and type of transplantation as blood cord transplant are part of the explanation. Genotyping of the resistant viruses (35 viruses) reveal mutations in the TK gene for 80% of them. Double population including resistant and susceptible viruses were recovered in 5 isolates (5/34 = 14%). Rapid diagnosis of HSV resistance, but also research on alternative treatment are more than ever of interest.

### S09.4 **MYCOPLASMA GENITALIUM**

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*M. genitalium* infections explain 15–25% of symptomatic male NGU and causes sexually transmitted urethritis, cervicitis, and PID in women. The bacterium is extremely difficult to isolate by culture, and consequently, the knowledge about antimicrobial resistance and its underlying molecular mechanisms has been slow to accumulate.

In the few randomised trials of *M. genitalium* conducted to date, doxycycline has been compared with a 1 g single dose of azithromycin, and together with results from open trials, it is evident that doxycycline is inefficient in eradicating *M. genitalium* with eradication rates around 35%. The eradication rate after azithromycin 1 g single dose has most often been significantly higher, but differs greatly between studies. Remarkably, older studies appear to have higher eradication rates than the more recent ones, and in the latest study from the US, no significant difference between doxycycline and azithromycin efficacy could be detected.

Although several mutations have been associated with increased macrolide MIC in strains selected by passage in the presence of macrolides, only mutations in the 23S rRNA gene at position 2058 and 2059 (*E. coli* numbering) have been detected in patients failing azithromycin treatment.

A number of rapid methods for detection of such mutations directly from clinical samples have been developed and have proved to be clinically useful in directing treatment. Pre-treatment mutations have been found in between 10–15% of contemporary samples where doxycycline is used as the primary NGU treatment and is most commonly around 40% in settings where azithromycin is the