

# GLOBAL OVERVIEW OF ANTIMICROBIAL RESISTANCE IN STD AGENTS

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# STDs & RTIs

- **HIV**
- **Gonococcal infections/ gonorrhoea**
- **Chlamydia trachomatis infections**
  - **LGV**
  - **Non LGV**
- **Syphilis**
- **Genital herpes**
- **Chancroid**
- **Donovanosis**
- **Trichomoniasis**
- **Bacterial vaginosis**
- **Vulvovaginal Candidiasis**

# STDs & RTIs

- For each STD / RTI
  - Recommended treatment regimens <sup>1</sup>
  - Current status of Antimicrobial resistance in causative organism
  - Reasons for limited data
- Way forward

# Difficulties

- Laboratory testing for confirmation of clinical diagnosis often not available/ not performed/ not sensitive or specific enough/too expensive
- Culture and antimicrobial susceptibility testing of STD pathogens difficult
- Recommendations for treatment often based on clinical experience rather than randomised controlled clinical trials

# Reasons for limited data

- Definitive criteria for cure or treatment failure not well established
- Often difficult to differentiate between treatment failure and reinfection
- Concomitant HIV infection may delay treatment response

# *N. gonorrhoeae* infections

- Recommended regimens
  - Ceftriaxone 250mg I/M in a single dose
  - OR
  - Cefixime 400mg orally in a single dose
- Alternative regimens
  - Azithromycin 2 g orally in a single dose
  - Ceftizoxime, cefoxitin (injectable cephalosporin)
  - Cefpodoxime (oral cephalosporin)
  - Spectinomycin

# AMR in *N. gonorrhoeae*

- *N. gonorrhoeae* has the ability to develop resistance to antimicrobial therapies
- **Quinolone** resistant *N. gonorrhoeae* strains emerged within 5-7 years of use as 1<sup>st</sup> line treatment
- now widely disseminated
- No longer recommended for treatment of gonorrhea and associated conditions like PID

# AMR in *N. gonorrhoeae*

- The proportion of isolates demonstrating decreased susceptibility to **ceftriaxone** or **cefexime** has remained very low
- But treatment failure has been suspected in some cases (still few)
  - More so for oral cephalosporins
  - from Asian countries and Hawaii
- Decreased susceptibility of *N. gonorrhoeae* to cephalosporins is likely to spread



# Alternative Regimens

- Spectinomycin
  - Useful in persons who cannot tolerate cephalosporins
  - Expensive, injectable
  - Not available in many countries
- Azithromycin 2 gm is very effective but
- *N. gonorrhoeae* can develop resistance to macrolides very easily
- hence use should be restricted

# AMR in *N. gonorrhoeae*

- Surveillance of AMR in *N.gonorrhoeae* is crucial
  - Gonococcal antimicrobial susceptibility program (GASP)
  - CDC's Gonococcal Isolate Surveillance Project (GISP)
- Surveillance by clinicians is also crucial
- Should report suspected treatment failures
- Submit samples for culture and AST in such cases

# Chlamydial infections (non LGV)

- Recommended regimens
  - Azithromycin 1 gm orally in a single dose  
or
  - Doxycycline 100 mg orally BD x 7 days
- Alternative regimens
  - Erythromycin 500 mg orally four times a day for 7 days
  - Levofloxacin 500 mg orally once daily for 7 days
  - Ofloxacin 300 mg orally twice a day for 7 days

# Chlamydial infections

- **Azithromycin** and **Doxycycline** equally efficacious with microbial cure rates of 97%
- **Levofloxacin** and **ofloxacin** are effective treatment alternatives
- Post treatment infections result from reinfection caused by
  - failure of sex partners to receive treatment
  - initiation of sexual activity with a new infected partner

# Chlamydial infections

- Recurrent / persistent infection occurs in 10-15 % women
- Heterotypic resistance seen
- No in vitro homotypic resistance seen
- Recently 4 clinical isolates showed in vitro resistance to macrolides
- Carried mutations in the 23S rRNA gene

# Chlamydial infections

- clinically significant multidrug-resistant *C. trachomatis* was reported in 2000
- Isolates showed multidrug resistance to doxycycline, azithromycin, and ofloxacin
- clinical treatment failure with azithromycin was also seen

# Chlamydial infections

- There are only a few reports describing isolation of antibiotic resistant *C.trachomatis* strains from patients
- Although majority of the resistant isolates were associated with clinical treatment failure,
- all of the isolates displayed ‘heterotypic resistance’ ,
- a form of phenotypic resistance in which a small proportion of an infecting microbial species is capable of expressing resistance at any one time.

# Chlamydial infections (LGV)

- Recommended regimens
  - Doxycycline 100 mg orally twice a day for 21days
- Alternative regimens
  - Erythromycin 500 mg orally four times a day for 21days
  - Azithromycin 1 gm orally once a week for 3 weeks



# Chlamydial infections (LGV)

- resurgence of LGV reported in 2003 in men who have sex with men
  - Outbreak in Europe
  - More in HIV positive men
  - Mostly due to L2b serovar
- Some patients who have shown failure with extended doxycycline treatment respond to **fluoroquinolone**-based treatment

# Genital Herpes

- First clinical episode
- Recurrent genital herpes
  - Suppressive therapy/ Episodic therapy
- Recommended regimens
  - **Acyclovir** 400 / 200 mg orally three/ five times a day for 7-10 days
  - **Famciclovir** 250 mg orally three times a day for 7-10 days
  - **Valacyclovir** 1g orally twice a day for 7-10 days

# Genital Herpes

- If lesions persist or recur in a patient receiving antiviral treatment HSV resistance should be suspected
- Sample should be submitted for viral culture and sensitivity testing
- Susceptibility testing methods
  - Plaque reduction assay
  - Genotypic assay

# Genital Herpes

- Genital herpes is epidemic in USA
- long term acyclovir therapy is common
- In 15 years since it was licensed
  - 0.1% HSV-2 isolates from HIV negative patients resistant to acyclovir
  - 5.3% HSV-2 isolates from HIV positive patients resistant to acyclovir esp. in patients with low CD 4 counts
- Continued surveillance is essential

# Genital Herpes

- All acyclovir resistant strains are to valacyclovir and majority are resistant to famciclovir
- **Foscarnet** 40 mg/kg IV every 8 hours until resolution is attained
- IV **cidifovir** once weekly also effective
- Clinical management of antiviral resistance remains challenging

# Syphilis

- Recommended regimens
  - Benzathine penicillin G in different doses & duration depending on stage of disease
  - Aqueous procaine or Aqueous crystalline penicillin
- Alternative regimens
  - Doxycycline 100 mg orally twice a day for 14 days
  - Ceftriaxone 1 g daily IM for 10-14 days
  - Azithromycin 2 g oral dose

# Syphilis

- Treatment failure can occur with any regimen
- Assessing response to treatment is difficult
- Patients whose signs or symptoms persist or recur or who have a sustained fourfold increase in nontreponemal test titer have either failed treatment or are reinfected
- Retreatment is recommended

# Syphilis

- Syphilis has reemerged in several countries like China , USA
- penicillin is still effective
- clinically significant resistance to macrolides has emerged <sup>2</sup>
- Macrolide resistant strains of *T. pallidum* are now prevalent in several developed countries
- Macrolide resistance occurs due to a single point mutation



# Syphilis

- No penicillin resistance seen as it requires
  - horizontal gene transfer (by plasmids/ phages/ transposons) and *T. pallidum* lacks all these
  - multiple mutations
- There is no documented resistance of *T. pallidum* to doxycycline

# Chancroid

- Recommended regimens
  - Azithromycin 1 gm orally in a single dose  
or
  - Ceftriaxone 250 mg intramuscularly in a single dose  
or
  - Ciprofloxacin 500 mg orally twice a day for 3 days  
or
  - Erythromycin 500 mg orally 4 times a day for 7 days

# Chancroid

- Causative organism *Hemophilus ducreyi*
- Fastidious organism
- Two enriched special selective culture media required
- Sensitivity of culture is <80%
- Culture not widely available
- Limited data on current prevalence of antimicrobial resistance

# Chancroid

- Plasmid mediated antimicrobial resistance has been documented for penicillins, tetracyclines, chloramphenicol, sulfonamides, and aminoglycosides.
- Much less is known about chromosomally mediated resistance to antimicrobials in *H ducreyi* but decreased susceptibility has been described for penicillin, ciprofloxacin, ofloxacin, and trimethoprim
- There is little, if any, antimicrobial surveillance occurring in countries where chancroid is common.

# Chancroid

- A recent double blind randomised controlled trial in Kenya demonstrated comparable **cure rates** for both single dose **ciprofloxacin** (92%) and a 1 week course of **erythromycin** (91%)\*
- Treatment failures have also been reported in African patients treated with single doses of **ceftriaxone**
- **Co-existing HSV infection**, particularly in immunosuppressed **HIV seropositive patients**, may account for some of the observed cases where treatment has failed to cure chancroid.

\**Sex Transm Infect* 2003;**79**:68-71 doi:10.1136/sti.79.1.68

# Granuloma inguinale (Donovanosis)

- Recommended regimens
  - Doxycycline 100 mg orally twice a day for 3 weeks or until all lesions completely healed
- Alternative regimens
  - Azithromycin 1 gm orally once per week for 3 weeks
  - Ciprofloxacin 750 mg orally twice a day for 3 weeks
  - Trimethoprim-sulphamethoxazole 160mg/800mg orally twice a day for 3 weeks

# Granuloma inguinale (Donovanosis)

- Relapse can occur 6-18 months after effective therapy
- Causative organism *Klebsiella granulomatis* very difficult to culture/ not cultivable
- Antimicrobial susceptibility testing not done

# Way forward

## **Renewed effort required to**

- Improve availability, reliability & cost of rapid diagnostic tests
- Labs need to update their testing methods for early diagnosis and detection of resistance
- Perform Molecular surveillance for early detection of antibiotic resistance
- Perform genotyping of microorganisms to differentiate between treatment failure and reinfection



# Way forward

- Prolong effectiveness of available antimicrobials
- Develop new, single dose, oral antibiotics to ensure patient compliance
- Develop vaccines to prevent infection



THANK YOU

# Bacterial Vaginosis

- Polymicrobial clinical syndrome
- Replacement of normal hydrogen peroxide producing lactobacillus species in the vagina with high concentrations of
  - anaerobic bacteria (*Prevotella & Mobiluncus*)
  - *Gardnerella vaginalis*
  - *Ureaplasma*
  - *Mycoplasma*
  - Other fastidious / uncultivable anaerobes

# Bacterial Vaginosis

- Recommended regimens
  - Metronidazole 500mg orally twice daily for 7 days
  - Metronidazole gel 0.75 % one full applicator intravaginally once a day for 5 days
  - Clindamycin cream 2% one full applicator intravaginally once a day for 7 days
- Alternative regimens
  - Tinidazole 2/1gm orally once daily for 2/5 days

# Bacterial Vaginosis

- Recurrence of BV is common
- Isolation and AST of BV associated organisms is not done
- Limited data available for women with early treatment failure or recurrences
- Prolonged treatment with the same topical regimen
- Suppressive therapy with topical agents etc.

# Trichomoniasis

- Recommended regimens
  - Metronidazole 2 g orally single dose
  - Tinidazole 2 g orally single dose
- Alternative regimens
  - Metronidazole 500mg orally twice daily for 7 days

# Trichomoniasis

- High rate of reinfection seen
- 17% reinfected within 3 months
- Due to
  - Sex with an untreated partner
  - Diminished susceptibility to metronidazole
- Low level of metronidazole resistance has been reported in 2-5 % cases
- high level resistance is rare

# Trichomoniasis

- If treatment failure occurs despite
  - prolonged / repeated therapy
  - partner treatment
- susceptibility testing should be done
- Possible in reference labs



# Vulvovaginal Candidiasis

- Recommended regimens
  - Intravaginal agents
    - Butoconazole, clotrimazole, miconazole, tioconazole
    - Nystatin
    - Terconazole
  - Oral agent
    - Fluconazole

# Vulvovaginal Candidiasis

- Vaginal cultures should be obtained from patients with recurrent vulvovaginal candidiasis to identify unusual species or non-albicans species esp. *Candida glabrata*
- Antimycotic therapies are less effective against these species
- Optimal treatment of non albicans VVC remains unknown