

# "Antimicrobial Resistance and Syndromic Management of STIs



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**100**  
1908 - 2008



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# STI PATHOGENS

## BACTERIA

- ▣ *Neisseria gonorrhoeae*
- ▣ *Chlamydia trachomatis*
- ▣ *Treponema pallidum*
- ▣ *Haemophilus ducreyi*
- ▣ *Klebsiella granulomatis*
  
- ▣ *Gardnerella vaginalis*
- ▣ *Ureaplasma urealyticum*
- ▣ *Mycoplasma hominis*
- ▣ *Mycoplasma genitalium*

## VIRUSES

- ▣ HIV
- ▣ HSV
- ▣ HPV
- ▣ HBV

## PARASITES

- ▣ *Trichomonas vaginalis*

## FUNGUS

- ▣ *Candida albicans*

# What have we learned from sexually transmitted infection research in sub-Saharan Africa?

David Mabey, Francis Ndowa, Ahmed Latif

Sex Transm Infect 2010;86:488-492

## ABSTRACT

Many of the most important research findings on STIs in the past 30 years have come from sub-Saharan Africa. African researchers and their international collaborators have led the way in the development and validation of syndromic STI management, in furthering our understanding of the interactions between HIV and other STIs, in the development of evidence-based strategies for the control of HIV and other STIs in high risk groups and in the general population, and in clinical, microbiological and epidemiological studies on syphilis, chancroid and ophthalmia neonatorum. This review summarises the major achievements of STI researchers in Africa in the past 30 years, and discusses the reasons underlying the success of STI research in Africa.

# SYNDROMIC MANAGEMENT of STIs

A series of evaluations of the syndromic management flowcharts was commissioned by WHO and UNAIDS in the 1990s, and the results were published as a supplement in Sexually Transmitted Infections in 1998.

Of the 16 study sites, 10 were in Africa. The main conclusions from these studies were that the flowcharts for urethral discharge and genital ulcer are reasonably sensitive and specific, whereas the flowchart for vaginal discharge is neither sensitive nor specific

# WHY SYNDROMIC

## ADVANTAGES

1. Treatment at point of first contact
2. Treatment is immediate
3. Efficient, comprehensive and good quality
4. Does not require specialists
5. Laboratory tests not needed
6. Can be implemented at different settings;  
Family Planning Clinic, Antenatal Clinic, etc.
7. Allows more time for counseling and contact management (4Cs)

# WHY SYNDROMIC

## DISADVANTAGES

1. Over treatment in some cases
2. Compliance of treatment
3. Asymptomatic infections not detected

**Protocols for the  
management of a person  
with a**

**Sexually  
Transmitted  
Disease**

**According to the Essential Drugs List**



**AIDS HELPLINE**  
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the European Union

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June 1998



DEPARTMENT OF HEALTH

- ▣ **National Department of Health guidelines developed in 1996**
- ▣ **Revision 2009**  
(resistance in GC & emergence of HSV)

**FIRST LINE COMPREHENSIVE  
MANAGEMENT AND CONTROL OF  
SEXUALLY TRANSMITTED  
INFECTIONS (STIs)**

*Protocol for the management of a person with a  
Sexually Transmitted Infection*

*According to the Essential Drug List*



# **Chapter 12: Sexually transmitted infections**

- 12.1 Lower abdominal pain (LAP)**
- 12.2 Vaginal discharge syndrome (VDS)**
- 12.3 Male urethritis syndrome (MUS)**
- 12.4 Scrotal swelling (SSW)**
- 12.5 Genital ulcer syndrome (GUS)**
- 12.6 Bubo**
- 12.7 Balanitis/balanoposthitis (BAL)**
- 12.8 Syphilis serology and treatment**
- 12.9 Treatment of more than one STI syndrome**
- 12.10 Genital molluscum contagiosum (MC)**
- 12.11 Genital warts (GW) Condylomata Accuminata**
- 12.12 Pubic lice (PL)**

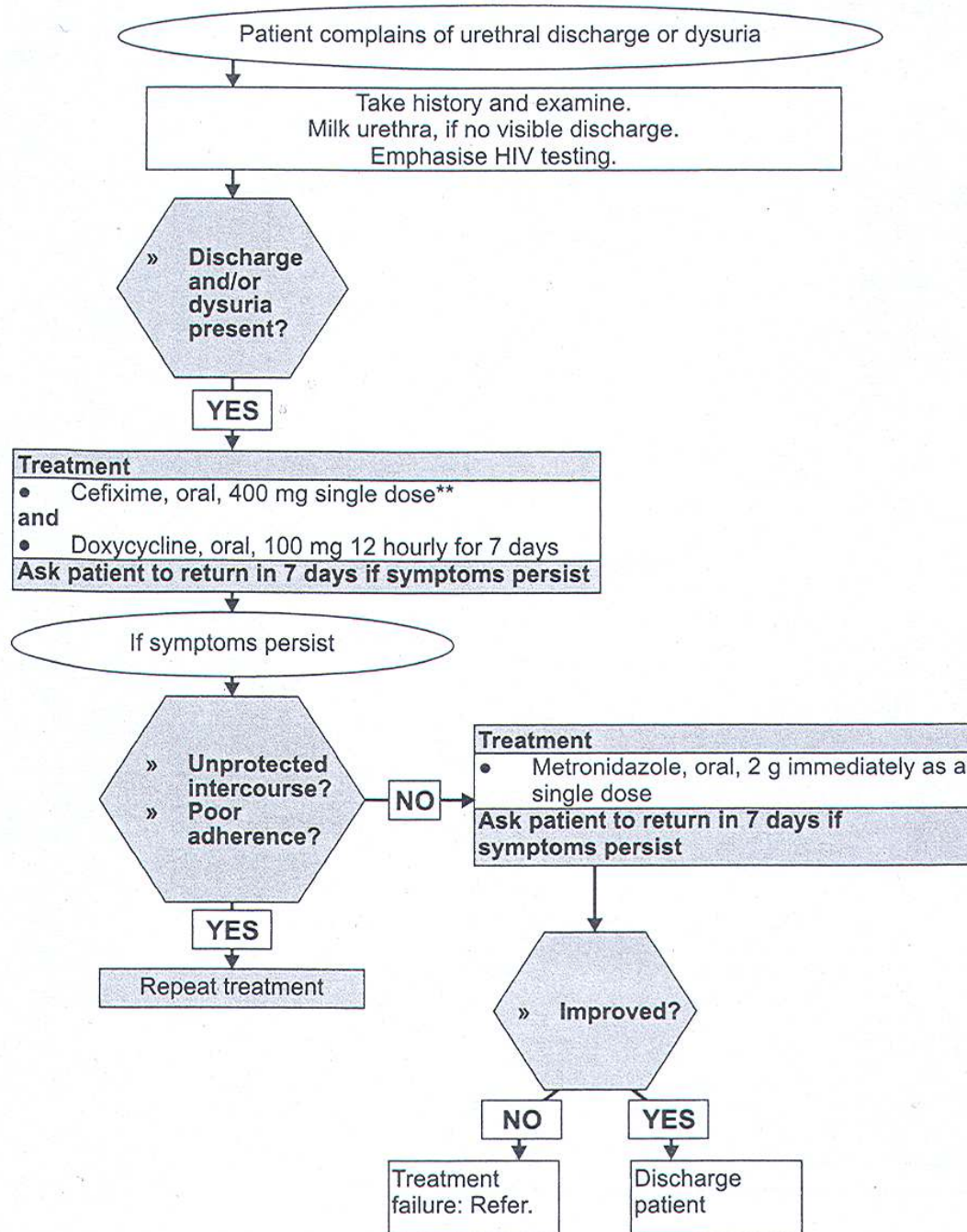


# ADULT MALE URETHRAL DISCHARGE

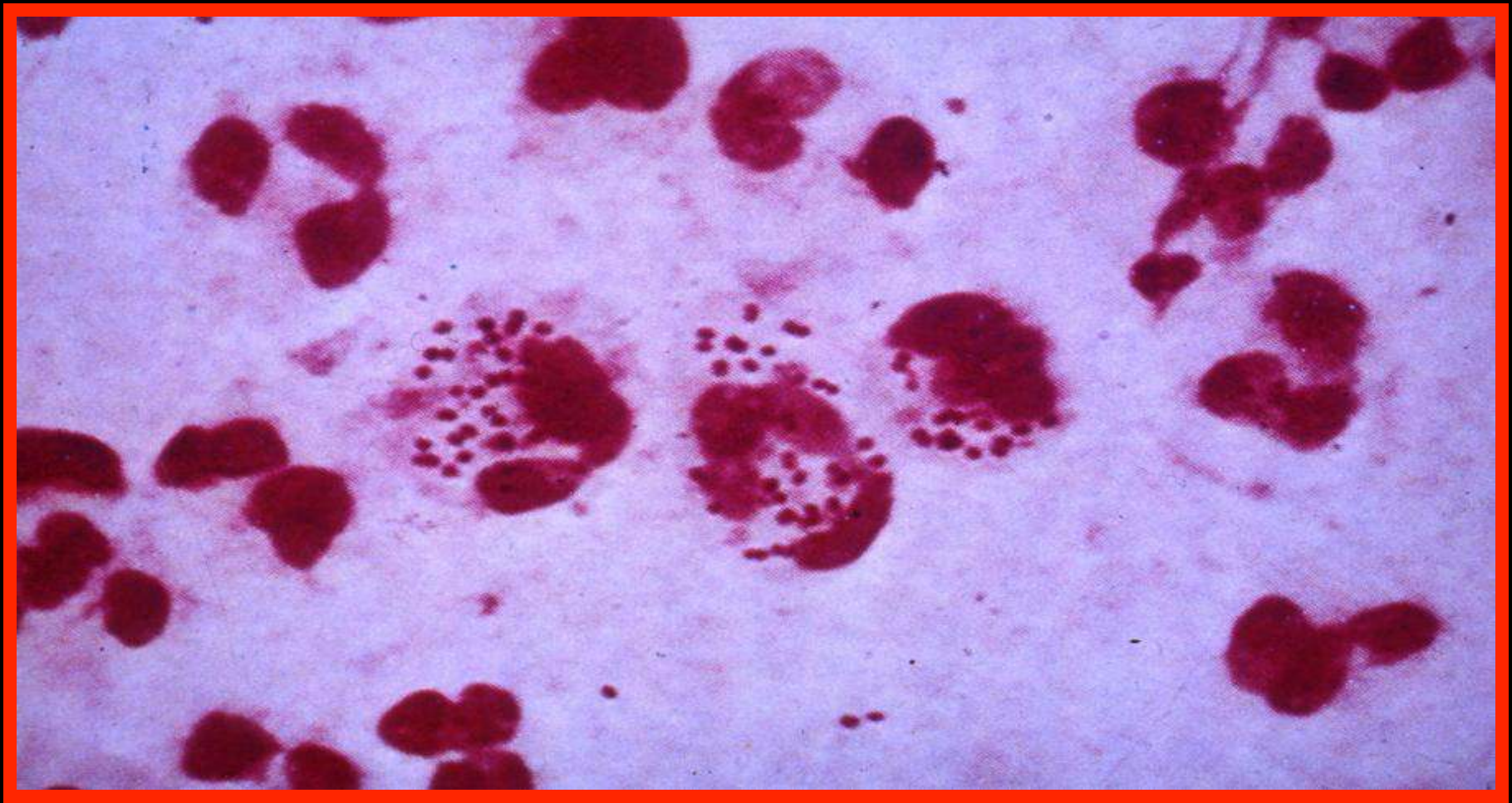
- ▣ ***Neisseria gonorrhoeae*.....40 – 95 %**
  - Ceftriaxone, cefixime, spectinomycin
- ▣ ***Chlamydia trachomatis*.....+/- 20 %**
  - Tetracyclines, macrolides, azithromycin
- ▣ ***Mycoplasma genitalium*.....4 – 16%**
  - Macrolides, azithromycin
- ▣ ***Trichomonas vaginalis*.....3 – 5 %**
  - Metronidazole; tinidazole
- ▣ ***Ureaplasma urealyticum*.....1- 5 %**
  - Tetracycline; azithromycin

## 12.3 Male urethritis syndrome (MUS)

N34.1



# *Neisseria gonorrhoeae*



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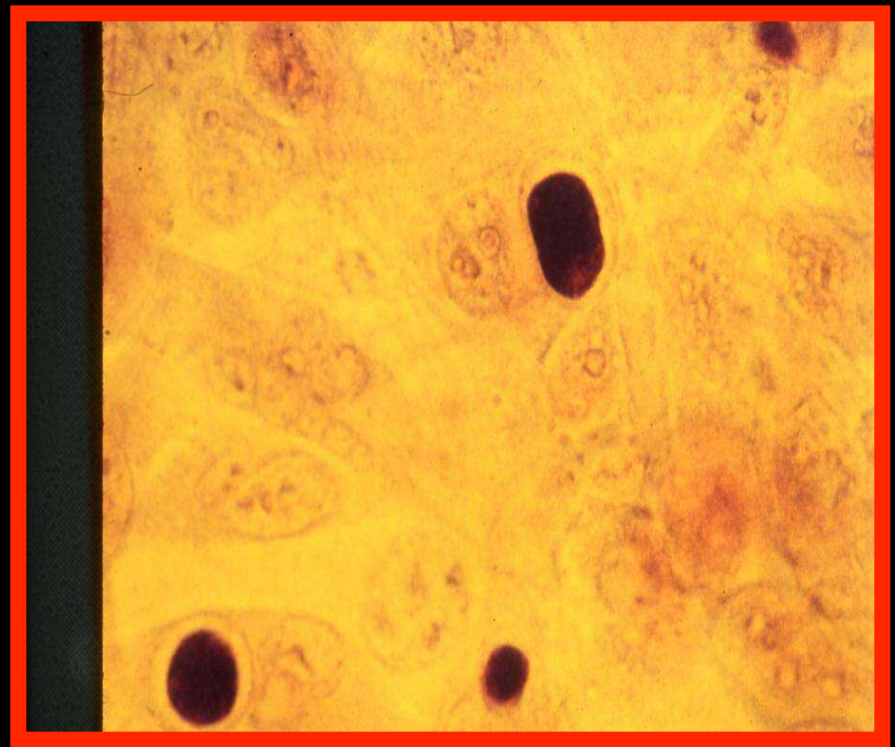
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# *Neisseria gonorrhoeae:* Which agents?

- ▣ **Ceftriaxone & cefixime** – currently used
  
- ▣ **Spectinomycin**
  - If parenteral treatment is preferred, spectinomycin seems suitable, although isolates with decreased susceptibility to spectinomycin have been reported
  - Spectinomycin bind to the ribosome and interferes with protein synthesis.
  
  - **Resistance**
    - ▣ Resistance to spectinomycin usually occurs via a single-step chromosomal mutation, resulting in high-level resistance

# *Chlamydia trachomatis*



## Antibiotic resistance in Chlamydiae

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<sup>1</sup> Molecular & Cellular Biology Program & the Department of Biomedical Sciences, College of Veterinary Medicine, Oregon State University, Corvallis, OR 97331–4804, USA

### Abstract

There are few documented reports of antibiotic resistance in *Chlamydia* and no examples of natural and stable antibiotic resistance in strains collected from humans. While there are several reports of clinical isolates exhibiting resistance to antibiotics, these strains either lost their resistance phenotype *in vitro*, or lost viability altogether. Differences in procedures for chlamydial culture in the laboratory, low recovery rates of clinical isolates and the unknown significance of heterotypic resistance observed in culture may interfere with the recognition and interpretation of antibiotic resistance. Although antibiotic resistance has not emerged in chlamydiae pathogenic to humans, several lines of evidence suggest they are capable of expressing significant resistant phenotypes. The adept ability of chlamydiae to evolve to antibiotic resistance *in vitro* is demonstrated by contemporary examples of mutagenesis, recombination and genetic transformation. The isolation of tetracycline-resistant *Chlamydia suis* strains from pigs also emphasizes their adaptive ability to acquire antibiotic resistance genes when exposed to significant selective pressure.



# GENITAL MYCOPLASMAS



# *Mycoplasma genitalium*

- ▣ Smallest self-replicating prokaryote
- ▣ Lacks cell wall
- ▣ Genome of only 580 kilobase pairs
- ▣ Characteristic pear/flask shaped morphology with terminal tip organelle for attachment
- ▣ Role in disease difficult to establish – difficult to grow in culture, long duration, low yield
- ▣ Molecular assays – led to number of studies (qualitative & quantitative)
- ▣ Studies – developed countries show an association between *M genitalium* and male urethritis

# MATERIALS AND METHODS

## Specimens:

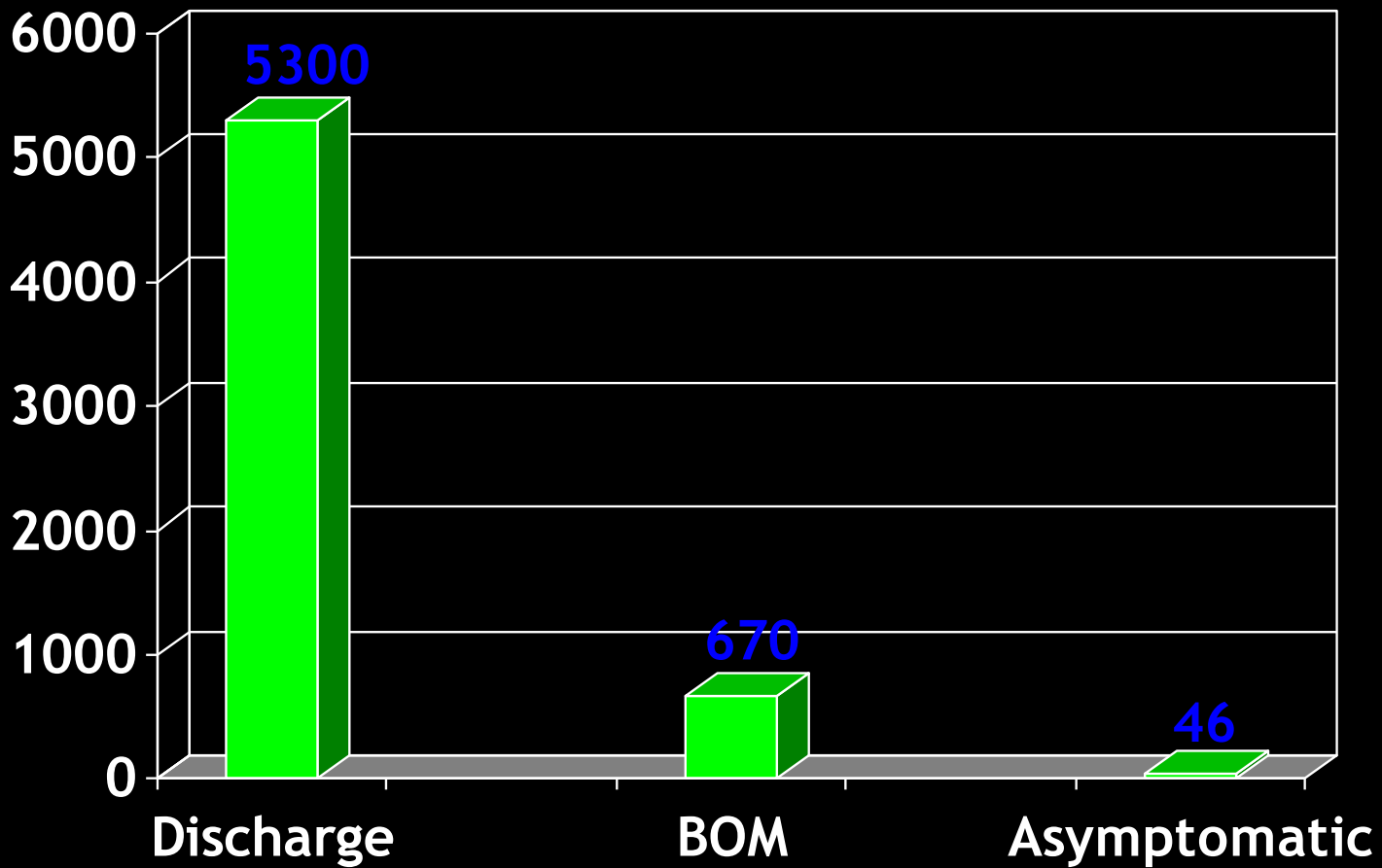
- ▣ Urine specimens from men attending a private practitioner in Pretoria
- ▣ **300** men presenting with urethral signs & symptoms
  - Visible discharge (**94**)
  - Burning on micturition (**206**)
- ▣ **75** asymptomatic men



# RESULTS

- ▣ At least 1 pathogen detected in 138 (46%) patients
- ▣ **Urethral organisms detected :**
  - **In symptomatic men (n=300):**
    - MG was detected in 52 (17.3%)
    - NG in 50 (16.7%)
    - CT in 37 (12.3%)
    - TV in 24 (8.0%)
  - **In asymptomatic men (n=75):**
    - MG was detected in 5 (6.6%) ( $p = 0.03$ )
    - CT in 4 (5.1%) ( $p = 0.04$ )
    - NG in 2 (2.6%) ( $p < 0.001$ )
    - TV in 1 (1.3%) ( $p = 0.03$ )

# BACTERIAL LOAD



# *Mycoplasma genitalium*

## TREATMENT

- ❑ Lacks cell wall - beta-lactams inherent resistance
- ❑ Susceptible to those that inhibit protein synthesis
- ❑ CDC guidelines - macrolides, tetracyclines & flouoroquinolones
- ❑ Cannot determine MIC – because not easy to culture & intra-cellular location
- ❑ Clinical trials – test of cure by detection of organism, bacterial load

# ***Mycoplasma genitalium***

## **TREATMENT**

- ❑ **Hannan 1998 – in-vitro study showed susceptibility to azithromycin but not doxycycline & ciprofloxacin**
- ❑ **Falk 2003, Swedish study where patients were re-tested after 4-5 weeks – tetracycline did not eradicate *M genitalium* & azithromycin was more active**
- ❑ **Bradshaw *et al* 2006, Australian study reported significant treatment failure with single dose Azithromycin (resistance to macrolides) & infection cleared with 400mg moxifloxacin for 10 days.**
- ❑ **Bjournalius *et al* 2008 recommend 500mg Azithromycin first day followed by 250mg for 4 days for treatment failures**

# *Trichomonas vaginalis*





# VAGINAL DISCHARGE AND LOWER ABDOMINAL PAIN

## ▣ **CERVICAL DISCHARGE**

- *Nisseria gonorrhoeae*
- *Chlamydia trachomatis*

## ▣ **VAGINAL DISCHARGE**

- *Trichomonas vaginalis*
- *Candida albicans*
- *Gardnerella vaginalis* (BACTERIAL VAGINOSIS)

- ▣ **Bosseman EA, et al. Utility of antimicrobial susceptibility of in *Trichomonas vaginalis*-infected women with clinical treatment failure. Sexually Transmitted Diseases 2011; 38: 983- 7**
  
- Nitro-imidazole resistance 2-6% suggested in USA
  
- Women who had failed at least 2 courses of standard therapy Alternate treatment based on susceptibility testing
  
- Clinical & microbiologic cure rates were higher for women treated according to results of in-vitro tests compared to lower dose of different drug

# *Trichomonas vaginalis*

## LOCAL STUDY

- ▣ For MIC & MLC: All isolates tested were considered to be susceptible (CLSI guidelines: MIC  $\leq$  32  $\mu\text{g/ml}$ , MLC  $\leq$  50  $\mu\text{g/ml}$ )
- ▣ Generally values obtained under aerobic conditions were similar to values obtained anaerobically- differences observed were minimal
- ▣ Metronidazole remains an appropriate agent for treatment of trichomoniasis

## LIMITATIONS

- ▣ No reference ATCC strain with known MIC or MLC was available

## CONSIDERATIONS

- ▣ *In vitro* values of metronidazole susceptibility are only indicators of the degree of sensitivity or resistance of a specific trichomonad isolate under fixed laboratory conditions

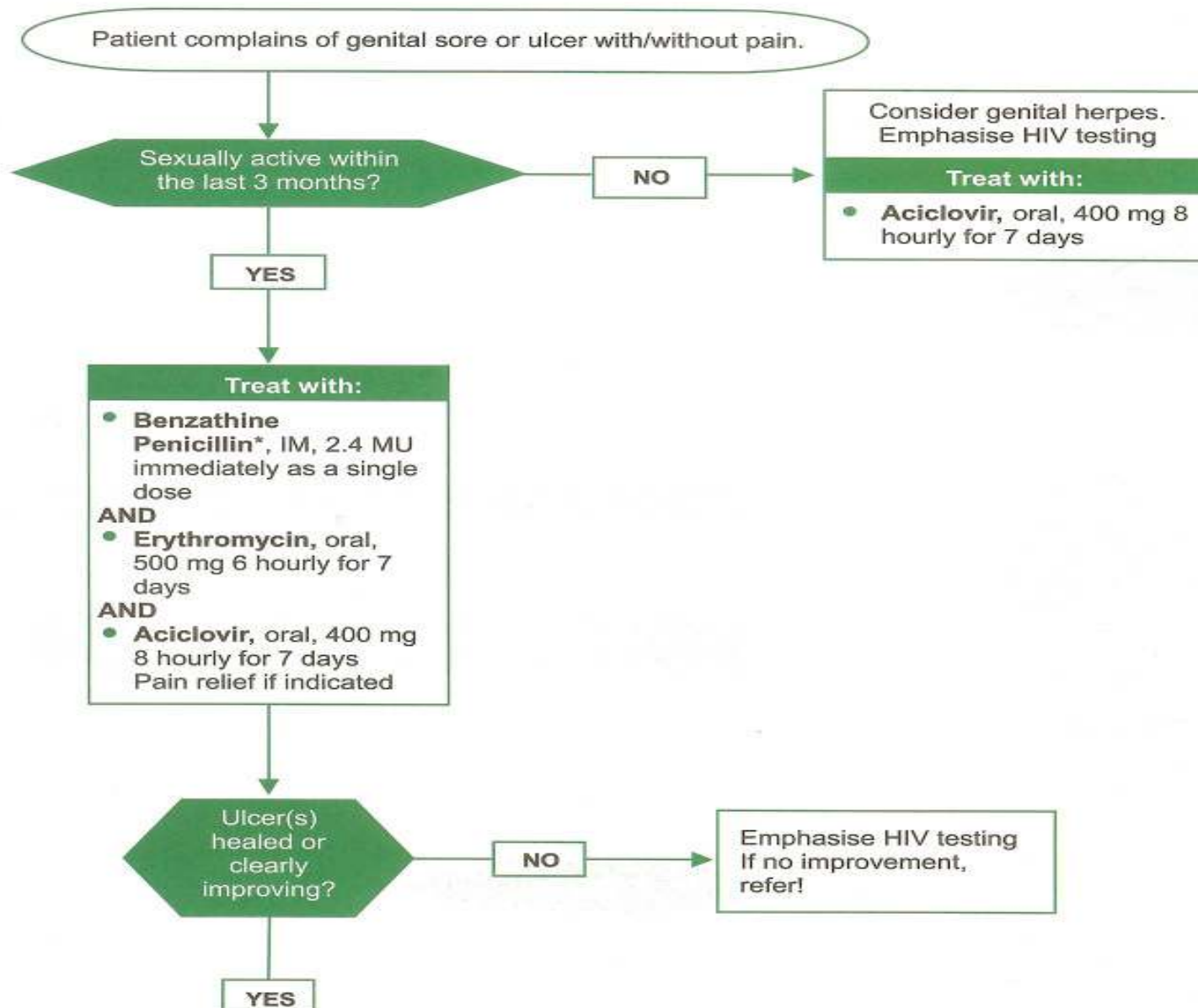


# EPIDEMIOLOGY OF GENITAL ULCER DISEASE

▣	<b>SYPHILIS</b>	<b>40%</b>
▣	<b>CHANCROID</b>	<b>40%</b>
▣	<b>HERPES</b>	<b>15%</b>
▣	<b>LGV</b>	<b>3%</b>
▣	<b>GI/DONOVAN</b>	<b>1%</b>

▣	<b>HERPES</b>	<b>60%</b>
▣	<b>SYPHILIS</b>	<b>30%</b>
▣	<b>CHANCROID</b>	<b>15%</b>
▣	<b>LGV</b>	<b>15%</b>
▣	<b>GI/DONOVAN</b>	<b>1%</b>

## GENITAL ULCER SYNDROME (GUS)



# GENITAL HERPES

- ▣ Studies conducted in Mwanza, Tanzania, also demonstrated high prevalence rates of HSV infection: 50% of women and 25% of men were HSV-2 seropositive by the age of 25 years.(1)
- ▣ Other studies confirmed the high prevalence of HSV-2 in other African countries. (2)
- ▣ The importance of HSV-2 in facilitating the sexual transmission of HIV was demonstrated in a case control study of HIV seroconverters in the Mwanza cohort, which found that 22% of new HIV infections in women and 74% in men could be attributed the co-factor effect of HSV-2. (3)
- ▣ Unable to show impact on HIV with suppressive treatment
- ▣ 1. Obasi A, Mosha F, Quigley M, et al. Antibody to herpes simplex virus type 2 as a marker of sexual risk behavior in rural Tanzania. *J Infect Dis* 1999;179:16-24.
- ▣ 2. Orroth KK, Freeman EE, Bakker R, et al. Understanding the differences between contrasting HIV epidemics in east and West Africa: results from a simulation model of the Four Cities Study. *Sex Transm Infect* 2007;83(Suppl 1):i5-16.
- ▣ 3. del Mar Pujades Rodríguez M, Obasi A, Mosha F, et al. Herpes simplex virus type 2 infection increases HIV incidence: a prospective study in rural Tanzania. *AIDS* 2002;16:451-62.

# Macrolide-resistance testing and molecular subtyping of *Treponema pallidum* strains from South Africa

Etienne E Müller, Gabriela Paz Bailey, David A Lewis

ISSTDR 2011 ABSTRACT

## Objectives

- To determine whether the main 23S rRNA mutation (A2058G) that confers macrolide resistance in *Treponema pallidum* is present among DNA obtained from syphilitic ulcers in South Africa and to determine the strain subtype distribution using molecular methods.

## Results

- **None of the samples analysed contained the 23S rRNA gene point mutation that confers macrolide resistance.** A total of 8 *arp* repeat sizes, 8 RFLP patterns and a combined total of 17 subtypes were identified in this study population. The most common subtypes were 14d (43%), followed by 17d (13%), 14b (7%), 22b (5%) and 23b (5%).



# CHALLENGES WITH DRUG RESISTANT STIs

- ▣ Diverse aetiological agents – bacteria, viruses, protozoan
- ▣ Some organisms cannot be cultured/difficult to culture on artificial media
- ▣ Intracellular location
- ▣ Mixed infections in high-risk behaviour populations
- ▣ Management strategies such as syndromic management
- ▣ Impact of HIV

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