Mycoplasma genitalium:

The new "kid" on the STI block

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Objectives

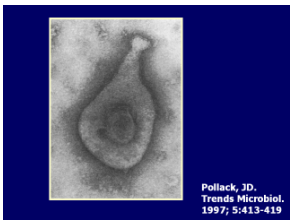
- Biology of the organism
- Detection methods
- Estimates of prevalence
- Normal flora or sexually transmitted
- Evidence for *M. gen* as a pathogen
  - Men
  - Women
- Future directions

M. genitalium biology

- Mollicute
- Smallest living single celled organism
- Lacks cell wall
  - Not visible on gram stain
  - Resistant to penicillins and cephalosporins
- Fastidious
  - Difficult to culture
- Genome sequenced
  - http://cmr.tigr.org/tigr-scripts/CMR/GenomePage.cgi?database=gmg

Mycoplasma species

- Clinically significant mycoplasmas
  - *M. pneumonia*
    - Atypical pneumonia
  - *M. hominis*
    - normal vaginal flora
    - Post abortal fever
  - *M. genitalium*



How do we detect M Gen?

MG Detection Methods

- First isolated 1981- 2 men with urethritis
- Culture difficult 4-8 weeks
- Culture vs NAAT concerns
  - Multiple in house PCRs
  - Newer TMA platform (Aptima)
  - No gold standard
- What's the best test?

MG Detection- Questions

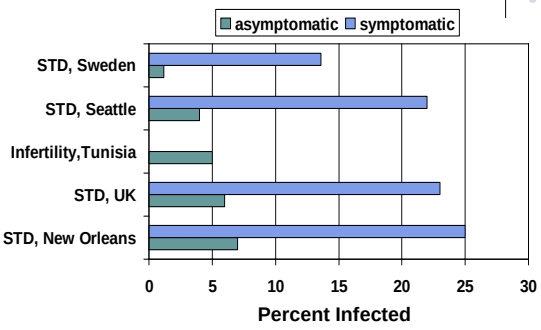
- Specimens for NAAT:
- Swab
  - Urethra
  - Cervix
  - Vagina
- Urine
  - Ad Health data

How much *M. Genitalium* is out there?

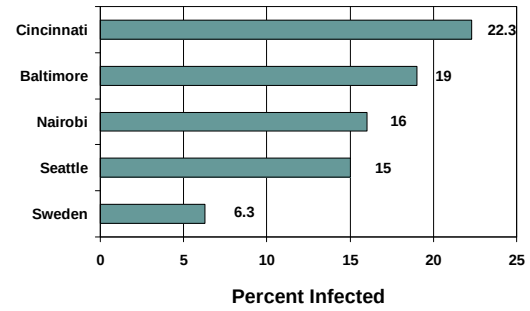
Estimates of "Prevalence"

- Most prevalence estimates are based on surveillance data
- Surveillance is limited:
  - those with access to and seeking health care
  - Usually study symptomatic groups
  - Some are compared to asymptomatic controls
- For MG, testing is restricted to research studies

MG in Men: Observational data



MG in Women: Observational data



MG "prevalence" in women

- Other studies
  - 15% Seattle STD clinic, 18-27 yo women
  - 19% Baltimore STD clinic, adult women
  - 16% Nairobi sex workers,18-35 yo
  - 6.3% Sweden STD clinics
- Huppert study 22.3% (age 14-21)
  - No difference in those <18 (21.3%)
  - As high as CT and TV
- High prevalence in adolescents due to:
  - Adolescents at high risk for all STIs
  - Vaginal swabs have excellent sensitivity for MG.

Wroblewski, 2006
Hardick, 2006
Cohen, 2006
Anagrius, 2005

Add Health: population survey

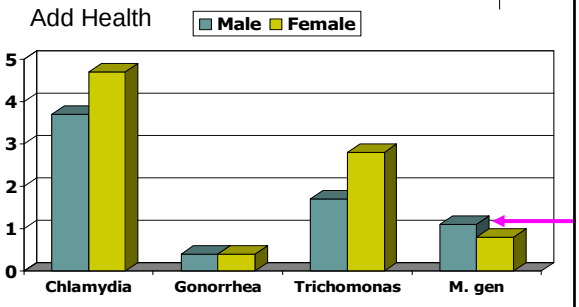
- National Longitudinal Study of Adolescent Health
- Wave 1-In school (N~18,000)(1994-95)
- Wave 2- Follow up in home
- Wave 3- In Home (2002)
  - N=14,000, 18-26 year olds
  - Urine STI screening: 87%
  - MG testing: N=2932

MG population estimates

- National sampling weights applied
- **Overall MG 1.0%**
- No association with reported discharge or dysuria
- MG Higher in
  - Blacks
  - Living with sex partner
  - Used condoms at last sex

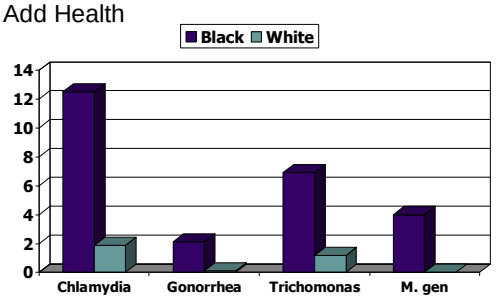
MG: higher in young adult men

Add Health



MG: higher than gonorrhea

- Add Health



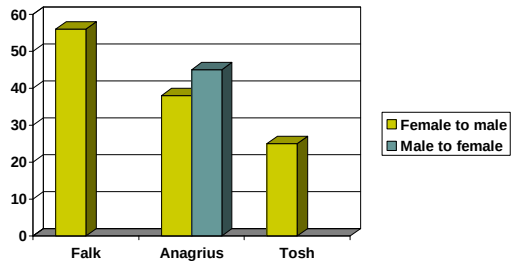
Is MG sexually transmitted?

Or is it just part of normal flora?

Evidence of sexual transmission:

- Prevalence vastly higher in sexually experienced young adults: (Manhart 2007)
  - 0.05% in never sexually active (2 / 341)
  - 1.3% ever SA (RR=27)
- Concordant infections:
  - 38- 56% of male partners of MG+ females had MG (Anagrius 2005,Falk 2005)
    - (59% of male partners of CT+ females had CT)
  - 45% of female partners of MG+ males had MG (Anagrius 2005)

Partner concordance



Caveat:

- MG Detected in women who denied ever sexually active
  - Manhart 2/341= .05%
  - Tosh 1/65= 1.5%
- Explanations
  - False positive NAAT
  - Error in report of Sexual behavior
  - Non-sexual transmission

Consistent with sexual transmission

- Increased prevalence of MG with:
- Sexual risk behaviors
  - Multiple partners
  - Condom use
- Other STIs
  - Chlamydia
  - HIV

Does MG cause disease? Is it normal flora?

Normal flora or pathogen?

- Some infections are transient
  - Higher prevalence with recent sexual contact (Huppert 2007)
  - Spontaneous clearance in women
    - 70-90% of MG resolved in 3-7 months after initial + (Cohen 2006)
    - 80% resolve in 12 weeks (Tosh 2007)
- Is treatment necessary?
- Does MG cause disease?

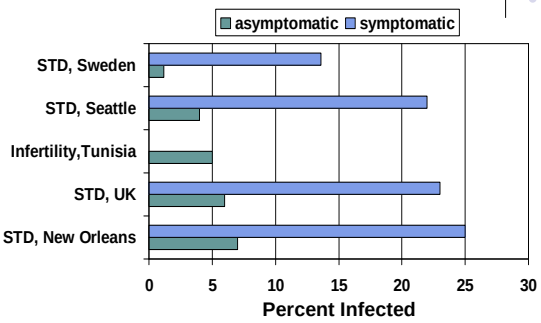
Koch's postulates

- The suspected causal organism must be strongly associated with the disease.
- The suspected causal organism must be isolated from an infected person and propagated.
- When a healthy susceptible host is inoculated with the pathogen, symptoms of the original disease must develop.
  - Treatment of the infection relieves the symptoms of the disease

Evidence that MG causes urethritis in men:

- Multiple studies
- Consistent results
- Higher MG in men with
  - Symptoms of urethritis
    - Absence of GC or CT
  - Elevated PMNs
  - Co-infected with Chlamydia

MG: higher in symptomatic Men



MG and Men

- Relationship with other outcomes less clear
  - Chronic urethritis (Horner 2001)
  - Other outcomes?

Koch's 3rd postulate:

- When a healthy susceptible host is inoculated with the pathogen, symptoms of the original disease must develop.

Animal studies

- Confirm that symptoms are produced in healthy animals after inoculation
  - Male chimps: urethritis
  - Female chimps: vaginal shedding
  - Grivet monkeys: salpingitis
  - Baboons: parametritis

MG and symptoms in women: Conflicting results

- **Associated with MPC:**
- 3 cross sectional studies
  - Mucopurulent cervicitis (MPC):
    - 1.6- 3-fold higher among women with MG than without MG.
      - (Pepin 2006, Manhart 2003)
  - Vaginal discharge **was** associated with MG
    - MPC **was not**
      - (Korte 2006)

MG and symptoms in women: Conflicting results

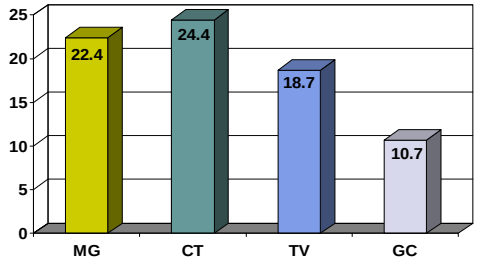
- **Not associated:**
- 2 longitudinal, 2 cross sectional studies
  - Clinical signs were **not** associated with MG
    - Abnormal discharge, cervicitis
  - Patient symptoms were **not** associated with MG
    - Discharge, pain, dysuria
    - (Cohen 2006, Tosh 2007, Falk 2005, Huppert 2007)

Huppert Study Results

- 369 adolescent women recruited
- 331 with samples for MG
- Mean age:17.7 years (range 14-21)
- 82% black
- 63% vaginal symptoms

- MG was detected in 74 (22.4%) subjects, CT in 79 (24.4%), TV in 62 (18.7%) and GC in 35 (10.7%) subjects.

Prevalence of STIs in Young women



Huppert 2008

History variables associated with MG

	Total N=331	Mg positive N=74	Mg negative N=257	P value
Condom used at last sex	**159 (48.0)**	**37 (50.0)**	**122 (47.5)**	**.70**
Hormonal contraception used	**116 (35.0)**	**19 (25.7)**	**97 (37.7)**	**.055**
History of prior STI	**206 (62.2)**	**47 (63.5)**	**159 (61.9)**	**.79**
> 1 sexual partner in last 3 months	**86 (25.9)**	**26 (35.1)**	**60 (23.4)**	**.04**
Recent sexual contact (≤ 7 days)	**153 (46.2)**	**43 (58.1)**	**110 (42.8)**	**.02**

Huppert 2008

Symptoms and signs and MG

Symptoms reported by subject (n=331)	Total N=331	MG + N=74	MG - N=257	
Vaginal discharge	175 (51.9)	39 (52.7)	136 (52.9)	.97
Any vaginal symptoms	211 (63.9)	44 (59.6)	167 (64.9)	.38
Dysuria	63 (19.0)	9 (12.2)	54 (21.0	.09
Any genitourinary symptoms	295 (89)	64 (86.5)	231 (89.9)	.40
Signs noted by provider (N=318)	N=318	N=71	N=247	
Abnormal discharge	148 (46.5)	31 (43.6)	117 (47.4)	.58
Mucopurulent cervicitis	47 (14.8)	7 (9.9)	40 (16.2)	.18
Friable cervix	52 (16.4)	11 (15.5)	41 (16.6)	.82
Abnormal cervix	87 (27.4)	17 (23.9)	70 (28.3)	.46
Cervical Motion tenderness	39 (12.3)	6 (8.4)	33 (13.4)	.27
Uterine tenderness	22 (6.9)	2 (2.8)	20 (8.1)	.18*
Adnexal tenderness	48 (15.1)	7 (9.9)	41 (16.6)	.16

Lab and STI associations with MG

	Total N=318	MG+ N=71	MG - N=247	
Any clue cells [e]	70 (23.7)	14 (20.0)	52 (23.1)	.58
Any WBC on wm [d]	233 (79.5)	57 (83.4)	176 (77.5)	.12
Co-infections (n=331 unless noted)				
TV on wet mount	31 (9.4)	7 (9.5)	24 (9.3)	.9
Any TV test +	62 (18.7)	18 (24.3)	44 (17.1)	.16
CT [a]	79 (24.4)	27 (37.5)	52 (20.6)	.003
GC [b]	35 (10.7)	10 (13.9)	25 (9.8)	.33
Either CT or GC [c]	97 (30.0)	31 (43.6)	66 (26.2)	.005
Any other STI (CT,GC or TV)	129 (39.0)	40 (54.0)	89 (34.6)	.003

Logistic Model: Predictors of MG

N=324	Unadjusted		Final model	
	OR	95% CI	AOR	95% CI
+ CT	2.3	1.3 - 4.1	2.5	1.4 - 4.4
Recent sexual contact (≤ 7 days)	1.8	1.1 - 3.1	2.0	1.1 - 3.2
Dysuria	0.52	0.24 – 1.1	0.44	0.20 - 0.96
Hormonal contraception	0.59	0.33 - 1.1	0.55	0.3 - 1.0
>1 partners in last 3 months	1.8	1.0 - 3.1		

Huppert 2008

Explanations for Conflicting data

- MG does not cause symptoms
- Symptoms and signs measured differently in each study
  - Pt reported vaginal discharge
  - vaginal PMN, cervical friability, mucopus
- MG measured differently
  - Culture vs PCR vs TMA
- MG site differed
  - Urine, vaginal swab, cervical swab

Discussion: CT and MG

- High degree of coinfection
  - CT+ : 34% had MG, vs 18% of CT-
  - CT+: 2.5 OR of MG infection
- Similar results from a longitudinal cohort of Nairobi sex workers.
  - Incident CT increased the hazard of acquiring MG by 2.5 fold [Cohen, 2006]
- May help understand the pathogenicity and best treatment of MG.

MG and PID: mixed results

- Small studies:
  - 14% MG prevalence in women with clinical and biposy diagnosis of PID (n=50) (no control group) (Haggerty 2006)
  - 16% MG in women with endometritis vs 2% in those without. (n=115) (Cohen 2002)
  - 7% MG of those w laparoscopic salpingitis (n=123), 1 recovered from tube, no control group. (Cohen 2005)
- In vitro: MG (but not M Hominis) caused tubal changes (Baczynska 2006)
- MG antibodies- not associated with PID, ectopic pregnancy- (Jurstrand 2007)

MG and HIV

- Association with HIV
  - Greater than 2- fold increased risk of *M. genitalium* infection if HIV positive (Cohen 2007)
  - 3- fold increased chance of shedding HIV from cervix if have high burden of *M. genitalium* ¨(Manhart JID 2008)

MG and OB outcomes

- Preterm labor : conflicting results
  - **Increased** odds of preterm delivery (OR 3.5) USA, N=134
    - (Edwards 2006)
  - **No** association with miscarriage or preterm labor UK, n=914, low prevalence (0.7%)
    - (Oakshott 2006)

Is Mg associated with BV or vaginal abnormalities?

- NEW STUDY:
- Recruited 217 Sexually active females aged 14-21
- Vaginal swabs tested for:
  - pH (pHydrion paper)
  - Amines (whiff test)
  - clue cells (wet mount)
  - Sialidase (BV Blue test)
- MG testing :TMA
- Clinical BV (Amsel's criteria)
  - Clue cells + pH>4.5 + amine positive

MG preliminary results

	Total positive/ tested Number (%)	MG Positive N (%)	MG Negative N (%)	P value
pH>4.5	**118 / 211 (56)**	**23 (77)**	**95 (52)**	**0.013**
Clinical BV	39 / 209 (19)	3 (10)	36 (20)	0.19
Sialidase	22 / 105 (21)	3 (20)	19 (21)	0.922
Amine	109 / 210 (52)	15 (52)	94 (52)	0.983
Clue Cells	71 / 215 (33)	7 (23)	64 (35)	0.224

MG and disease: summary

- Men: urethritis
- Women:
  - No proven associations with
    - Vaginal discharge
  - Possible increase in
    - Dysuria
    - Cervicitis
    - Endometritis
    - PID
    - Preterm labor/ miscarriage
  - Inverse relationship to Bacterial vaginosis
- Further studies needed

Treatment

- Few studies
- Theoretically sensitive to tetracyclines and macrolides
  - Doxy or Azithromycin in “Chlamydia” doses
- Reports of TCN resistance
  - Males already treated with Doxycycline: Azithromycin 1.0-1.5 gm > erythromycin
    - (Wikstrom 2006)
- Case report Azithromycin 1 gm resistance: moxifloxacin
  - (Bradsaw 2006)

Clinical Scenarios where one might consider MG

- Persistent or unresponsive NGU
  - Black males?
- Atypical PID
- Persistent cervicitis

Strategy if MG suspected

- Obtain NAAT if available
- Rule out other conditions-
  - ie CT, GC, HSV, Trich
- Empiric treatment
  - Doxycycline 100 mg PO BID X 7 days
  - Azithromycin 1-2 gm po once
  - Moxifloxicin 400 mg po daily X 5 (?)
- Consider treating the partner

Future Directions

- Better diagnostic methods
- Longitudinal studies
  - Determine natural history
  - Other transmission- oral, anal
  - Outcomes: PID, HIV acquisition
- Treatment data
  - Is clearance of infection associated with resolution of symptoms/ signs?
  - Does treatment of MG prevent other outcomes?

Objectives

- Biology of the organism
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  - Men
  - Women
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Questions?

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