URETHRITIS

Urethritis

- leukocytes > 4 at x 1000 magnification **(IUSTI)**
- +/- dysuria **>2 (CDC)**
- **+/−urethral discharge**

Urethritis

- Is characterized by urethral inflammation, can result from infectious and non-infectious conditions.
- **Symptoms**, if present, include dysuria; urethral pruritis; and mucoid, mucopurulent, or purulent discharge.
- Signs of urethral discharge on examination can also be present in persons without symptoms.

Cervicitis

-usually asymptomatic

- **Two major diagnostic signs** characterize cervicitis:

1) a purulent or mucopurulent endocervical **exudate** visible in the endocervical canal or on an endocervical swab specimen (commonly referred to as mucopurulent cervicitis)

2) sustained endocervical **bleeding** easily induced by gentle passage of a cotton swab through the cervical canal

Etiology of urethritis

Neisseria gonorrhoeae

Gonorrhoeal urethritis (GU)

Table 1. Prevalence of the most common pathogens isolated from patients with NGU.

Micro-organism	Prevalence	References
C. trachomatis	11–50%	3,4,6,8,10–13,14,15,16,17–24
M. genitalium	6–50%	3–6,8,11,13–16,19,21–27
Ureaplasmas	5–26%	3,11,13,15,21,23,24,28,29
T. vaginalis	1–20%	3,6,14,16,24,30–32
Adenoviruses	2–4%	8,33
Herpes simplex virus	2–3%	8,34

*Horner i wsp. 2016

- Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis,

- *Mycoplasma genitalium* has also
- been associated with urethritis and, less commonly, prostatitis

Other etiological factors of urethritis

- Intestinal flora (after anogenital contact)
- Oral flora e.g. Corynebacterium propinquum (after oral contact)
- Gardnerella vaginalis and Leptotrichia/Sneathia (causative agents of bacterial vaginosis)
- Foreign bodies
- stenosis of the urethra
- Other (i.e. IUD or erosion on the cervix or menstruation in the partner)

Estimated incidence of of certain STDs (in millions of cases per year)

	1995 *	1999 *	2005 *	2008 *	2012**	2020*
Chlamydial infection	89	92	101	106	131	129
Gonorrhoea	62	62	88	106	78	82
Trichomoniasis ***	170	174	248	276	143	156
Syphilis	12	11	10	12	6	7

M. genitalium **?**

***not very common in Europe and rarely causes urethritis

*WHO

**Newman i wsp. 2015

Estimated number of people worldwide living with viral sexually transmitted diseases (WHO)

- genital herpes 490 million people
- HPV infection300 million women
- hepatitis B 296 million people

Global incidence and prevalence of gonorrhoea

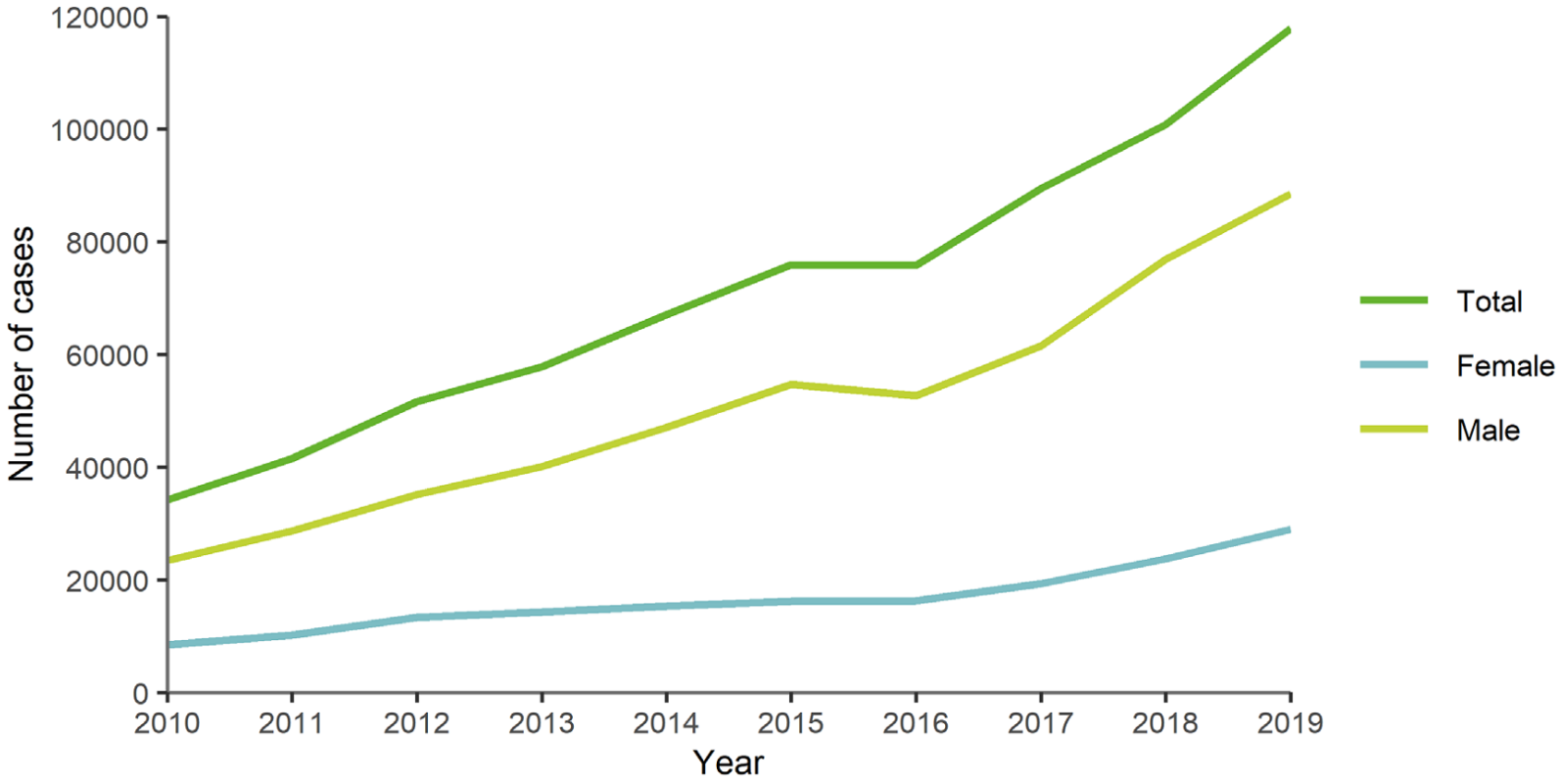
- World Health Organization (WHO) estimates that in 2020, there were 82.4 million [47.7 million–130.4 million new cases of gonorrhoea worldwide. The global incident rate of 19 (11–29) per 1000 women and 23 (10–43) per 1000 men.
- Most cases were in the WHO African Region and the Western Pacific Region.

Gonorrhoea in Europe

- According ECDC (European Centre for Disease Prevention and Control) overall notification rate in 2019 was **31.6** cases per 100 000 population
- Men who have sex with men (MSM) accounted for more than half of the reported cases (54%) in 2019

Gonorrhoea in Europe

Figure 4. Number of confirmed gonorrhoea cases by sex and year in EU/EEA countries reporting consistently, 2010–2019



Source: Country reports from Belgium, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

AETIOLOGY AND TRANSMISSION

Gonorrhoea (meaning 'flow of seed' in old Greek) and its related clinical manifestations are caused by infection with the Gram-negative bacterium *Neisseria gonorrhoeae*.

Infection predominantly involves the columnar (and squamous) epithelium of the urethra, endocervix, rectum, pharynx and conjunctivae. Although it usually remains localized to the initial sites of infection, it can ascend to the upper genital

tract to cause pelvic inflammatory disease (PID) and epididymo-orchitis or disseminate as

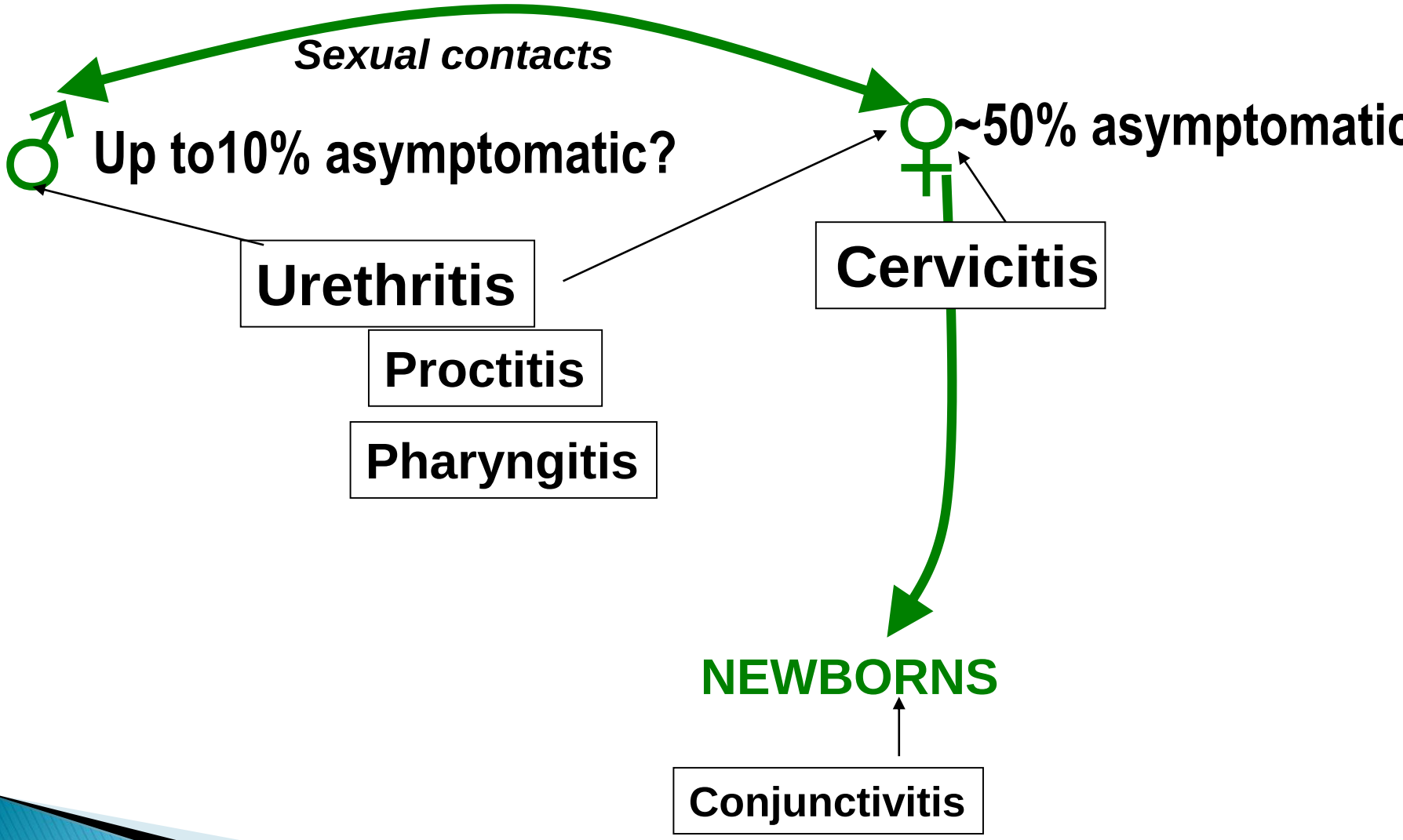
bacteraemia

Transmission

- the bacterium easily dies when exposed to external factors, and therefore infection through objects is usually not possible

Transmission is by direct inoculation of infected secretion from one mucosa to another, i.e. genital–genital, genital–anorectal, oro–genital or oro–anal contact or by mother–to child transmission at birth.

GONORRHOEA


Sexual contacts
Up to10% asymptomatic?
~50% asymptomatic
Urethritis
Proctitis
Pharyngitis
Cervicitis
NEWBORNS
Conjunctivitis

Symptoms in men

- incubation period 2-7 days
- more than 90% of men symptomatic
- usually severe urethritis with purulent discharge and heavy dysuria

In women, genital tract symptoms relate to endocervical and urethral infection and include increased or altered vaginal discharge (50%), lower abdominal pain (25%), dysuria (10–15%) and rarely intermenstrual bleeding or menorrhagia.

Endocervical infection is commonly asymptomatic (<50%)

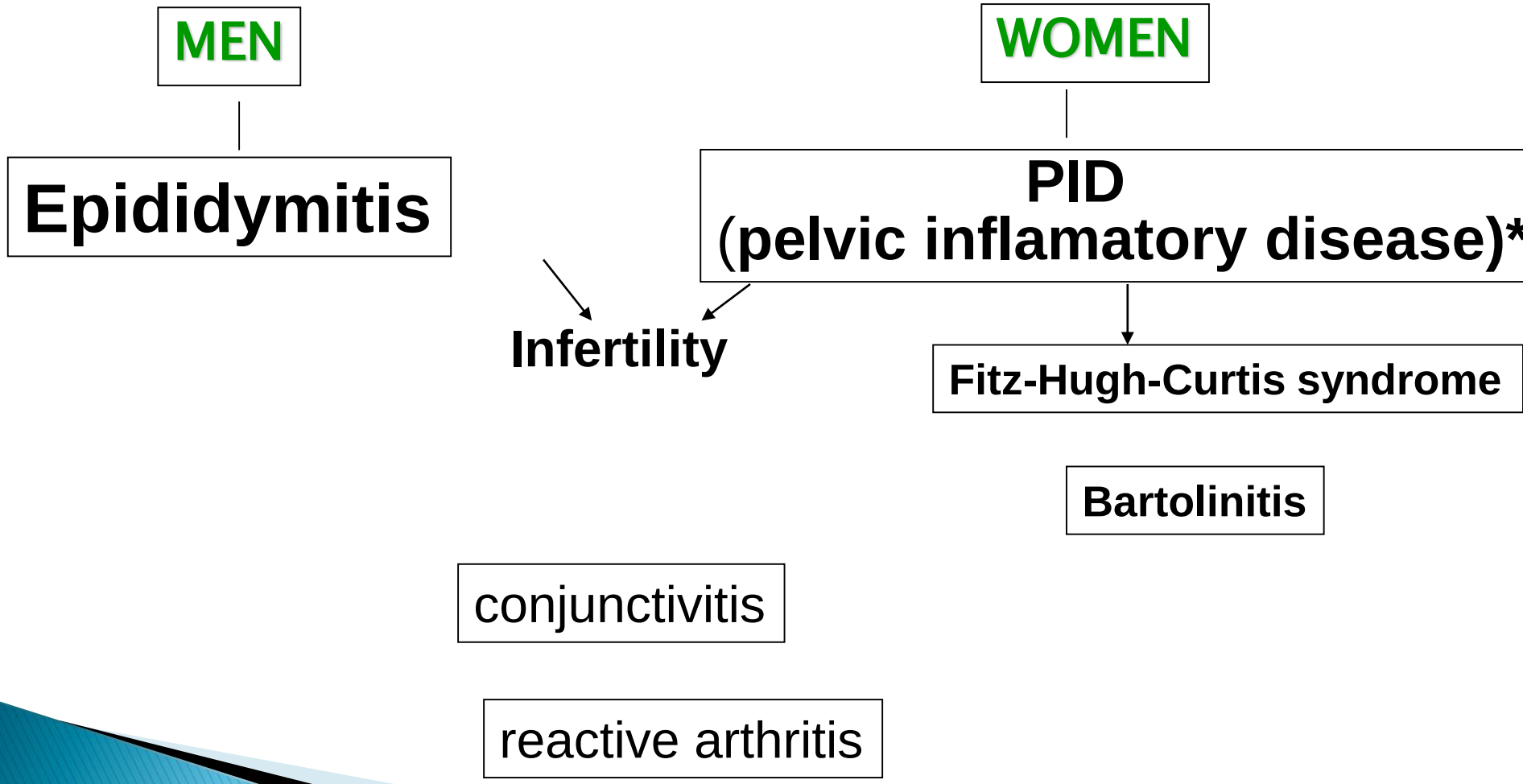
Rectal and pharyngeal infections are usually asymptomatic

severe conjunctivitis in the newborn
(due to the prophylactic use of silver nitrate
or erythromycin eye drops the problem is rare)

Incubation period 3– 5– 7 days !!!

women	men	newborn	children
cervicitis		conjunctivitis	vaginitis
urethritis	urethritis	rhinopharyngitis	urethritis
proctitis	proctitis		proctitis
			oropharyngitis
oropharyngitis	oropharyngitis		

COMPLICATIONS COMMON TO INFECTIONS WITH N. GONORRHOEAE AND C. TRACHOMATIS



Pelvic inflammatory disease — *C. trachomatis* and *N. gonorrhoeaeoae* can ascend to the upper reproductive tract (uterus, fallopian tubes, and ovaries), where pelvic inflammatory disease (PID) can result.

When symptoms of PID are present, abdominal and pelvic pain are the most common. Signs of PID include cervical motion and uterine or adnexal tenderness

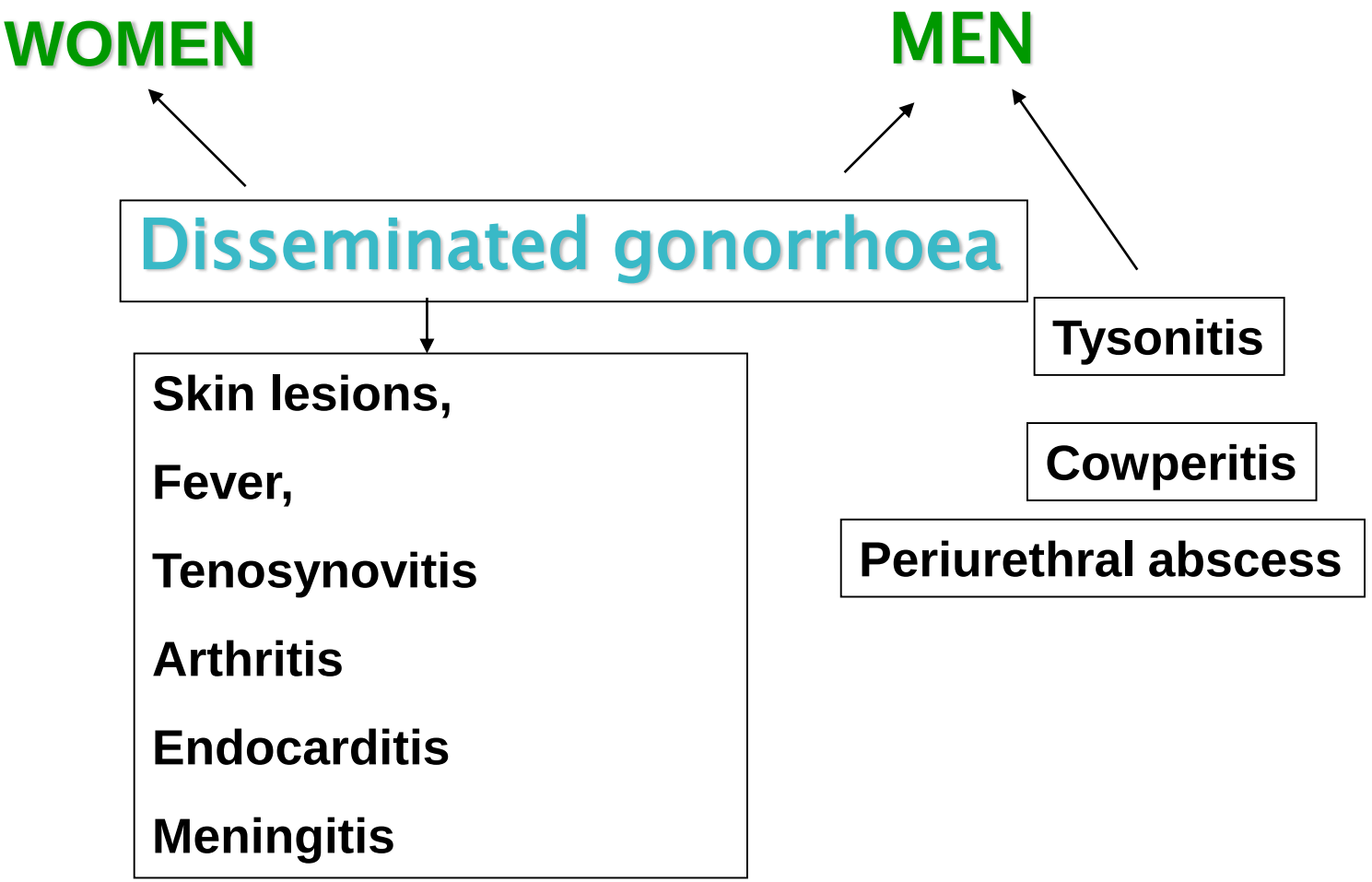
Complications in pregnant women

- Abortus — Chlamydia trachomatis
- Graviditas extrauterina — Neiseria gonorrhoeae; Chlamydia trachomatis

EPIDIDYMITIS

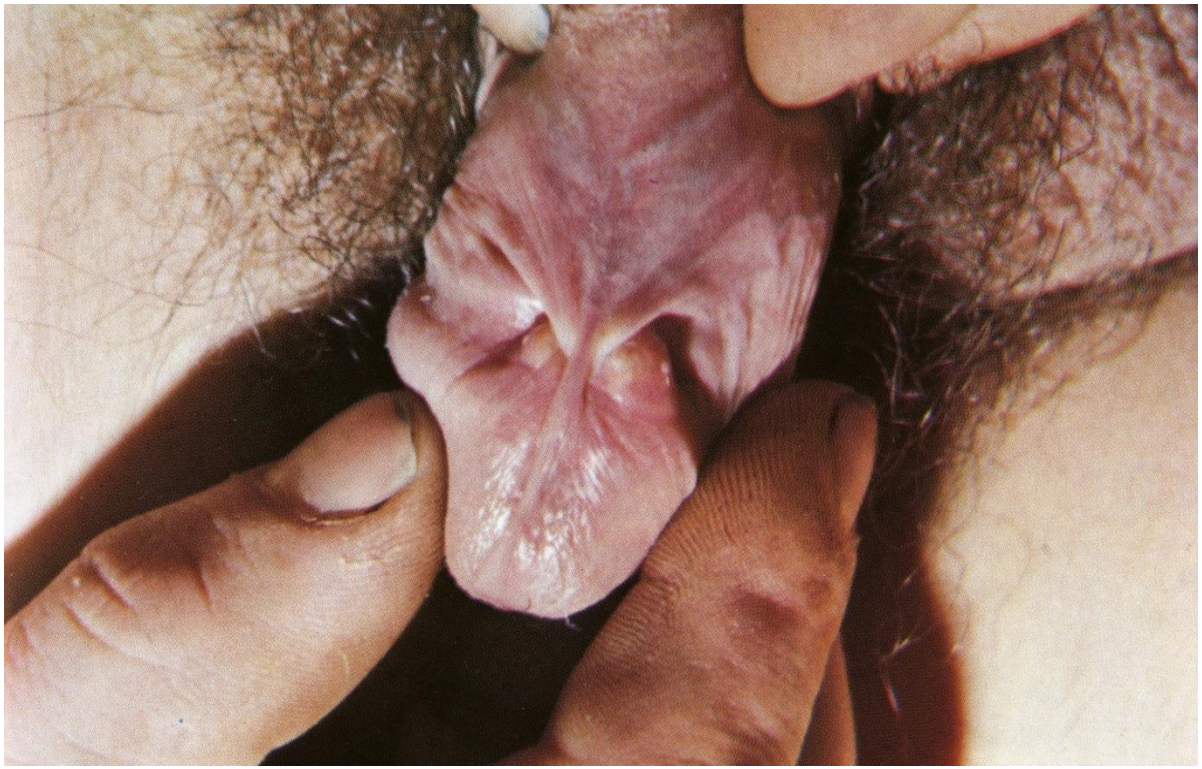
- Unilateral (on one side)
- Pain, edema, erythema
- Difficulties in establishing borders of the testis (on palpation)

COMPLICATIONS SPECIFIC TO GONORRHEA



Disseminated gonorrhoea

TYSONITIS

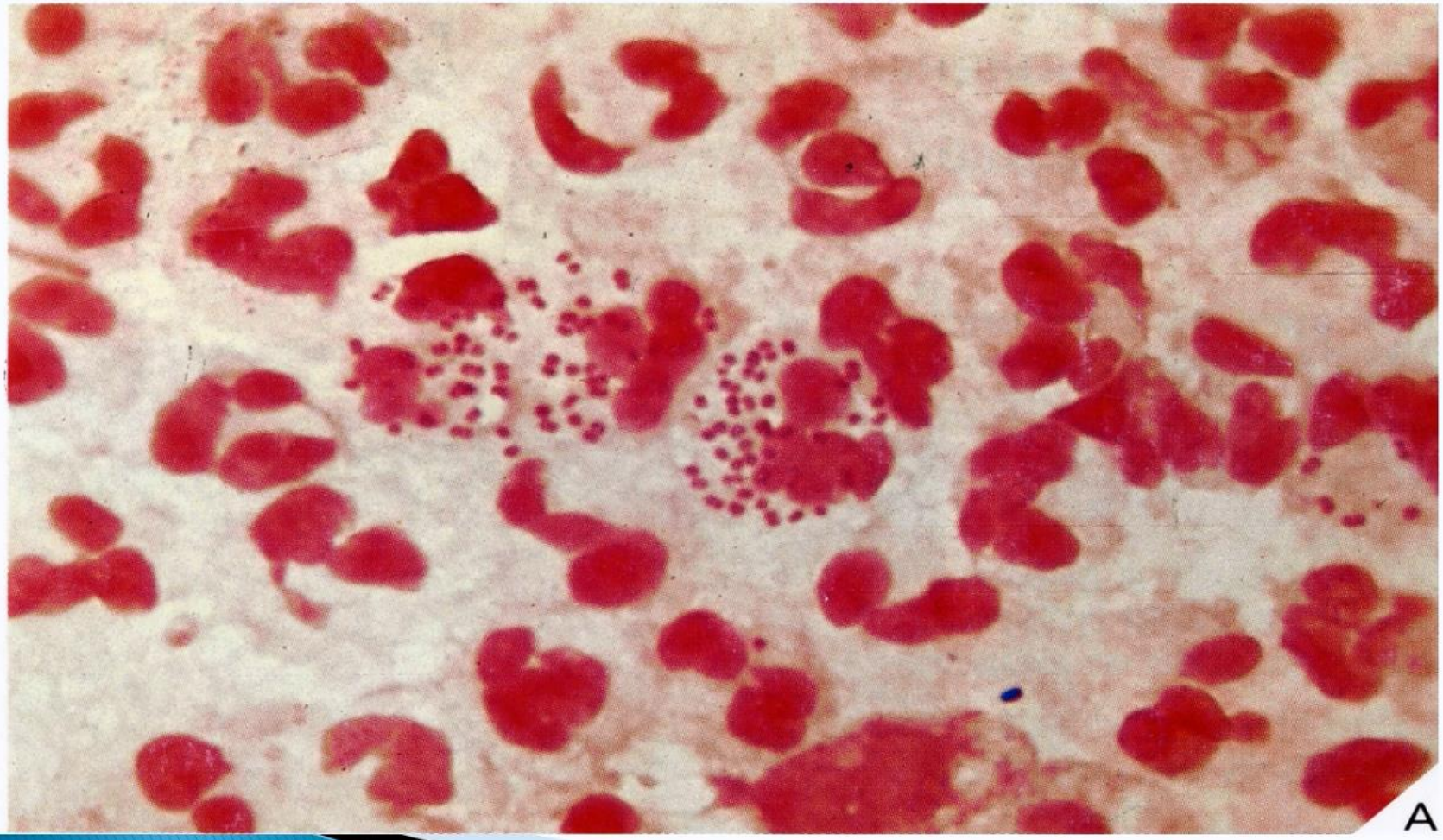


- The diagnosis of uncomplicated gonorrhoea is established by identification of *N. gonorrhoeae* in genital, rectal, pharyngeal or ocular secretions

Microscopy (x1000) using Gram or methylene blue staining for identification of diplococci within polymorphonuclear (PMN) leukocytes….

offers good sensitivity (95%) and specificity as a rapid diagnostic test in symptomatic men with urethral discharge

Neisseria Gonorrhoeae



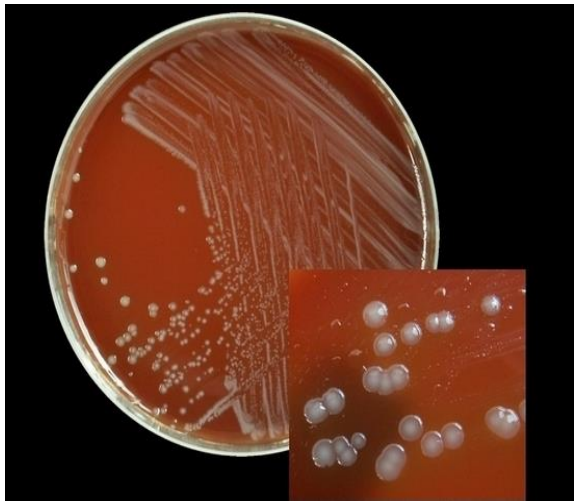
- **Culture** offers a specific and cheap diagnostic test that readily allows confirmatory identification.

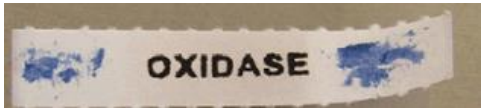
- It is the only diagnostic test that enables antimicrobial susceptibility testing and capacity to perform culture remains essential to detect and monitor evolving antimicrobial resistance.

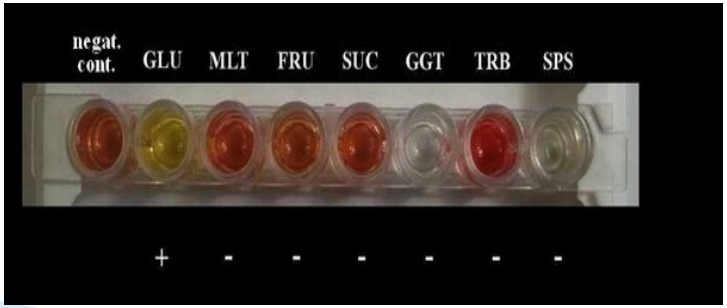
DIAGNOSTICS OF GONORRHEA

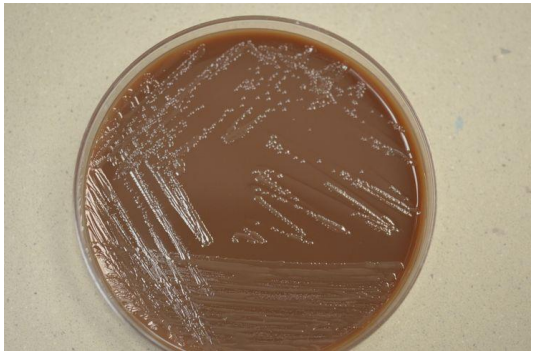
- CULTURE

15% O_2,
75–80% N_2,
5–10% CO_2



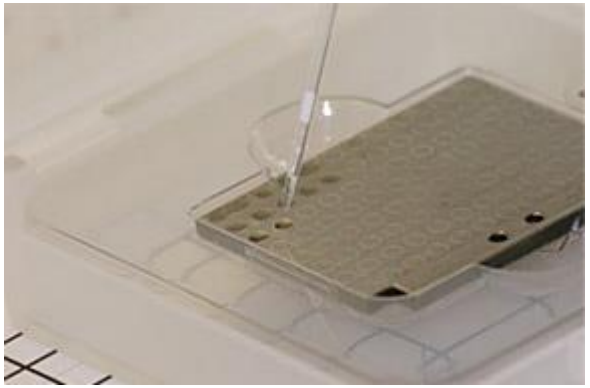






Identification –by biochemical methods or mass spectrometry–a quick and inexpensive method, but also possible only after culturing

Maldi biotyper



Vitek 2 MS

NAATS

- Detection directly in material from the patient most often by Real-time PCR
- High sensitivity, not decreasing significantly if material has to be transported
- Simultaneous detection of several pathogens possible (sometimes, however, lower sensitivity than single tests)

Indications for testing (IUSTI)

- Symptoms of urethral discharge in men;
- Vaginal discharge with risk factor for STI

(age < 30 years, new sexual partner or multiple partners)

- Mucopurulent cervicitis;
- Persons diagnosed with any other STI;
- Sexual partner of persons with an STI or PID;
- When screening young adults (<25 years of age) for STI;
- When screening individuals with new or multiple recent sexual partners;

Recommended treatments for uncomplicated N. gonorrhoeae infections of the urethra, cervix and rectum in adults and adolescents (IUSTI)

Ceftriaxone 1g intramuscularly (IM) as a single dose together with **Azithromycin** 2 g as single oral dose.

NOTE: Azithromycin tablets may be taken with or without food but gastrointestinal side effects can be less if taken after food.

Recommended Regimen for Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum Among Adults and Adolescents (CDC)

- Ceftriaxone 500 mg* IM in a single dose for persons weighing <150 kg

- If chlamydial infection has not been excluded, treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

- * For persons weighing ≥150 kg, 1 g ceftriaxone should be administered.

Alternative regimens

- Cefixime 400 mg oral as a single dose together with azithromycin 2 g as a single oral dose. This regimen is only an alternative option if ceftriaxone is not available or administration of injectable antimicrobials is not possible or refused by the patient.

- Ceftriaxone 1g* intramuscularly as a single dose. This regimen is only an alternative option if azithromycin is not available or patient is unable to take oral medication.

- Spectinomycin 2 g intramuscularly as a single dose together with azithromycin 2 g as a single oral dose.

* If chlamydial infection has not been excluded, providers should treat for chlam with doxycycline 100 mg orally 2 times/day for 7 days

Alternative Regimens (CDC)

- **If cephalosporin allergy**:
- **Gentamicin** 240 mg IM in a single dose
- PLUS
- **Azithromycin** 2 g orally in a single dose
- **If ceftriaxone administration is not available or not feasible**:
- **Cefixime** 800 mg* orally in a single dose

* If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days

Antimicrobial-Resistant *N. gonorrhoeae*

Easily develops resistance to antibiotics

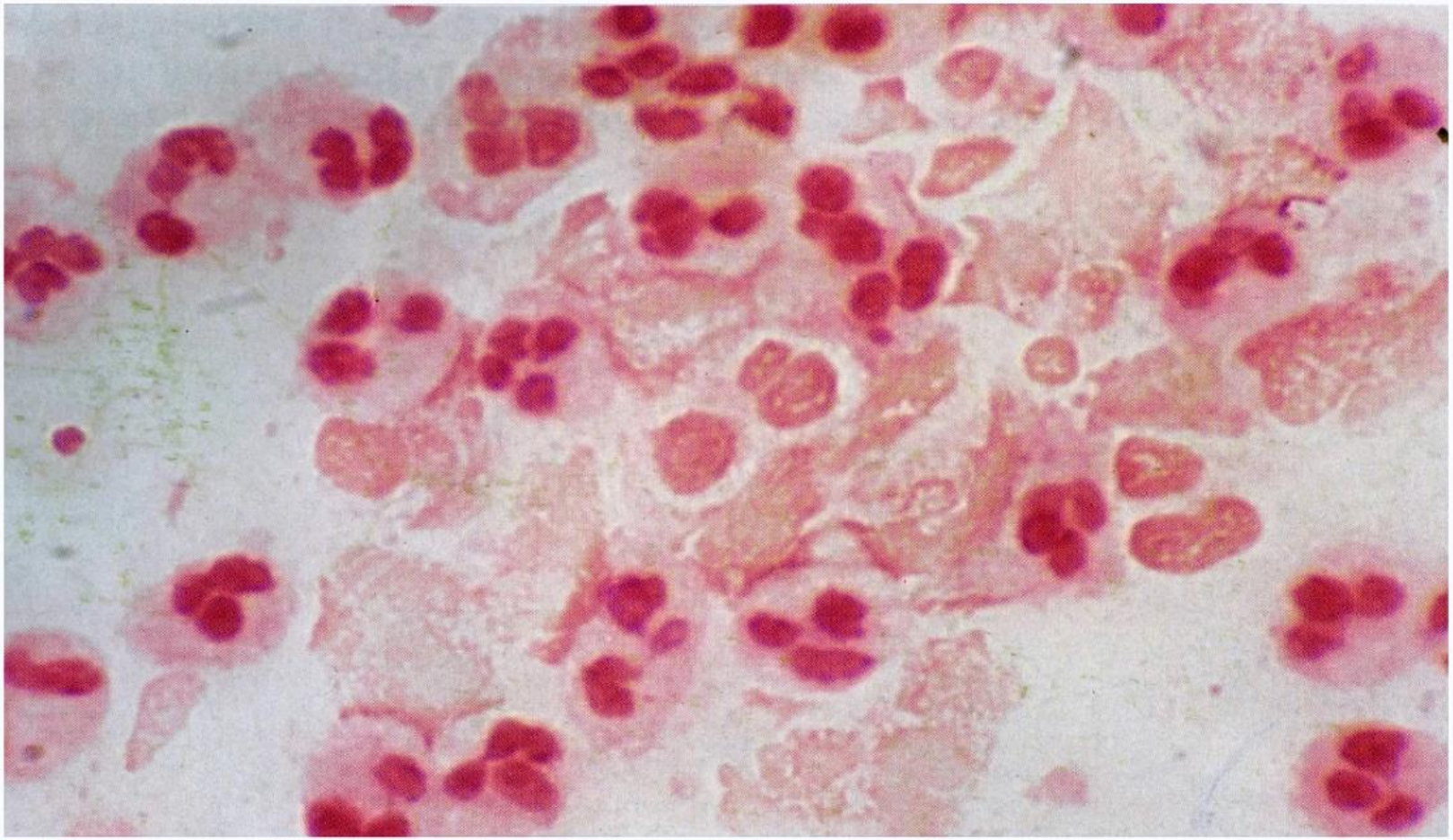
Drug resistance monitoring:

- European Gonococcal Antimicrobial Surveillance Programme- Euro-GASP (ECDC)
- Gonococcal Isolate Surveillance Project -GISP- (CDC)

If necessary, new therapeutic recommendations

Nongonococcal urethritis

NGU



- **Chlamydia** is the most frequently reported STI in Europe, accounting for the majority of all reported STI.

- In 2019, over 350 000 cases of chlamydia were reported in 24 EU/EEA Member States, an overall rate of 186 per 100 000 population.

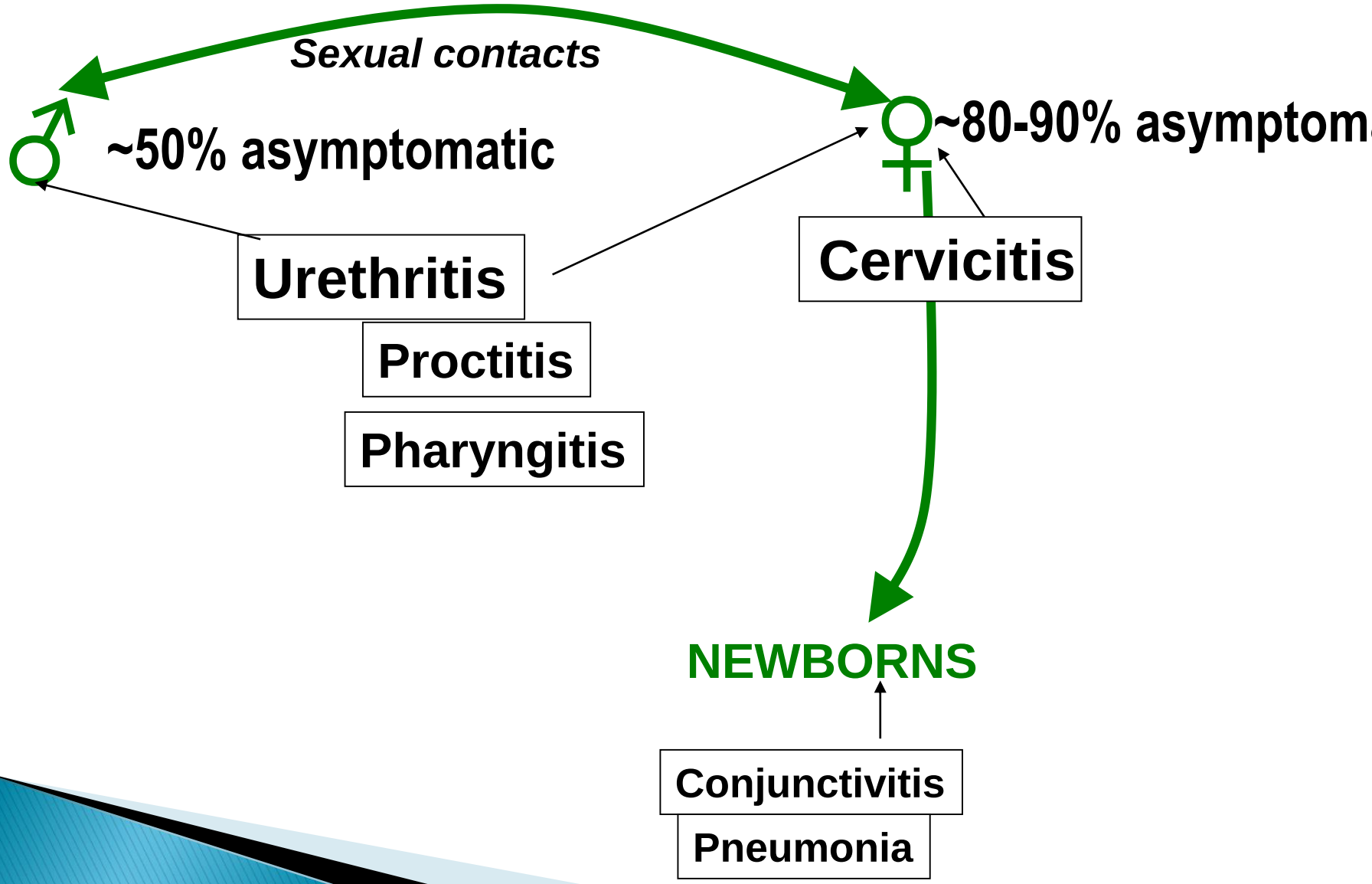
Chlamydia was reported more often in women than in men, with an overall rate of 203 per 100 000 in women and 145 per 100 000 in men.

The true incidence of chlamydia is likely to be considerably higher than reported here.

Three quarters (75%) of all **chlamydia** cases were reported in **young people between 15 and 24** years of age, with the highest rates reported among women aged 15 to 19 years

Overall trends over time in the various countries show a general increase

CHLAMYDIOSIS



NGU - Incubation time: 3- 5- 7 weeks !!!

women	men	newborn	children
cervicitis		conjunctivits	vaginitis
urethritis	urethritis	rhinopharyn-gitis	urethritis
proctitis	proctitis	pneumonia neonatorum	proctitis
oropharyngitis	oropharyngitis	otitis media	oropharyngitis

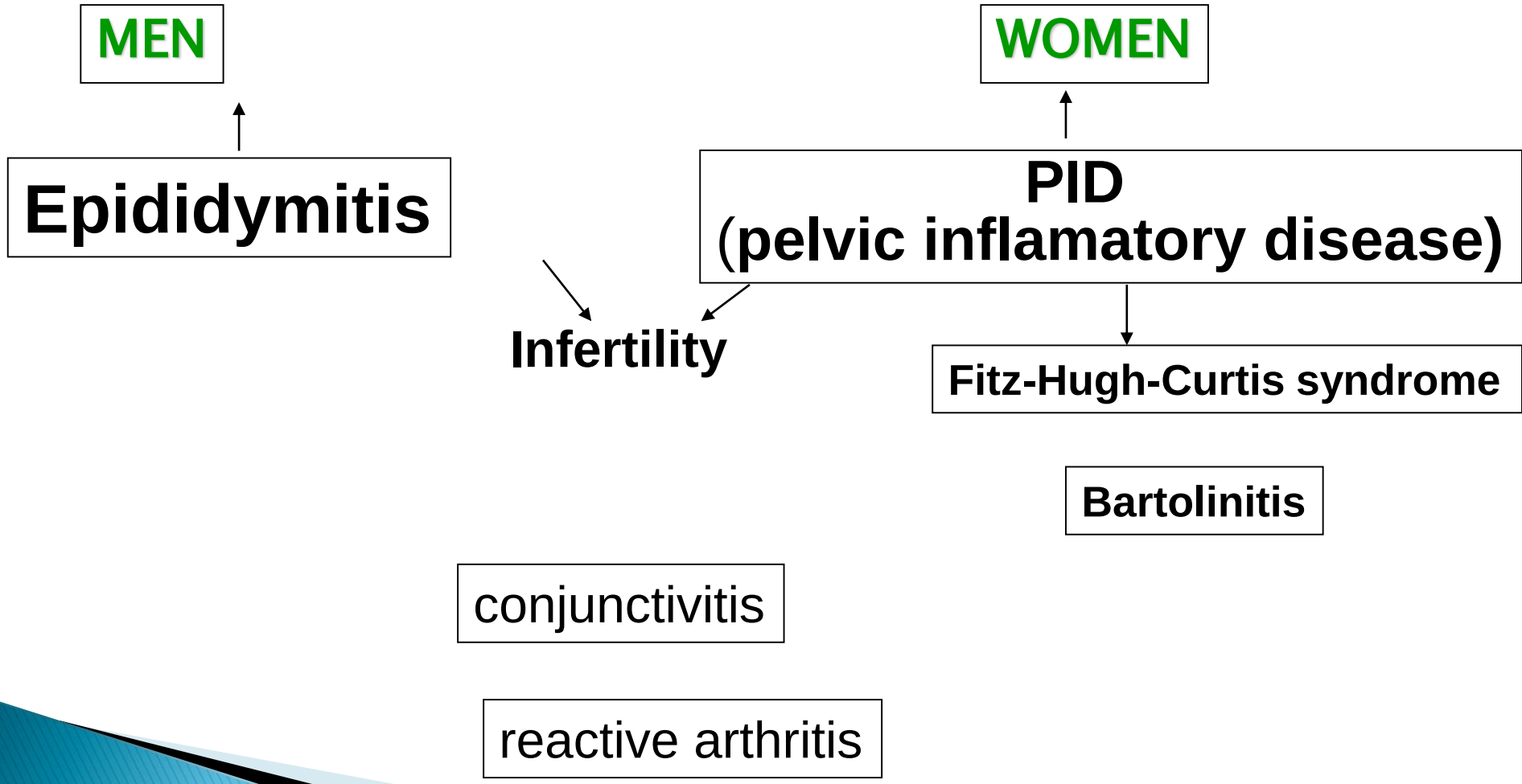
Chlamydia trachomatis is the most common bacterial cause of sexually transmitted genital infections.

The majority of affected persons are asymptomatic and, thus, provide an ongoing reservoir for infection.

In infants born to mothers through an infected birth canal, conjunctivitis and pneumonia can occur.

Moreover, both men and women can experience clinical syndromes due to infection at common epithelial sites, including the rectum and conjunctivae.

COMPLICATIONS COMMON TO INFECTIONS WITH N. GONORRHOEAE AND C. TRACHOMATIS



Complications in pregnant women

- Abortus — Chlamydia trachomatis
- Graviditas extrauterina — Neiseria gonorrhoeae; Chlamydia trachomatis

Complications of Chlamydia infection

Perihepatitis (Fitz-Hugh-Curtis syndrome) — Occasionally, patients with chlamydia infection develop perihepatitis, an inflammation of the liver capsule and adjacent peritoneal surfaces.

Perihepatitis is more commonly seen in the setting of acute PID, occurring in 5 to up to 15 percent of cases. It is associated with right-upper quadrant pain or pleuritic pain, but there are typically no liver enzyme abnormalities.

may give symptoms of acute abdomen
Less commonly, it may be a complication of gonorrhea

SARA (sexually acquired reactive arthritis)/ and Reiter's syndrome.

These terms are not exact synonyms.
Reiter's syndrome: the classic triad of symptoms - urethritis, conjunctivitis and arthritis – which he associated with *C. trachomatis* infection and some intestinal bacteria infections

SARA refers to sexually transmitted infections mainly with *C. trachomatis* but also *N. gonorrhoeae* and possibly mycoplasmas.
The syndrome is more common in men and in people who have HLA-B27.

Other symptoms include tendon sheath and adhesion inflammation, low back pain, vulvar or acuminous papulitis, psoriasis-like skin lesions, keratoderma blennorrhagica, nail dystrophy, oral lesions, erosions, geographic tongue, fever, weight loss, cardiac and nephrologic disorders, and others.

REITER'S SYNDROME

- HLA-B 27, **More frequent in men**

Triada:

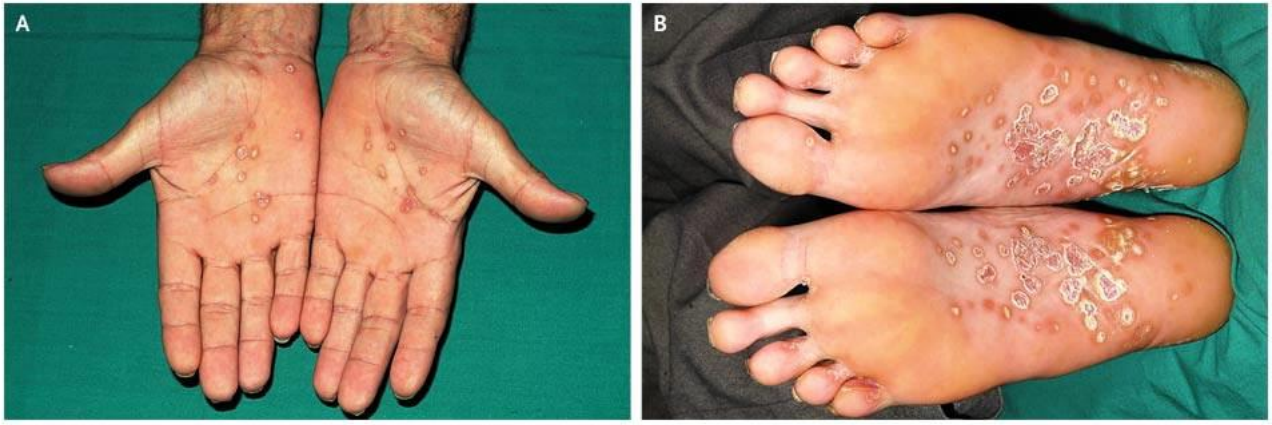
- urethritis,
- arthritis,
- conjunctivitis, and

- balanitis circinata/vulvitis circinata
- Erosions on oral mucosa

Arthritis

Conjunctivitis

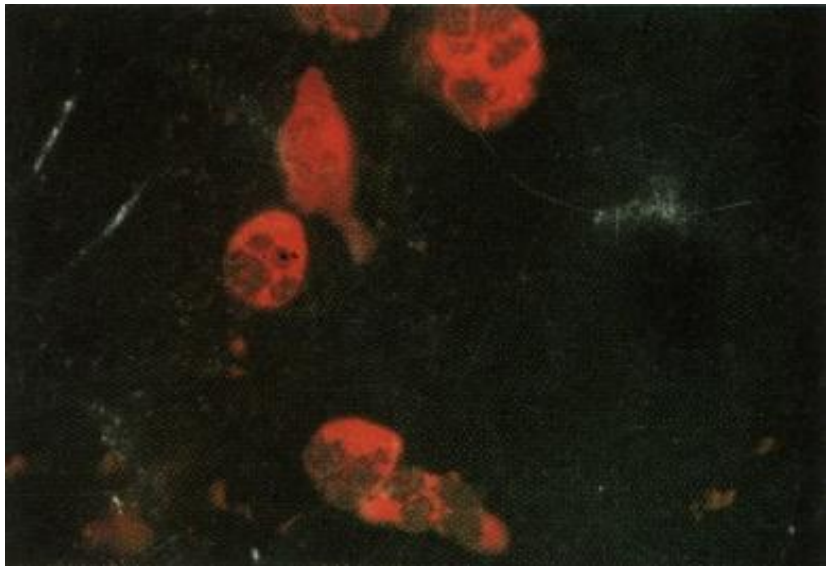
keratoderma blennorrhagica

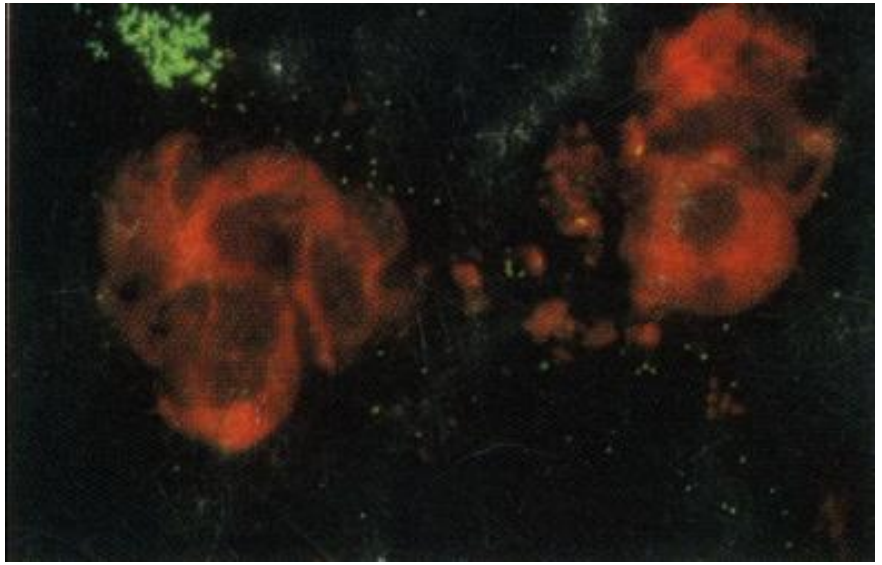


balanitis

DIAGNOSTICS OF CHLAMYDIOSIS(D-K types of C. trachomatis)

- NAATs (mostly real time PCR)
- Direct immunofluorescence
- Culture
- Blood antibody testing is not recommended (except for IgM testing in newborns with pneumonia)





- Documentation of chlamydial infection as the etiology of NGU **is essential** because of the need for partner referral for evaluation and treatment to prevent complications of chlamydia, especially in female partners.

Complications of *C. trachomatis*–associated

- NGU among males include epididymitis, prostatitis, and reactive arthritis.

Treatment of *Chlamydia trachomatis* infections

- **Doxycycline 2 x 100 mg/day (7–10 days)**

OR
Azithromycin 1 g orally in a single dose
OR
Erythromycin 500 mg twice a day for7 days
OR
Levofloxacin 500 mg orally once daily for 7 days
OR
Ofloxacin 200 mg twice a day for 7 days
OR
Amoxicillin 500 mg three times a day for 7 days

Recommended Regimens if *M. genitalium* Resistance Testing is Available (CDC)

- If *macrolide sensitive:* **Doxycycline** 100 mg orally 2 times/day for 7 days, followed by **azithromycin** 1 g orally initial dose, followed by 500 mg orally once daily for 3 additional days (2.5 g total)
- **If macrolide resistant: Doxycycline** 100 mg orally 2 times/day for 7 days followed by **moxifloxacin** 400 mg orally once daily for 7 days

Recommended treatment for uncomplicated *M. genitalium* infection (IUSTI)

- **in the absence of macrolide resistance mutations or resistance testing**
- Azithromycin 500 mg on day one, then 250 mg od days 2–5 (oral)
- Josamycin 500 mg 3 times daily for 10 days (oral)

- **in the presence of macrolide resistance mutations**
- Moxifloxacin 400 mg od for 7 days (oral)

- **after azithromycin treatment failture**
- Moxifloxacin 400 mg od for 7 days (oral)

TRICHOMONIASIS

women

Intensive discharge

Erythema and edema of vaginal mucosa

Men

Frequently asymptomatic!!!

urethritis –in alcoholics

balanoposthitis

phimosis

epididymitis

Diagnostics

- Microscope preparation (fast, but relatively low sensitivity -45-60%)
- Point-of-care tests
- Culture
- NAATs (mostly real time PCR)

Trichomoniasis - treatment

- Tinidazolum 4 tab. 500 mg (single dose)

- Metronidazole 2 x 250 mg/day (10 days)
- + intravaginal tabs. a 500mg (women)

GARDNELLOSIS

Women

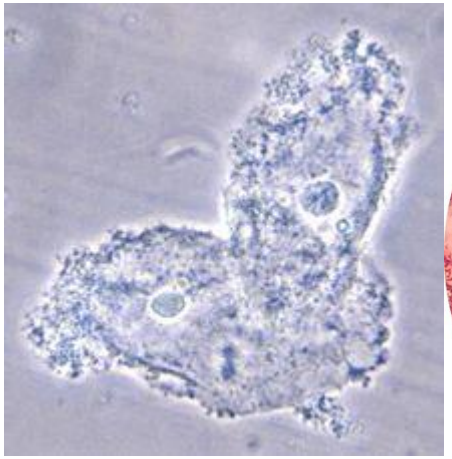
Discharge, disuria (characteristic „fish-like smell”)

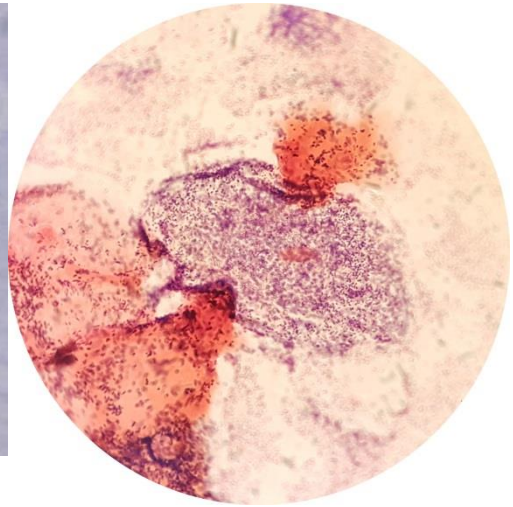
Men

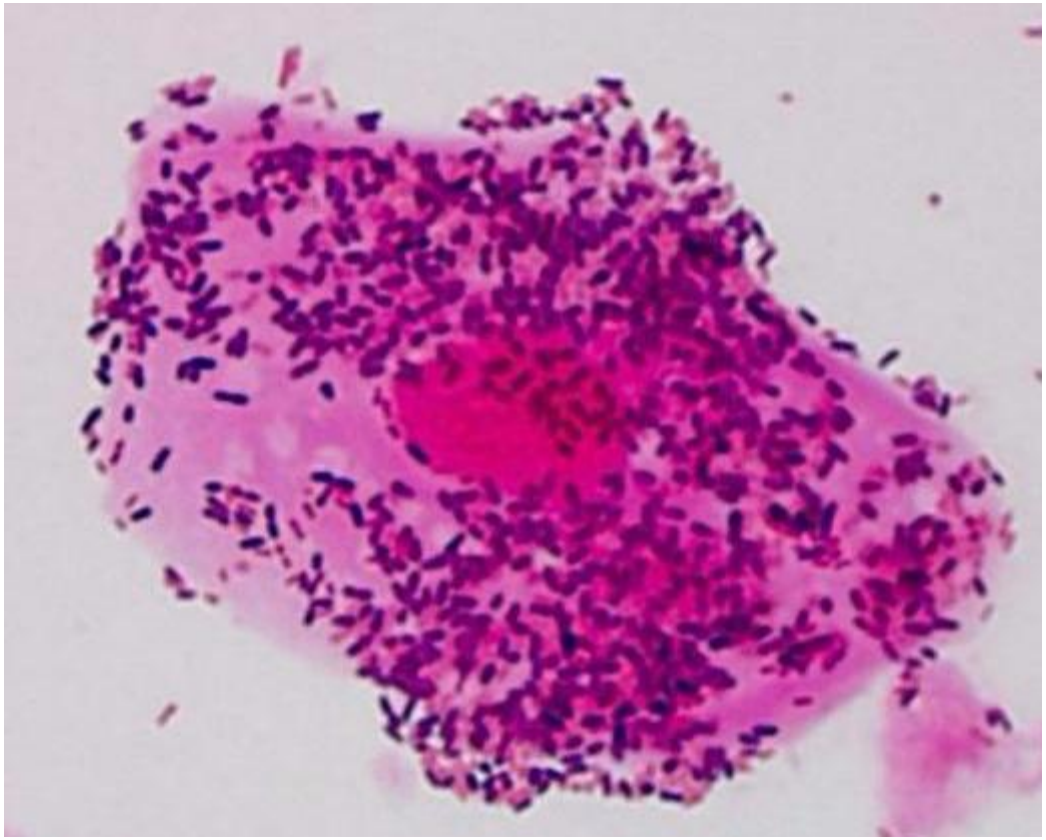
Typical symptoms of NGU

Diagnostics

- **Microscope preparation – the best method**
- NAATs
- Others?







Gardnellosis -treatment

- Metronidazole 2 x 250 mg/day (for10 days)
- + intravaginal tablets a 500mg (women)

- 2 % cream with clindamycin) – intravaginal (7 days)