PID: presentation, pathogens, problems and ping-pong

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The referral . . .

Dear Dr Oanji,

Please review this lovely 21 year old woman. She has recent onset lower abdominal pain ?endometriosis, family history of same.

Otherwise well.

No significant past medical history.

No meds, NKDA.

Kind regards,

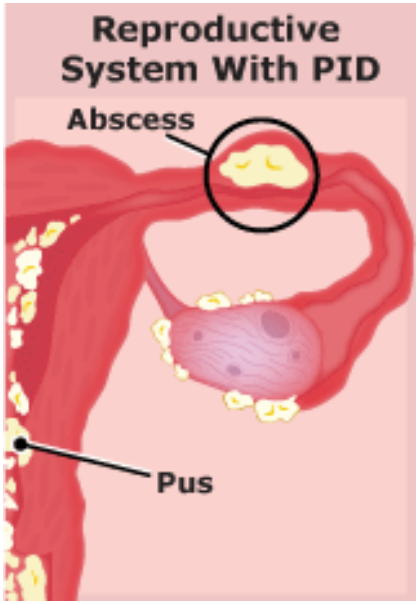
Sally

What do we want to know?

What testing will you do?

What is PID?

- Inflammatory disorder affecting upper female genital tract including:
  - Salpingitis
    - Most important feature
  - Endometritis
  - Tubo-ovarian abscess
  - Pelvic peritonitis
- Caused by micro-organisms which ascend from the cervix or vagina

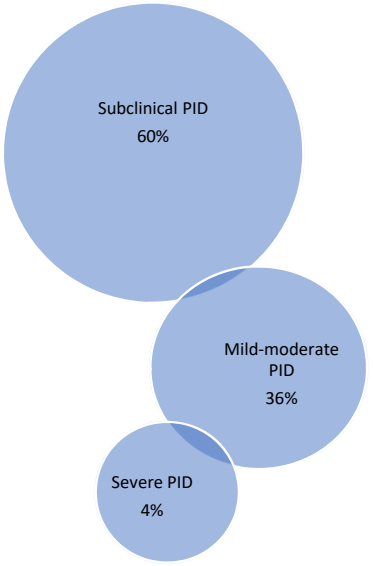


How common is PID?

- Highest incidence in ages 20-29
- 10,000 women treated for PID in Australian hospitals annually
  - 10-30x more treated as outpatients
- About 2/3 of cases remain undiagnosed
- 30-75% of infertile women with post-infection tubal obstruction report no history of PID
  - Indicates subclinical infection accounts for majority of PID and tubal infertility

Presentation of PID

- Lower pelvic pain
  - Bilateral or localised
- Deep dyspareunia
- Vaginal/cervical discharge
- Irregular vaginal bleeding
  - Intermenstrual, post-coital, menorrhagia (new)
- Dysuria
- Systemic symptoms
  - Fever, nausea, vomiting
- Right upper quadrant pain



Discharge in chlamydial cervicitis

Extra-genital and intra-abdominal infection

- NG and CT may enter abdominal cavity and cause inflammation of serosal surfaces
- Peri-appendicitis
  - Serositis, not involving intestinal mucosa
  - 1-15% of acute appendicitis
- Peri-hepatitis
  - Fitz-Hugh Curtis syndrome
  - Occurs in 5-15% of acute salpingitis
  - Acute, severe pleuritic RUQ abdominal pain
  - Inflammation of liver capsule and adjacent peritoneum
  - Normal liver parenchyma
  - Normal liver enzymes

PID presentation in pregnancy

- Not common as cervical mucous plug and decidua form a barrier that protects the uterus from ascending bacteria
- Therefore tends to occur only in 1st trimester
- Women do have new/other partners during pregnancy and early post-partum!

DDx acute pelvic pain

Positive pregnancy test

- Ectopic pregnancy
- Miscarriage
- Corpus luteal haemorrhage

Negative pregnancy test

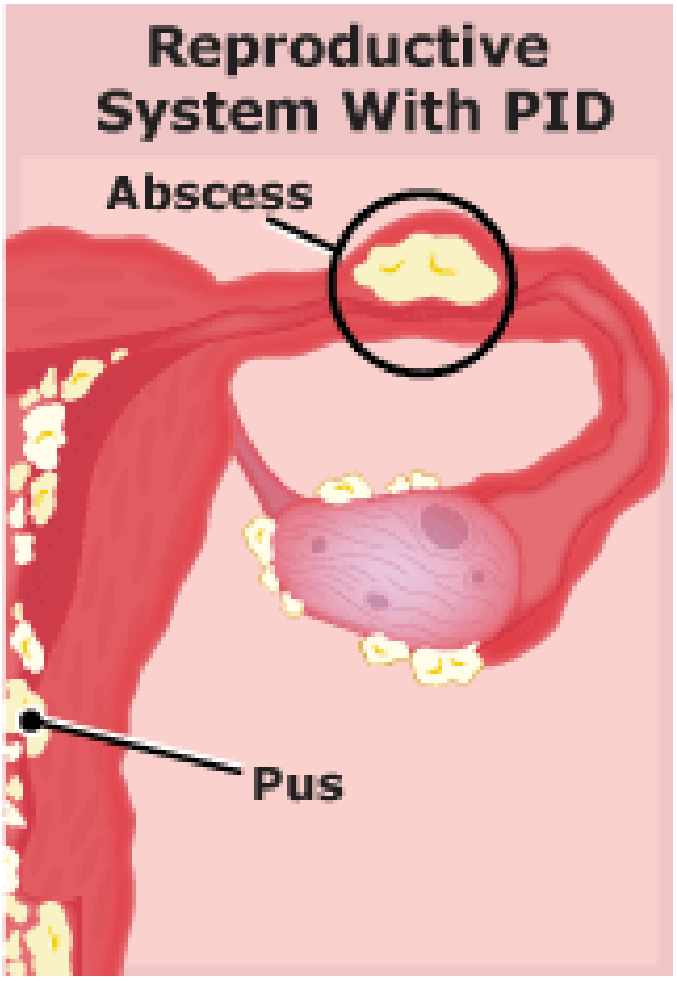
- Gynaecologic Causes:
  - PID/endometritis
  - Ovarian cyst accidents/torsion
  - Endometriosis – acute flare
  - Degenerating fibroids
  - Mittelschmerz/dysmenorrhoea
- Non-Gynaecologic Causes:
  - Appendicitis
  - Acute cystitis
  - Diverticulitis
  - Urinary tract calculi
  - Abdominal wall trauma

Causes of PID

Neisseria gonorrhoea (NG)

Chlamydia trachomatis (CT)

Mycoplasma genitalium (MG)

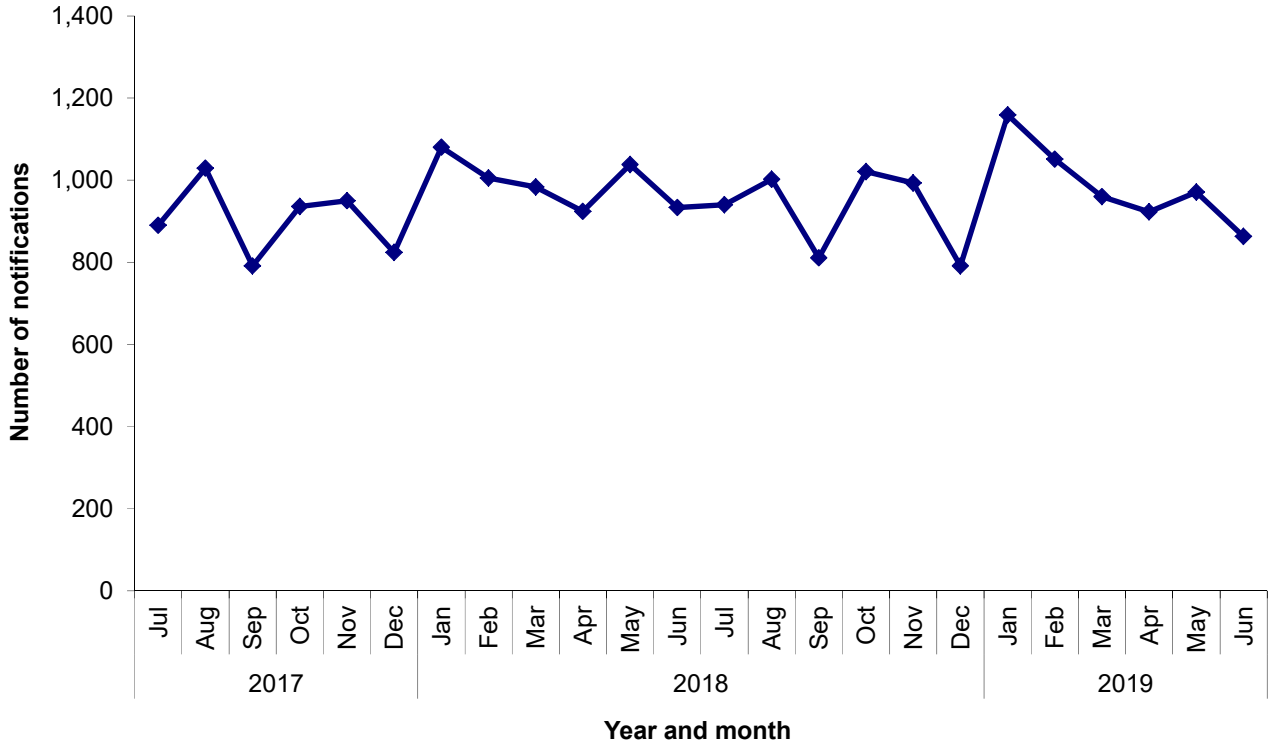


BVAB/polymicrobial

Herpes simplex virus (HSV)

Other –TV, TB, HI, Strep, etc

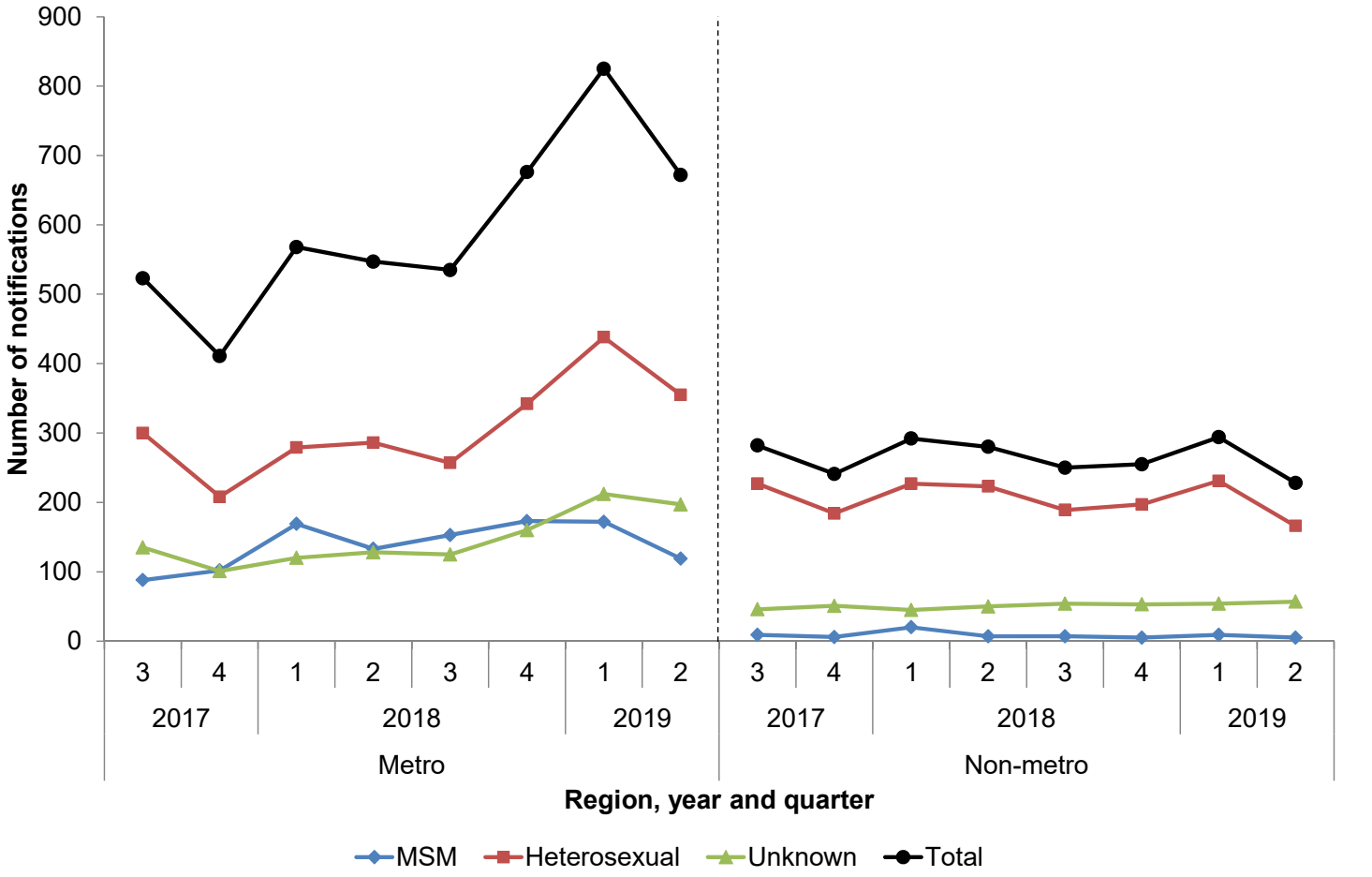
Chlamydia notifications, WA (2017-2019)



Chlamydia trachomatis PID

- CT salpingitis usually mild clinical manifestations with severe tubal disease
- Affects same population as uncomplicated cervical CT
  - Peak in sexually active teenagers
- Most common STI so causes most PID (~1/3 of all cases)
- ~15% of cervical CT ascends to cause PID
- 20-30% of patients with cervical CT have NG co-infection and vice versa

Gonorrhoea notifications by sexual identity (WA), 2017-2019



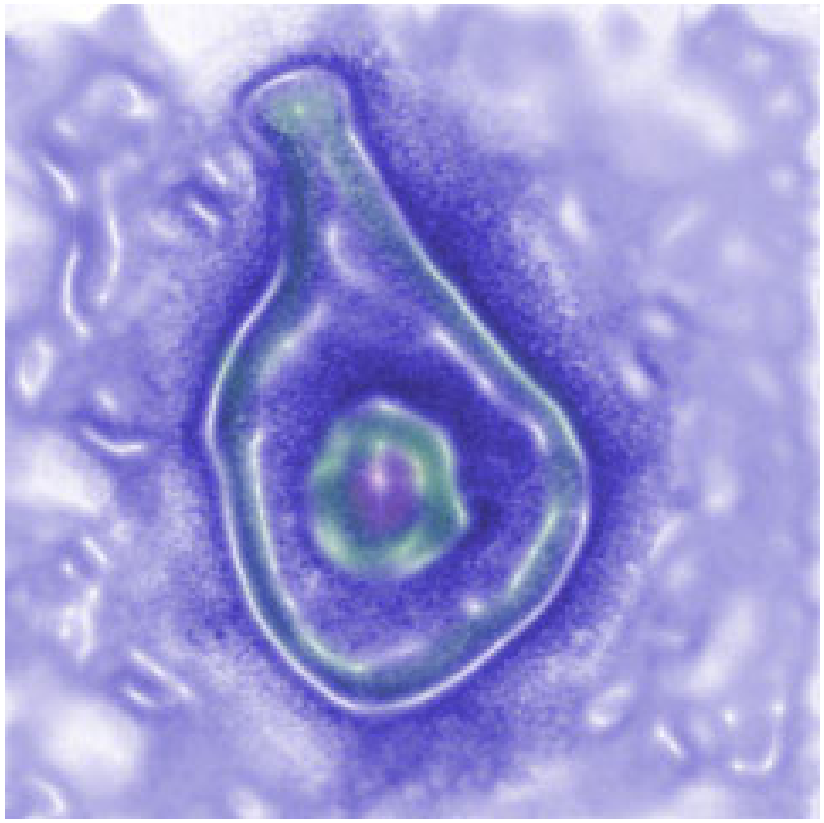
Source: Immunisation, Surveillance and Disease Control Program, Communicable Disease Control Directorate (CDCD)

Neisseria gonorrhoea PID

- ‘Classic’ bacterial cause of PID
- Causes tubal cilia damage due to cytotoxic effect of gonococcal endotoxin
- 10-19% of women with NG in cervix have clinical signs of acute PID
  - Rate of NG isolation from UGT is inversely related to duration of symptoms
- Pain onset occurs in first part of menstrual cycle
  - Rapid ascent of NG into UGT after cervical mucous is lost with menses
- UGT involvement causes severe symptoms with mild tubal disease

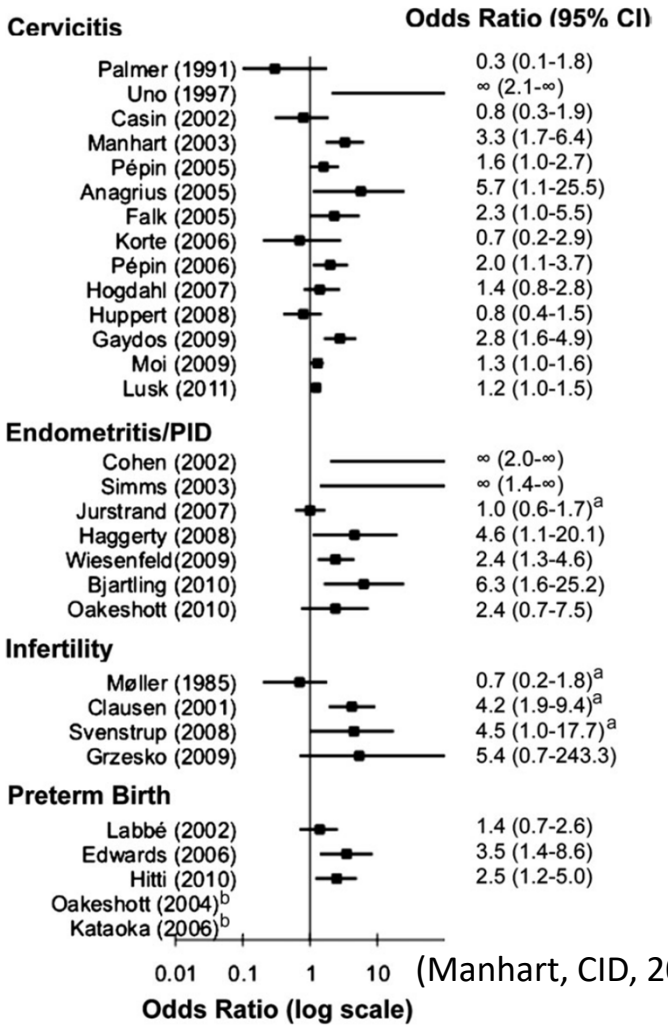
Mycoplasma genitalium

- Smallest self-replicating organism known (580kb)
- Fastidious growth requirements
- Difficult to culture
- Bottle-shape with terminal rod-like structure
- Gliding motility
- Adheres via an attachment (adhesin) protein
- Invades epithelial cells with nuclear localization
- Intracellular location might protect from immune response and antibiotics



Evidence of MG-related female disease

- Cervicitis
- Urethritis
- PID
- Tubal Factor Infertility (TFI)
- Obstetric outcomes



(Manhart, CID, 2011)

Other organisms

- Other organisms can be isolated in presence or absence of STIs

- Bacterial vaginosis
  - Anaerobic organisms
  - Normal vaginal flora in higher concentrations
  - Cervicitis with BV associated with absence of H_2O_2 producing Lactobacillus
  - May increase susceptibility of cervix and UGT to bacterial invasion
  - Higher risk post-procedural PID
  - Greater risk in increased frequency of intercourse

- Associated with severe suppurative disease, recurrent PID and tubo-ovarian abscess

No identified causes of PID

- 20-70% have unidentified cause
  - Commonly in:
    - Older women
    - Longer duration of pelvic pain
    - Mild inflammation on laparoscopy

- Many organisms can’t be cultured, only identifiable by DNA techniques

Risk factors

- Post gynaecological surgical procedures
  - Precedes onset of PID in up to 12%
- Puerperal infections
- IUDs
  - increases risk of developing PID but only for 4-6 weeks after insertion. This risk is probably highest in women with pre-existing gonorrhoea or *C. trachomatis*. TEST.
- Douching and BV
  - Upsets vaginal ecology and enhances bacterial invasion of uterus ?mechanism

Diagnosis

- Combination of clinical and laboratory findings
- Speculum examination and STI testing
  - Urine and ECS for PCR CT/NG/MG
  - HVS and ECS for MCS
  - Consider TV NAAT (FVU)
- Bimanual examination
  - Cervical excitation – sens 95%, spec 74%
  - Adnexal/uterine tenderness or mass – sens 48%, spec 75%
  - Absence of pain has high negative predictive value
- Urine pregnancy test
- Urinalysis +- MSU
- Pelvic ultrasound

Speculum examination & STI testing

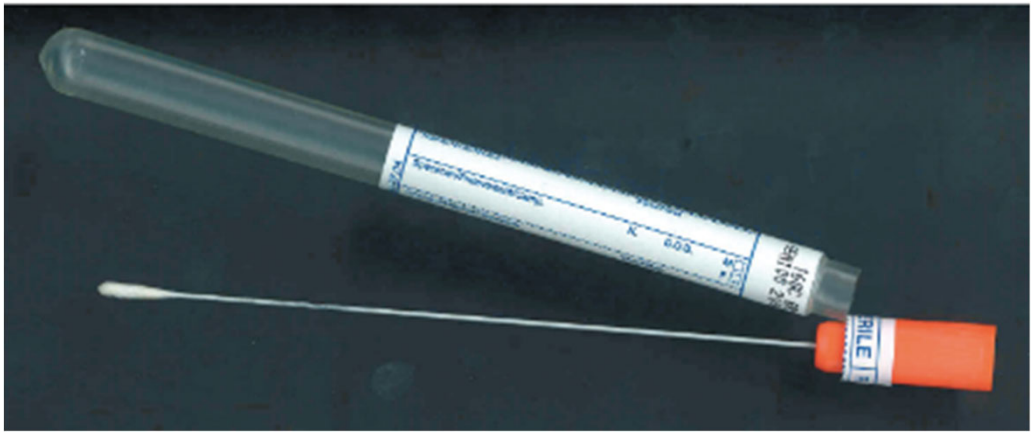
- Speculum examination and STI testing
  - ECS PCR CT/NG + ECS PCR MG (including resistance testing)

  - HVS and ECS for MCS
  - >30 WBC per high powered field – sens 87%, spec 38% for PID
  - WCC also gives information about BVAB & gonorrhoea sensitivities

- Consider TV NAAT (FVU) if high risk group

Testing for chlamydia, gonorrhoea and mycoplasma genitalium?

- **E**ndo**c**ervical **S**wab (ECS) (SOLVS OK)
- Consider **F**irst **V**oid **U**rine (FVU) if urethral symptoms



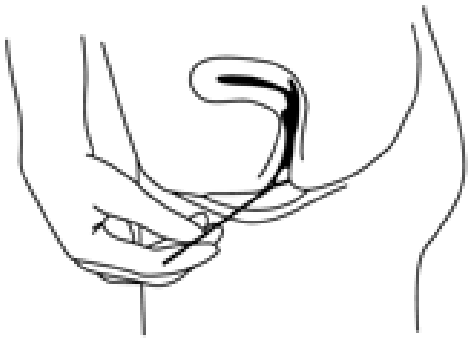
Gonorrhoea: what tests are available?

- PCR NG: detects gonorrhoea DNA
  - Some cross-reactive spp so laboratories do supplemental testing with different targets to make sure true NG infection

- MCS: used for antibiotic sensitivities/resistance

This is how to take your own swab for a SOLVS PCR test

Put the tip of the cotton swab stick about 2 cm (length of one finger joint) inside your vagina. Turn the swab around once.



Count to ten whilst leaving the cotton swab stick in the vagina.

Bimanual examination

- Cervical motion tenderness on bimanual examination (with or without palpable mass), uterine and adnexal tenderness
    - Cervical excitation – sens 95%, spec 74%
    - Adnexal/uterine tenderness or mass – sens 48%, spec 75%
    - Absence of pain has high negative predictive value

Imaging

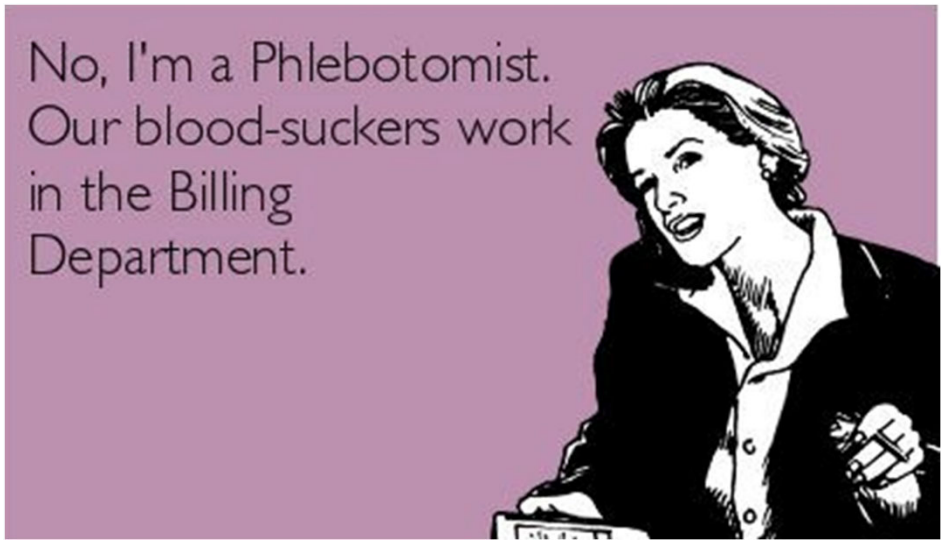
- Transvaginal ultrasound scanning if diagnostic uncertain
  - but frequently normal in early or uncomplicated disease
  - if done with power Doppler can identify inflamed and dilated tubes and tubo-ovarian masses / abscesses
  - may differentiate some cases from appendicitis, ectopics or ovarian cyst complications
  - insufficient evidence to support routine use
- CT may be indicated in patients with diffuse pelvic pain, peritonitis or equivocal ultrasound
- MRI has shown to be superior to TVUS in the diagnosis of PID but cost and availability are prohibitive.

KEMH Guidelines for Management of Acute PID, 2020

Other STI testing: BBV Serology

- Offer
  - HIV
  - HBV
  - Syphilis
  - HCV if IVDU (HCV RNA viral load if past infection)

- Inform re window periods



Other STI testing: Gonorrhoea/Chlamydia

- <u>High-risk women (eg SIWs):</u>

  Consider extragenital testing (thr/rec)

- <u>Asymptomatic women or those who refuse exam:</u>

  SOLVS

Presumptive Diagnosis

Clinical

- Cervical motion tenderness +/-
- Uterine tenderness +/-
- Adnexal tenderness
- Temp >38^{o}C
- Abnormal cervical discharge
- Pelvic abscess on bimanual exam

+

Laboratory

- ECS with gram –ve diplococci
- Positive CT/MG/NG PCR test
- Leucocytosis >11x10^{9}/L
- Elevated CRP or ESR

‘Definitive’ Diagnosis

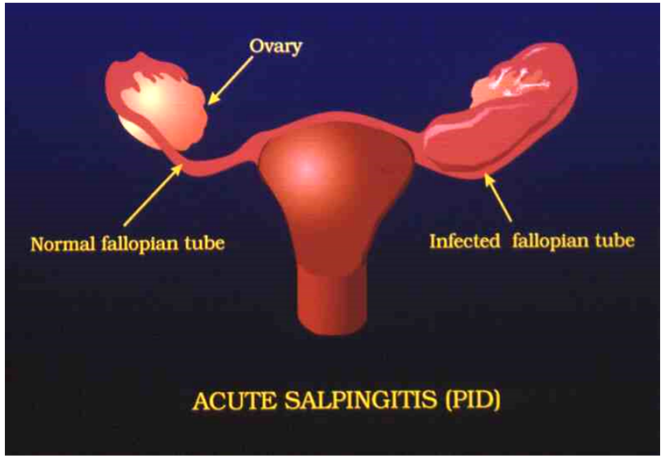
- Histopathologic evidence of endometritis on endometrial biopsy
- Thickened, fluid-filled fallopian tubes +/- free pelvic fluid or tubo-ovarian complex on transvaginal ultrasound
- Laparoscopy – Sensitivity ~50%, specificity ~100%. Good for confirming the dx of PID but not sensitive enough to be considered a diagnostic gold standard. Useful if:
  - sick patient with high suspicion of competing dx (eg appendicitis)
  - acutely ill patient who has failed outpatient Rx for PID
  - any patient not clearly improving after 72hrs inpatient Rx for PID.

PID: Why bother?

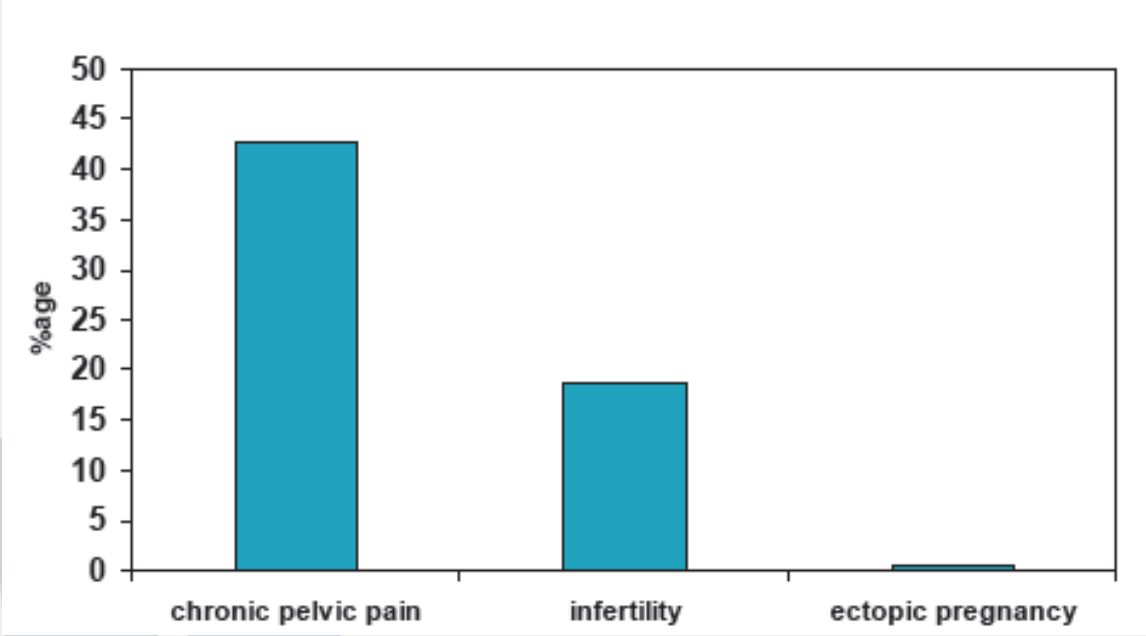
- PID and infertility
  - 15-20% of gonorrhoea infections develop PID
  - 8-10% chlamydia infections develop PID (worse with repeat infections)
  - 10-15% of those with PID have tubal infertility
  - More likely with increased no. episodes, increased severity, delay health care/Rx, copper IUD.

- PID and ectopic pregnancy
  - 7% risk after one episode PID
  - 15% after 2 and 40% with >2

- Chronic pelvic pain (CPP)
  - 30-40% develop CPP



PID complications after 7 years



Ness *Obstet Gynecol* 2005;106:573

Risk increases with time to treatment

How do we prevent complications?

- Screen asymptomatic women
- Treat early
- Avoid infections – treat partners, use condoms . . .

Empiric Therapy…

- Clinical symptoms and signs lack sensitivity and specificity
  - the positive predictive value of a clinical diagnosis is 65-90% compared to laparoscopic diagnosis.

- Early empiric therapy important due to sequelae of delayed diagnosis

Treatment

- Often empirical
  - Cover most frequently expected organisms
- Reduced rate of tubal infertility if given within 3 days of symptoms onset
- Elimination of signs and symptoms of infection in short term
- Reduction of risk of tubal damage in long term

australian STI MANAGEMENT GUIDELINES
FOR USE IN PRIMARY CARE

ASHA AUSTRALASIAN SEXUAL HEALTH ALLIANCE

How to use these Guidelines?

All STIs can cause disease without producing symptoms. Please refer to Populations & Situations for asymptomatic screening recommendations, Syndromes for guidance about managing specific clinical scenarios and to STIs for specific management of a diagnosed infection.

Latest Update

2016: Annual Critical Review Complete - what's changed?

Guidelines index

STI

- Chancroid
- Chlamydia
- Donovanosis
- Ectoparasites
- Genital warts
- Gonorrhoea
- Hepatitis A
- Hepatitis B
- Herpes
- HIV

SYNDROME

- Ano-genital Lumps
- Ano-genital Ulcers
- Ano-rectal Syndromes
- Cervicitis
- Epididymo-orchitis
- PID - Pelvic inflammatory disease
- Skin rash - generalised
- Skin rash - genital
- Urethritis - male

POPULATIONS & SITUATIONS

- Aboriginal and Torres Strait Islander People
- Adult Sexual Assault
- MSM - Men who have sex with men
- People in correctional facilities
- PLWHIV - People living with HIV
- Pregnant women
- PWID - People who inject drugs
- Refugees (and newly arrived

Australian STI guidelines: major changes 2018

- Major changes to management of:
  - *Mycoplasma genitalium*
  - Urethritis
  - Cervicitis
  - PID
  - Anorectal syndromes

PID

Mild to moderate: Outpatient treatment	Ceftriaxone 500mg in 2mL of 1% lignocaine IMI, or 500 mg IV, stat PLUS Metronidazole 400mg PO, BD for 14 days PLUS Doxycycline 100mg PO, BD for 14 days
Severe Inpatient treatment	Ceftriaxone 2g IV, daily OR Cefotaxime 2g IV, TDS PLUS Azithromycin 500mg IV, daily PLUS Metronidazole 500mg IV, BD

* If M.genitalium confirmed 2 weeks of Moxifloxacin 400mg daily for 14 days

Role of azithromycin?

- Azithromycin removed from Australian STI guidelines because
  - Supports subsequent M Gen. treatment
  - Rising rates of MG resistance suggest caution with unnecessary macrolide exposure when NG not confirmed

- Azithromycin 1g orally can be used as a single dose for women who are pregnant or suspected to be non- adherent to doxycycline, then Azithromycin 1g orally as a single dose 1 week later

Metronidazole??

- Metronidazole is included in some regimens to improve coverage for anaerobes although no data to show this is superior to regimens without.
- These are of relatively greater importance in patients with severe PID
- In fact, excellent clinical cure rates among women with mild to moderate PID with several regimens without dedicated anaerobic coverage (eg, ceftriaxone plus doxycycline). However, the long-term effects of not directly targeting anaerobic organisms is unknown.
- Most guidelines suggest metronidazole can be discontinued in patients with mild or moderate PID who are unable to tolerate it.

Background to STI management changes

- Increasing M gen resistance to azithromycin in Aus; 80% MSM, 50% heterosexuals
- Higher bacterial loads more likely to result in resistance, hence using doxycycline for 1/52 first to reduce load
- Similarly, if urethritis symptoms with CT, implies higher bacterial load
  - Doxy is 7% better at treating symptomatic urethritis than azith (Kong CID 2014)
- Estimated up to 70% of women are also infected in rectum (autoinoculation) and doxy is better for rectal infections (99% vs 83% with azith) (Rank RG Infect Immune 2014)

Doxycycline treatment efficacy

Study (yr)	Population	Regimen	Eradication Rate, % (n)
Anagrius (2013)	N=304,Sweden (1998-2005)	Doxy 200mg stat then 100mg 8/7	43% (73/171)
Manhart (2013)	N=422, USA (2007-2010)	Doxy 100mg bd 14/7	30% (157/206)
Schwebke (2011)	N=305, USA (2006-2009)	Doxy 100mg bd 7/7 (+/- Tinidazole 2g)	31% (12/39)
Mena (2009)	N=398, USA (2002-2004)	Doxy 100mg bd 7/7	45% (14/31)
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Azithromycin treatment efficacy

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Couldwell (2013)	N=33, Aust, 2008-2011	AZM 1g stat	46% (12/26)	
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Mycoplasma genitalium

- Asymptomatic screening not recommended
- Testing recommended in urethritis, cervicitis, PID and contacts of an MG index case
- Concurrent macrolide sensitivity testing recommended
  - Available with ACL, Clinipath, Pathwest and soon Westerns,
- Treat urethritis, cervicitis and proctitis with 1/52 doxycycline 100mg bd and test for MG. Add azithromycin/moxifloxacin as dictated by sensitivity testing.
- Other MG-infected patients (eg sexual partners) are also pre-treated with doxycycline which lowers the bacterial load, increasing the likelihood of cure with a second antibiotic. Doxycycline alone only cures 30% of infections.

Mycoplasma genitalium

Situation	Treatment recommendation	Alternative
M. gen infection known or suspected to be macrolide-susceptible	Doxycycline 100mg bd for 7 days FOLLOWED BY Azithromycin 1g stat then 500mg daily for three days (total 2.5g)*	Doxycycline 100mg bd for 7 days FOLLOWED BY Azithromycin 1g single dose*
M. gen infection known or suspected to be macrolide-resistant	Doxycycline 100mg bd for 7 days FOLLOWED BY Moxifloxacin 400mg daily for 7 days	
Pelvic inflammatory disease due to *M.gen*	Moxifloxacin 400mg daily for 14 days**	

***M. genitalium* results are often received about a week after PID treatment has begun. After a good response to treatment it may be reasonable to shorten the course of moxifloxacin to ten days, due to the cost and potential toxicity of this drug, however this has not been studied. Also, Doxycycline and Metronidazole can be ceased at one week if *M. genitalium* is the only pathogen detected.

M Gen – Other treatment options

- Pristinamycin (streptogramin, bacteriostatic (not cidal), safe in pregnancy and breastfeeding, some GI toxicity
  - 2gm daily (500mg qid). Used with doxycycline 100mg bd for 10/7

- Sitafloxacin (fluoroquinolone)– 100mg bd for 7-14 days (pre-treat with doxycycline). GI SFx (12% diarrhoea and 5% tendon/joint pain), hard to get.

- Spectinomycin (aminoglycoside, easy to get in Europe/UK, 2gm IMI daily for 7/7, painful, expensive ($700).

- Solithromycin – 1200mg daily, affected by macrolide resistance. Will need longer duration and combo regimen. Not available in Aust.

Cervicitis

Situation	Recommended treatment	alternative
Unknown organism	Doxycycline 100mg PO, BD for 7 days	Azithromycin 1g PO stat

- In the absence of a definitive causative organism, in a woman with increased risk of STI treat syndromically.
- Consider treatment for NG if patient is at risk, or in a community with high NG prevalence.
- If organism is known, see relevant STI guidelines for treatment recommendations

Revised chlamydia management 2018

Chlamydia:

Recommended	Alternative
Doxycycline 100mg PO, BD 7 days OR Azithromycin 1g PO, stat	

Treatment guidelines: Silver Book

Silver Book: Regional information

PRESENTATION	TREATMENT	NOTE
Signs and symptoms of *chlamydia* and/or *gonorrhoea*, acquired locally or in the Goldfields, Kimberley, Midwest or Pilbara region. GeneXpert point-of-care test not available.	"ZAP pack" (Amoxycillin 3 g, Probenecid 1 g and Azithromycin 1 g) prior to obtaining results	Single dose Directly observed therapy Do not wait for results before treating If patient has purulent discharge, take an MC&S swab for gonorrhoea culture in addition to urine/PCR swab
Signs and symptoms of *chlamydia* and/or *gonorrhoea*, acquired outside the Goldfields, Kimberley, Midwest or Pilbara region. GeneXpert point-of-care test not available.	"LAC pack" (Ceftriaxone 500 mg IMI in 2 mL of 1% lignocaine plus Azithromycin 1 g oral) prior to obtaining results	Single dose Directly observed therapy Do not wait for results before treating If patient has purulent discharge, take an MC&S swab for gonorrhoea culture in addition to urine/PCR swab
Positive laboratory or GeneXpert point-of-care test result of genital *gonorrhoea* and negative chlamydia result, acquired locally or in the Goldfields, Kimberley, Midwest or Pilbara region (if not already treated)	"ZAP pack" (Amoxycillin 3 g, Probenecid 1 g and Azithromycin 1 g	Single dose Directly observed therapy Send urine and/or PCR swab to PathWest for PCR testing of gonorrhoea for antibiotic sensitivities. If patient has purulent discharge take an MC&S swab for gonorrhoea culture in addition to urine/PCR swab.
Sexual partners of clients symptomatic of *chlamydia* and/or *gonorrhoea,* acquired locally or in in the Goldfields, Kimberley, Midwest or Pilbara	"ZAP pack" (Amoxycillin 3 g, Probenecid 1 g and Azithromycin 1 g) prior to obtaining results	Single dose Directly observed therapy Do not wait for results before treating

eTG guidelines – mild to mod PID

ceftriaxone 500 mg in 2 mL of 1% lidocaine intramuscularly, or 500 mg intravenously, as a single dose [Note 1]

PLUS

metronidazole 400 mg orally, 12-hourly for 14 days

PLUS EITHER

1. doxycycline 100 mg orally, 12-hourly for 14 days

OR for patients who are pregnant, breastfeeding [Note 2] or likely to be nonadherent to doxycycline

2. azithromycin 1 g orally, as a single dose, repeated 1 week later.

eTG – severe PID infection

1 ceftriaxone 2 g intravenously, daily; for adults with septic shock or requiring intensive care support, use 1 g intravenously, 12-hourly. See Modification and duration of therapy for severe PID

OR

1 cefotaxime 2 g intravenously, 8-hourly; for adults with septic shock or requiring intensive care support, use 2 g intravenously, 6-hourly. See Modification and duration of therapy for severe PID

PLUS (with either of the above drugs)

azithromycin 500 mg intravenously, daily; see Modification and duration of therapy for severe PID

PLUS

metronidazole 500 mg intravenously, 12-hourly; see Modification and duration of therapy for severe PID.

Management of acute PID

- *http://www.kemh.health.wa.gov.au/development/manuals/O&G_guidelines/sectionc/6/c6.pdf*

Management PID in pregnancy

- PID in pregnancy is uncommon but associated with an increase in both maternal and fetal morbidity, therefore parenteral therapy is advised although none of the suggested evidence based regimens have proven safety in this situation.

<u>For severe disease or pregnancy, KEMH recommends:</u>

- ceftriaxone 2g IV daily plus
- metronidazole 500mg IV 12 hourly plus
- azithromycin 500mg IV daily

Until the patient is afebrile and improved, then

- doxycycline 100mg 12 hourly orally for a minimum of two weeks and up to four weeks in complicated cases

(slow clinical resolution; pelvic collections) or Azithromycin if pregnant (1g po weekly)

plus

- amoxicillin plus clavulanate 875mg/125mg, orally, 12 hourly for a minimum of 2 weeks and up to 4 weeks

Management other STIs in pregnancy

- Doxycycline not recommended in pregnancy – can use repeat azithromycin as an alternative (eg chlamydia)
- Moxifloxacin is not recommended in pregnancy but is sometimes being used for MG cases. Recommended discussing with Micro KEMH. Don't test if you don't want to know!
- Pristinamycin has been used in pregnancy but little supporting data.
- Ceftriaxone is OK in pregnancy.

Removal of IUD?

- WHO guidelines state that there is no need to remove a copper IUCD in a patient with PID unless the patient requests removal
- Removal should occur after antibiotics have been commenced
- Emergency contraception may be required
- If PID worsens despite antibiotic therapy – remove the IUCD

Indications for admission

- Severe disease
  - Fever, peritonitis, tubo-ovarian abscess, nausea/vomiting
- Pregnancy
- Failure to respond to/tolerate/follow oral regimen
- Other surgical emergencies unable to be excluded
  - Appendicitis, ectopic pregnancy

HIV and PID

- Contrast is most marked amongst those with severe immune suppression
- Higher rate of abscesses
- Greater need for surgical intervention
- CDC recommends early hospitalisation and IV antibiotics

Gonorrhoea: treating urogenital infections

- Ceftriaxone 500mg IMI + azithromycin 1 gm stat po
  - eg contact NG or asymptomatic screen

- If patient presents with urethral discharge/NSU: may treat with ceftriaxone 500mg IMI + doxycycline 100mg bd for 1/52 (covers NG/CT/MG)

Gonorrhoea: treating throat infections

- Ceftriaxone 500mg IMI + 2gm azithromycin po stat

- Increased dose as pharynx common site for resistance + lower antibiotic penetration.

- Some controversy. UK has stopped azithromycin use (using higher doses ceftriaxone BUT they have MUCH higher azithromycin resistance rates than Australia. Still susceptible in Aus).

Contact tracing

Contact tracing

Why is it important?

- Interrupts transmission
- Prevents re-infection
- Identifies asymptomatic infection
- Provides early treatment to reduce complications
- Provides individual education and counselling

- Also remember notification and re-testing

Phone a friend?

- South Terrace Clinic (Fremantle Hospital) -9431 2149
- Royal Perth Hospital - 9244 2178
- Fiona Stanley Hospital Infectious Diseases/Sexual Health - 6152 2222

STI e-learning

Edith Cowan University and the Department of Health WA have developed a FREE online learning program for medical practitioners, nurses and other health professionals to improve your knowledge and skills in managing sexually transmitted infections.

http://sti.ecu.edu.au

This activity has been approved by the RACGP QI&CPD

Completion of Module 1 only attracts 6 Category 2 QI&CPD points

Completion of Modules 1 and 2 attract 40 Category 1 QI&CPD points

- Thanks to Dr Gawri Rajakaruna

PID: presentation, pathogens, problems and ping-pong

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