PID

Dr Gillian Dean
Consultant in HIV & Sexual Health
Brighton

Aims & objectives

• To understand
  – the epidemiology and pathogenesis of PID
  – the clinical presentation / differential diagnosis
  – the limitations regarding the diagnosis of PID

• To be aware of
  – the aetiological agents...and therefore the appropriate antibiotics
  – additional management steps
  – sequelae and long term outcomes
How would you define PID?

- Infection and inflammation of the female upper reproductive tract involving the endometrium, fallopian tubes, ovaries and pelvic peritoneum

- Following breakdown of the physical mucous barrier at the cervix, infection spreads to involve some or all of these structures

- The spectrum of disease ranges from asymptomatic or mild disease, through to severe infection with systemic symptoms and the presence of a tubo-ovarian abscess

Epidemiology

- Accurate measures of PID incidence difficult to obtain due to asymptomatic / nonspecific nature of many cases

- Symptomatic patients present to a variety of services - primary care, gynaecology, sexual health

- Precise case-finding challenging - almost certainly leads to widespread under-reporting
Risk factors – same as for acquiring STIs

- These include:
  - unprotected sexual intercourse with multiple sexual partners
  - young age at onset of sexual activity
  - previous chlamydia or gonorrhoea infection
  - low socioeconomic status
  - lower educational attainment
  - a history of PID

- Vaginal douching previously linked to PID (retrospective studies)
- A prospective study in 2005 showed no causal link

Incidence of PID in primary care - England

PID recorded in hospital inpatients, 15-44 year old women, 2000-2013

England population 15-44: 21,530,738
Females: 10,765,369
107.65 per 100,000

ACTUAL numbers: 232/100,000 = 25,000


PHE. Health Protection Report: Rates of Pelvic Inflammatory Disease (PID) in England (2000-2013); 2015.9.22
PID caused by *C. trachomatis* diagnosed in England 2006-2017

52% ↓

Total number of chlamydia diagnoses among women:
England, 2008 to 2017

- Data from specialist and non-specialist SHS (GUMCAD and CTAD returns)
- Chlamydia data from 2012 onwards are not comparable to data from previous years (please see ‘Notes’ slide for more details)
- Data type: service data
PID trends in other countries

• In the US no. of physicians visits for PID women aged 15–44 ↓ by 39.8% (from 123,000 to 88,000 visits 2004-2013)

• In Canada 1992-2009 PID hospitalisations decreased by 80% - physicians billing for cases of PID decreased by 70%

• Similar data have been reported from other countries including Sweden, Australia and Denmark

What's happening in your clinic?

WHY?
What proportion of chlamydia cases progress to PID?

- Natural history chlamydia poorly understood
  - 50% infections cleared spontaneously at 1 year

- 14.9% of women with chlamydia will go on to develop symptomatic PID
- 17.1% of infections if both symptomatic and asymptomatic PID is considered


Cost

£23 billion
Aetiology of PID

- Ascending infection from the endocervix causing:
  - endometritis, salpingitis, parametritis, oophoritis, tuboovarian abcess and/or pelvic peritonitis.
- *N. gonorrhoeae* & *C. trachomatis* causative agents, but account for <25% of UK cases
- *Mycoplasma genitalium* associated with upper genital tract infection in women
- *Gardnerella vaginalis*, anaerobes (including *Prevotella*, *Atopobium* & *Leptotrichia*) & other common vaginal organisms may be implicated

Changing aetiology?

- 1980s-1990s: C/GC detected in >50% cases, up to 77% of TOA¹
- 2016: only 20% PID ² to chlamydia (16-44 years) ²
  - 35% in 16-24 year old age
- 2011: USA 10% chlamydia, 4.4% GC, 2.6% both³
- Care switched to outpatient setting....less invasive tests

**Prevalence of Chlamydia trachomatis in women with PID**

<table>
<thead>
<tr>
<th>Population</th>
<th>Country</th>
<th>Prevalence</th>
<th>Test used</th>
<th>Sample size</th>
<th>Author / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Dept</td>
<td>USA</td>
<td>10%</td>
<td>NAATs</td>
<td>34/343</td>
<td>Burnett, 2012</td>
</tr>
<tr>
<td>GUM</td>
<td>UK</td>
<td>27%</td>
<td>LCR</td>
<td>12/45</td>
<td>Simms, 2003</td>
</tr>
<tr>
<td>Gynae clinic</td>
<td>India</td>
<td>33%</td>
<td>EIA</td>
<td>91/273</td>
<td>Shrikhande, 1995</td>
</tr>
</tbody>
</table>

If GC / CT account for only 20-25% of PID....

... what’s causing the rest??

N=330 with clinical PID

204 pathogen negative; 126 C/GC/MG/BV

- More likely to be age>30 (AOR 1.7)
- Had less evidence of vaginal inflammation (AOR 0.5)
- Reported less UPSI (AOR 0.6)
Detection of ‘novel’ organisms

Table 3. Detection of bacterial rDNA by 16S rDNA polymerase chain reaction (PCR) in Fallopian-tube specimens from women with acute salpingitis (the case patients) and women undergoing tubal ligation (the control subjects), stratified by the detection of Neisseria gonorrhoeae and Chlamydia trachomatis by multiplex PCR (MPCR).

<table>
<thead>
<tr>
<th>Results of 16S rDNA PCR</th>
<th>Case patients (n = 45)</th>
<th>Control subjects (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rDNA amplicons detected</td>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>N. gonorrhoeae detected</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>N. gonorrhoeae and C. trachomatis not detected</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>rDNA amplicons not detected&lt;sup&gt;c&lt;/sup&gt;</td>
<td>34</td>
<td>44</td>
</tr>
</tbody>
</table>

Hebb *JID* 2004;190:2109-20

16S rRNA

- highly conserved between different species of bacteria
- 16S rRNA gene sequences also contain hypervariable regions that can provide species-specific signature sequences useful for bacterial identification

16s rRNA and its use

![Image of 16s rRNA and its use](image-url)
Leptotrichia (Sneathia)

- Anaerobe
  - gram negative
  - slow growing and fastidious
- Detected by 16S rRNA amplification & sequencing
- Case reports
  - pyosalpinx \((L. \text{amnionii})\)
  - fetal death \((L. \text{amnionii})\)
  - bacteraemia in pregnancy \((L./\text{Sneathia sanguinegens})\)
  - post partum fever \((L. \text{amnionii} \text{ and } L./\text{Sneathia sanguinegens})\)

Atopobium vaginae

- Common commensal
- Found in BV
- Recognized in 1999
- Not readily identified by commercial diagnostic kits
- Clinical significance unknown
- Isolated from tubo-ovarian abcesses

Geißdorfer \textit{J Clin Microbiol} 2003;41:2788
What is the role of BV in PID?

- BV increases risk of incident GC/C infection
- BV is frequently present in women with PID (up to 70%)
  - does it independently cause PID?
  - does it facilitate the ascension of CT / GC?
  - is it an innocent bystander?

- Conflicting results (depends on BV definition e.g. gram stain vs culture)
  - when using microbial culture, a combination of BV-related microorganisms significantly elevated the risk of acquiring PID\(^1\)


Further thoughts...

- BV-associated microbes may form a biofilm on the endometrial surface - limit ability of antibiotics to eliminate colonization
- Prevotella species, found in half of women with PID, not covered by ceftriaxone/doxycycline\(^1\)
- PEACH study - only a single dose of 2\(^{nd}\) generation cephalosporin - sufficient to clear upper genital tract anaerobic infection?
  - short / long term outcomes similar between arms - large proportion in both arms had persistent endometritis at 30 days (45.9\% outpatient, 37.6\% inpatient; p=0.09)
- If anaerobes can cause ongoing inflammation following treatment with suboptimal regimens, sufficient anaerobic cover would seem to be essential

Petrina et al. Susceptibility of Endometrial Isolates Recovered from Women with Clinical PID or Histological Endometritis to Antimicrobial Agents, Anaerobe (2019)
Do we need anaerobic cover in mild disease?

- Treatment trials with and without anaerobic cover have shown excellent clinical & microbiological
- Few look at anaerobic end points specifically
- None illustrating whether short term treatment affects long term outcomes
- Consequently CDC state ‘until treatment regimens that do not cover anaerobic microbes have been demonstrated to prevent long-term sequelae as successfully as the regimens that are effective against these microbes, the use of regimens with anaerobic activity should be considered’

Pathogenesis

- Mechanism for ascending along mucosal surfaces unknown
- Disruption mucous barrier
  - Microbiological factors: proteolytic enzymes, virulence
  - Host factors: hormones, menstruation, uterine contractions, inflammatory response
  - Iatrogenic: IUD, TOP, hystero-salpingogram
- Fallopian tube diameter varies - particularly narrow (<1mm) at the opening into the uterine cavity
Pathologic changes in the epithelial surface (FT) after PID

Diagnosis

- Clinical diagnosis
- Laparoscopy
- Imaging
- Histology
- Clinical diagnosis
Symptoms

Severe PID 4%

Overt PID - mild to moderate 36%

Sub-clinical PID 60%

Clinical features - symptoms

- Lower abdominal pain - typically bilateral
- Deep dyspareunia - particularly of recent onset
- Abnormal vaginal bleeding ² cervicitis/endometritis
  - post coital
  - inter-menstrual
  - menorrhagia
- Abnormal vaginal/cervical discharge - often purulent
Clinical features - signs

- Lower abdominal tenderness - usually bilateral
- Adnexal tenderness on bimanual vaginal examination
- Cervical motion tenderness on bimanual vaginal examination
- Fever (>38°C)
- Right upper quadrant tenderness (?)

Perihepatitis (Fitz Hugh Curtis Syndrome)

4-14% of women
Diagnosis

- Even if present, symptoms & signs lack sensitivity & specificity (PPV of clinical diagnosis is 65-90% compared to laparoscopic diagnosis)
- Test for GC & chlamydia as positive result supports diagnosis...
- ... absence of infection does not exclude PID
- An elevated ESR or CRP supports diagnosis but non-specific
- The absence of endocervical or vaginal pus cells - good negative predictive value (94.5%) but presence is non-specific (poor PPV 17%)


Criteria for diagnosis

<table>
<thead>
<tr>
<th>Minimum diagnostic criteria (1 or more of)</th>
<th>Additional diagnostic criteria</th>
<th>Definitive diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower abdominal tenderness</td>
<td>Oral temperature &gt;38.3°C</td>
<td>Endometrial biopsy with histological evidence of endometritis</td>
</tr>
<tr>
<td>Adnexal tenderness</td>
<td>Abundant white blood cells on saline microscopy of vaginal secretions/wet mount (WBC&gt; epithelial cells)</td>
<td>Transvaginal ultrasound (or other imaging techniques) showing thickened fluid-filled tubes +/- free pelvic fluid or tubo-ovarian abscess</td>
</tr>
<tr>
<td>Cervical motion tenderness</td>
<td>Abnormal cervical mucopurulent discharge or cervical friability</td>
<td>Laparoscopy demonstrating abnormalities consistent with PID e.g. fallopian tube erythema +/- mucopurulent exudate</td>
</tr>
</tbody>
</table>

Elevated inflammatory markers (ESR, CRP)

Laboratory documentation of cervical infection with N. gonorrhoeae or C. trachomatis
**Aetiological agent & severity**

- GC more likely to have raised systemic inflammatory markers (ESR, WBC) than those with CT or MG
- GC more likely to present with fever, mucopurulent cervicitis, adnexal tenderness, higher pelvic pain score
  - PEACH: GC presented 1 week earlier than CT or MG
- GC more likely to remember the episode


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**Diagnosis**

- Clinical diagnosis
- Laparoscopy
- Imaging
- Histology
- Clinical diagnosis
Laparoscopy

Laparoscopic View of Normal Pelvis
Laparoscopy

- Historically gold standard diagnostic procedure against which other investigations have been compared
- Finding erythematous, oedematous fallopian tubes, with purulent exudate is highly specific for a diagnosis of PID
- Now management has shifted to outpatient setting, use has diminished...

Accuracy of Laparoscopy

- Does not exclude significant microscopic tubal disease
- Inflammation may be entirely internal
  - 12 women with previously normal laparoscopies
  - Attending with new ectopic pregnancy
  - 8 had salpingectomy - examined by same histopathologist
  - All had evidence of ongoing low-grade salpingitis in areas separate from ectopic pregnancy

Accuracy of Laparoscopy

- Laparoscopy compared with endometrial / fimbrial biopsy (1)
- Prevalence PID 46% (44/95)
- Laparoscopy sensitivity 50% (12/24); specificity 80% (40/50) for salpingitis if standard was fimbrial histopathologic diagnosis (p = 0.01)
- Suggested supplemental endometrial / fimbrial biopsy if laparotomy negative, to increase accuracy of PID diagnosis
- CO2 can cause hyperaemia
- Other studies have shown marked intra/inter observer variation (2)


Diagnosis

- Clinical diagnosis
- Laparoscopy
- Imaging
  - Histology
  - Clinical diagnosis
Transvaginal ultrasound

- Not readily available outside gynecology - insensitive in mild disease
- Specific only in severe PID when thickened tubal walls seen
  - fluid must be present in the tubal lumen for this sign to be evaluated
- Specificity increased by
  - free pelvic fluid
  - tubo-ovarian abscess
  - pyosalpinx (echogenic fluid in the tube)
  - cogwheel sign (protrusion of thickened mucosa into the lumen on cross section)
- Sensitivity 81%, specificity 78%, overall accuracy 80% \((\text{hospitalised})\)

Tukeva TA et al. Radiology 1999;210:209-16

- 'Power Doppler' transvaginal Ultrasound

  100% sensitive; 80% specific
  \((\text{overall accuracy 93%})\)
  \((\text{hospitalised})\)

Computerised Tomography

Advanced PID in 33-year-old. CT demonstrates dilated, thick-walled, enhancing fallopian tubes containing complex fluid (arrows), consistent with pyosalpinx.

Computerised Tomography

- Relatively insensitive
- Expensive
- Inaccessible
- Leads to unacceptable radiation exposure in women of reproductive age

- In hospitalised patients, with diagnostic uncertainty, CT useful in confirming alternative diagnoses e.g. acute appendicitis or urinary tract pathology
MRI vs TV Ultrasound

PYOSALPYNX

MRI

- Sensitivity 95%, specificity 89%, overall accuracy 93% (hospitalised)
- Higher cost
- Less easily available
- Not initial choice
- Superior tissue contrast / multiplanar capability
  - e.g. can easily distinguish haematosalpinx from pyosalpinx
- May be useful in complex or equivocal cases
- May reduce the need for diagnostic laparotomy

Tuveka TA et al. Radiology 1999;210:209-16
Diagnosis

- Clinical diagnosis
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- Imaging
- Histology
- Clinical diagnosis

Endometrial Biopsy

- Simple, relatively cheap, less invasive, outpatient procedure
- Results correlate with salpingitis
- **BUT** not 100% sensitive or specific
- endometritis common in ‘uncomplicated’ endocervicitis
- risk of introducing infection
- delayed diagnosis
- histopath definitions/interpretation

1 which would explain the lower specificities reported with this diagnostic test (63-87%)
BUT in future...

- Samples could undergo
  - traditional microbiological analysis
  - molecular testing for novel organisms
  - use newer methodologies to evaluate the interaction between pathogens and the host response in different individuals

Diagnosis

- Clinical diagnosis
- Laparoscopy
- Imaging
- Histology
- Clinical diagnosis
The US Center for Disease Control (CDC) recommends empirical PID treatment in sexually active young women (≤25 years of age) and other women at risk for STIs (multiple sexual partners or history of STI) if they are experiencing pelvic or lower abdominal pain, when no other cause can be identified, and if these criteria are present on pelvic examination.

A diagnosis of PID should be considered, and usually empirical antibiotic treatment offered, in any sexually active woman who has recent onset, bilateral lower abdominal pain associated with local tenderness on bimanual vaginal examination, in whom pregnancy has been excluded and no other cause for the pain has been identified.
Differential diagnosis

- Ectopic pregnancy - pregnancy should **always** be excluded
- Acute appendicitis
- Endometriosis
- Ovarian cyst - rupture, torsion
- Urinary tract infection
- Functional pain (e.g. Mittelschmerz)
- Irritable bowel syndrome
Appendicitis or salpingitis

- ‘Pain first, vomiting next and fever last’
- Umbilicus to RIF
- Rebound / guarding
- Rovsing’s etc.
- Anorexia

Differential diagnosis

- Ectopic pregnancy - pregnancy should always be excluded
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- Irritable bowel syndrome
Endometriosis

**Prevalence:**
10-15% of reproductive women; on average takes 9.2 ys to diagnose

**Symptoms:**
- Severe day 1 (+/-2) dysmenorrhea affecting work / school attendance / sport
- Painkillers +++ (ineffective)
- Hot water bottle / heat pad / hot bath
- Better on OCP, Depo or IUS, worse when not
- Mother, sister, aunt, cousin - similar problems
- Cyclical dyspareunia, cyclical haematuria, cyclical dyschezia, pain on tampon insertion

<table>
<thead>
<tr>
<th>Endometriosis or PID?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endometriosis</strong></td>
</tr>
<tr>
<td>Pelvic Pain</td>
</tr>
<tr>
<td>Menorrhagia</td>
</tr>
<tr>
<td>Dyspareunia</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
</tr>
<tr>
<td>Painkillers + Heat</td>
</tr>
<tr>
<td>Pain ↓ with OC Pill</td>
</tr>
<tr>
<td>Family History</td>
</tr>
<tr>
<td>Defecation Pain</td>
</tr>
</tbody>
</table>
Differential diagnosis

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• Irritable bowel syndrome

Ovarian cyst - rupture, torsion

• Presentation sudden onset of sharp, usually unilateral lower abdominal pain, in 70% accompanied by n&v +/- fever
• 3% of gynae emergencies; 70% of cases age 20-39 ys
• Greatest risk during pregnancy & menopause
• Risk factors include:
  – increased length of the ovarian ligaments,
  – pathologically enlarged ovaries (more than 6 cm), tumors
  – enlarged corpus luteum in pregnancy,
  – and jerky movements....
Differential diagnosis

- Ectopic pregnancy - pregnancy should always be excluded
- Acute appendicitis
- Endometriosis
- Ovarian cyst - rupture, torsion
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- Functional pain (e.g. Mittelschmerz)
- Irritable bowel syndrome
Differential diagnosis

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- Acute appendicitis
- Endometriosis
- Ovarian cyst - rupture, torsion
- Urinary tract infection
- Functional pain (e.g. Mittelschmerz)
- Irritable bowel syndrome

Other less common differential diagnoses?

- Acute Pyelonephritis
- Sigmoid volvulus / Meckel’s
- Ulcerative colitis / Crohn’s
- Diverticular abscess
- Red degeneration of fibroid
- Diabetic ketoacidosis
- Sickle Cell crisis
- Acute Porphyria
- Heroin withdrawal
- Psoas Abscess
- Renal stone
Poorly Investigated Diagnosis

• Biologically covert disease
• Wide presentation
• Wide differential diagnosis
• Delayed microbiology
• Insensitive ultrasound
• Inaccurate laparoscopy
• Invasive histology, safe?

Diagnosis

• Mainly clinical - no simple diagnostic test
• Low index of suspicion
• Temperature
• (STI screen - testing for chlamydia, gonorrhoea, anaerobic infection)
• (ESR / CRP)
• (Ultrasound scan)
• (Laparoscopy)
Therapeutic goal for PID treatment is two-fold:

1. short-term microbiologic and clinical cure
2. long-term prevention of sequelae (tubal infertility, ectopic pregnancy, and chronic pelvic pain)
Inpatient or outpatient treatment?

- PEACH study, RCT
- Comparison of:
  - *inpatient*: parenteral cefoxitin 2g qds plus doxycycline 100mg bd 14ds
  - *outpatient*: stat. intramuscular cefoxitin 2g plus probenecid 1g plus doxycycline 100mg bd 14 days
- F/U 5 & 30 days, plus mean f/u of 3 years, every 4 months
- Primary outcomes
  - frequency of documented pregnancy, time to pregnancy
  - side effects, adverse events
  - infertility, recurrent PID, chronic pelvic pain, ectopic pregnancy

*Am J Obstet Gynecol* 2002;186:929-937

### Table 3
Summary of short-term and long-term effects of outpatient compared to inpatient therapy for mild-moderate PID in the PEACH trial

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
<th>Inpatient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short term (30 days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonorreha positive</td>
<td>3.9%</td>
<td>2.4%</td>
<td>0.44</td>
</tr>
<tr>
<td>Chlamydia positive</td>
<td>2.7%</td>
<td>3.6%</td>
<td>0.52</td>
</tr>
<tr>
<td>Persistent tenderness</td>
<td>20.6%</td>
<td>18.4%</td>
<td>0.50</td>
</tr>
<tr>
<td>Endometritis</td>
<td>45.9%</td>
<td>37.6%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

|                      |            |           |         |
| **Long term outcomes (mean 35 months)** |            |           |         |
| Pregnancy            | 59.4%      | 55.6%     | NS      |
| Ectopic              | 1.2%       | 0.2%      | NS      |
| Infertility           | 16.7%      | 20.6%     | NS      |
| Chronic pelvic pain  | 40.7%      | 44.6%     | NS      |
| Recurrent PID        | 18.4%      | 24.3%     | NS      |

Adapted from Ness et al 2002 [61], and Ness et al 2005 [62]

NS = Not statistically significant
Indications for hospital admission

- Patients with severe clinical disease
- Marked systemic symptoms - fever,
- Unable to tolerate oral antibiotics - n&v
- Surgical emergency can’t be ruled out
- Tubo-ovarian abscess - mass on pelvic examination
- Lack of response to oral therapy
- Pregnancy

Antibiotic treatment

- Prompt treatment essential

<table>
<thead>
<tr>
<th>OR of infertility / ectopic pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 days</td>
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<tr>
<td>&gt; 3</td>
</tr>
</tbody>
</table>

- Association strongest for women with chlamydia
- Impaired fertility in:
  - 17.8% of delayed care
  - 0.0% of prompt care

Antibiotic treatment

- Needs to be polymicrobial / broad spectrum to cover:
  - *N. gonorrhoeae*
  - *C. trachomatis*
  - anaerobic infection
- Also desirable to cover other possible pathogens:
  - *M. genitalium*
  - streptococci, staphylococci
  - *E. coli*
  - *H. influenzae*
- Recent data suggest few antibiotics are effective against *M. genitalium* (moxifloxacin, azithromycin (?))

Which Antibiotics?

<table>
<thead>
<tr>
<th>Gonorrhoea</th>
<th>Aerobes</th>
<th>Chlamydia</th>
<th>Anaerobes</th>
<th>Mycoplasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>METRONIDAZOLE</td>
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<td>CLINDAMYCIN</td>
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<td>OFLOXACIN</td>
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<td>AZITHROMYCIN</td>
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<td></td>
<td>DOXYCYCLINE</td>
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<td>Moxifloxacin</td>
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<td>Azithromycin?</td>
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<td>CEFTRIAXONE</td>
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</table>
European Medicines Agency guidance

- the potential for disabling / permanent side effects with fluoroquinolones
- tendons, muscles, joints and the nervous system
  - tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance
  - neuropathies associated with paraesthesia,
  - depression, fatigue, memory impairment, sleep disorders, impaired hearing, vision, taste and smell
- not to be used for mild to moderate bacterial infections when alternative antibiotic therapy is available
- PID guideline updated to move fluoroquinolones from 1st to 2nd line-use, except for M genitalium associated PID

2018 PID guidelines
Oral Treatment Regimens for Pelvic Inflammatory Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage / route / frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1g intramuscular</td>
<td>Single dose</td>
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<tr>
<td>Doxycycline</td>
<td>100mg orally BD</td>
<td>14 days</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>400mg orally BD</td>
<td>14 days</td>
</tr>
<tr>
<td><strong>2nd line</strong></td>
<td></td>
<td></td>
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<tr>
<td>Ofloxacin</td>
<td>400mg orally BD</td>
<td>14 days</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>400mg orally BD</td>
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<tr>
<td><strong>2nd line</strong></td>
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<td></td>
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<tr>
<td>Moxifloxacin</td>
<td>400mg OD</td>
<td>14 days</td>
</tr>
</tbody>
</table>

Parenteral Treatment Regimens for Pelvic Inflammatory Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage / frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Option 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2g intravenous (IV)</td>
<td>Until 24h after clinical improvement</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100mg IV / orally if tolerated</td>
<td>To complete 14 days</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>400mg orally BD</td>
<td>Start when ceftriaxone finishes; to complete 14 days</td>
</tr>
<tr>
<td><strong>Option 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2mg/kg loading dose, then 1.5mg/kg TDS</td>
<td>Until 24h after clinical improvement</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>900mg IV TDS</td>
<td>Until 24h after clinical improvement</td>
</tr>
<tr>
<td>then Clindamycin</td>
<td>450mg orally QDS</td>
<td>To complete 14 days</td>
</tr>
<tr>
<td>or Doxycycline plus</td>
<td>100mg orally BD</td>
<td>To complete 14 days</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>400mg orally BD</td>
<td>To complete 14 days</td>
</tr>
<tr>
<td><strong>Option 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400mg IV BD</td>
<td>Until 24h after clinical improvement</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500mg IV TDS</td>
<td>Until 24h after clinical improvement</td>
</tr>
<tr>
<td>then Ofloxacin plus</td>
<td>400mg orally BD</td>
<td>To complete 14 days</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>400mg orally BD</td>
<td>To complete 14 days</td>
</tr>
</tbody>
</table>
Do we always need to cover gonorrhoea?

1.3-2.6% PID recorded as GC PID in PHE data tables

Recent UK multi-centre PID study showed 0.4% GC

Figure 10: Percentage of gonococcal isolates resistant to ciprofloxacin by gender and male sexual orientation. GRASP clinics: 2004-2014
What about moxifloxacin liver toxicity?

- 11 deaths in Europe over past 2 years
  - all aged over 60; 9 in Germany, 2 in Netherlands
- 12 cases liver toxicity reported in the UK from 2003-16 with no deaths
What about *Mycoplasma genitalium*...?

**Mycoplasma genitalium**

- **Tubal factor infertility** – Clausen et al.
- **Salpingitis** – Cohen et al.
- **Cervicitis** – Falk et al., Manhart et al., Pepin et al.
- **Endometritis** – Cohen et al., Haggerty et al.; Simms et al.
M. Genitalium – meta-analysis

- M. genitalium infection was significantly associated with increased risk of:
  - cervicitis (OR 1.66; 95% CI: 1.35, 2.04)
  - pelvic inflammatory disease (OR 2.14; 95% CI: 1.31, 3.49)
  - preterm birth (OR 1.89; 95% CI: 1.25, 2.85)
  - spontaneous abortion (OR 1.82; 95% CI: 1.10, 3.03)
  - risk of infertility (OR 2.43; 95% CI: 0.93, 6.35)

- In sub-analyses accounting for co-infections, all associations were stronger and statistically significant


Forest plot of the association between M. genitalium & PID

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lind</td>
<td>1987</td>
<td>0.23 (0.01, 4.70)</td>
<td>2.39</td>
</tr>
<tr>
<td>Cohen</td>
<td>2002</td>
<td>10.29 (1.36, 84.10)</td>
<td>4.47</td>
</tr>
<tr>
<td>Sissna</td>
<td>2005</td>
<td>12.34 (0.67, 226.77)</td>
<td>2.54</td>
</tr>
<tr>
<td>Justroad*</td>
<td>2007</td>
<td>1.00 (0.40, 2.70)</td>
<td>19.92</td>
</tr>
<tr>
<td>Haggerty*</td>
<td>2008</td>
<td>2.00 (1.00, 4.20)</td>
<td>16.55</td>
</tr>
<tr>
<td>Hjorting*</td>
<td>2010</td>
<td>6.29 (1.56, 25.20)</td>
<td>8.34</td>
</tr>
<tr>
<td>Oudshoort</td>
<td>2010</td>
<td>2.40 (0.72, 7.98)</td>
<td>10.08</td>
</tr>
<tr>
<td>Hjorting*</td>
<td>2012</td>
<td>9.00 (1.62, 49.89)</td>
<td>6.18</td>
</tr>
<tr>
<td>Taylor-Robinson</td>
<td>2012</td>
<td>2.13 (0.49, 9.30)</td>
<td>7.71</td>
</tr>
<tr>
<td>Vandepitte</td>
<td>2012</td>
<td>1.41 (0.95, 2.15)</td>
<td>21.80</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>2.14 (1.31, 3.49)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
### Prevalence of *M. genitalium* in women with PID

<table>
<thead>
<tr>
<th>Population</th>
<th>Country</th>
<th>Prevalence</th>
<th>Test used</th>
<th>Sample size</th>
<th>Author / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUM</td>
<td>UK</td>
<td>13%</td>
<td>PCR (ref lab)</td>
<td>6/45</td>
<td>Simms 2003</td>
</tr>
<tr>
<td>STI clinic</td>
<td>Kenya</td>
<td>16%</td>
<td>PCR</td>
<td>9/58</td>
<td>Cohen, 2002</td>
</tr>
<tr>
<td>ED, gynae, STI</td>
<td>USA</td>
<td>15%</td>
<td>PCR</td>
<td>88/311</td>
<td>Haggerty 2008</td>
</tr>
<tr>
<td>ED</td>
<td>Brazil</td>
<td>5%</td>
<td>Genprobe</td>
<td>7/133</td>
<td>Savaris 2007</td>
</tr>
<tr>
<td>GUM</td>
<td>UK</td>
<td>11.9%</td>
<td>NAATs</td>
<td>5/42</td>
<td>Med student project, 2010</td>
</tr>
<tr>
<td>GUM</td>
<td>UK</td>
<td>8.2%</td>
<td>NAATs</td>
<td>22/274</td>
<td>Dean, 2011-15</td>
</tr>
</tbody>
</table>

### Failure to eradicate mycoplasma

- **PEACH**
- **N=682, cefotixin & doxycycline**
- **Mycoplasma in 15%**
- **Of whom 41% tested positive at day 30 following treatment**
- **C.f. 2-4% persistent/recurrent GC or chlamydia**
- **Infertility, chronic pelvic pain & recurrent PID more common in MG positive women**

Haggerty CL, Sex Transm Infect 2008;84
Mycoplasma guidelines

- Azithromycin extended course (1g stat, 500mg od 2 days) preceded by 1 week doxycycline
- Increasing incidence of Rx failure last 5 years - rapid emergence of macrolide resistance (30-100%)
- Moxifloxacin currently one of the most active drugs against *M. genitalium* - been used as 2\textsuperscript{nd} line agent
- Moxifloxacin effective in 88% of cases failing azithromycin (although 12% of patients receiving moxi failed to clear MG - all had pre-treatment fluoroquinolone mutations detected)\textsuperscript{1}
- All cleared infection with oral pristinamycin 1g qds 10 days

\textsuperscript{1} Bissessor M, Tabrizi SN, Twin J et al. Macrolide resistance and azithromycin failure in a mycoplasma genitalium-infected cohort and response of azithromycin failures to alternative antibiotic regimens. *Clinical Infectious Diseases*. 2015; 60(8): 1228–1236

Special considerations
Tubo-ovarian abscesses

- Serious & potentially life-threatening complication
- Patients more likely to be systemically unwell; have higher levels of pain
- Palpation of an adnexal mass, or lack of response to therapy, should prompt imaging studies
- TOA is an indication for hospital admission for IV antibiotics, with anaerobic cover, and to monitor for signs of rupture or sepsis
Tubo-ovarian abscesses

- Conservative management can be effective - studies show resolution in 70-84% of women, particularly those with smaller abscesses (<9 cm)\(^1\)

- Norwegian cohort, transvaginal ultrasound-guided aspiration, together with antibiotic therapy led to successful treatment and avoidance of surgical intervention in 93.4%\(^2\)

- Failure of improvement by 72 hours, or clinical deterioration in the interim should be indication for surgical exploration

PID and IUDs

- Most strongly related to the insertion procedure & background risk of STIs

- A metanalysis of 22,908 IUD insertions and 51,399 woman years of follow-up showed PID was 6 times higher during the first 20 days after insertion, and an infrequent event thereafter (1.6 cases per 1000 woman years)


IUD removal

- If an IUD user is diagnosed with PID, the IUD does not need to be removed immediately

- If no improvement occurs after 48–72 hours, then removal should be considered whilst continuing antibiotics (CDC 2015)

- A systematic review of evidence found that treatment outcomes did not generally differ between women with PID who retained the IUD and those who had the IUD removed

UK PID Guidelines 2019

‘Removal of the IUD when the patient presents should be considered and may be associated with better short term clinical outcomes’

‘When antibiotic treatment is commenced and the IUD is left in situ a review should be performed after 48-72 hours and the IUD removed if significant clinical improvement has not occurred’

‘The decision to remove the IUD needs balancing against risk of pregnancy if UPSI in last 7 days. Hormonal emergency contraception may be appropriate in this situation’.

Pregnancy

- PID in pregnancy uncommon but assoc. with ↑ in maternal & fetal morbidity - parenteral therapy advised
- Insufficient data from clinical trials to recommend a specific regimen
- Empirical therapy with agents effective against GC, C & anaerobes
- Taking into account local antibiotic sensitivity patterns
  - e.g. i.m. ceftriaxone plus oral or i.v. erythromycin +/- oral or i.v. metronidazole 500mg 3 times daily in clinically severe disease
### Effect of HIV on PID Outcome

Nairobi, Kenya 2006; laparoscopically confirmed PID  
140 hospitalised - 53 HIV positive / 97 HIV negative

<table>
<thead>
<tr>
<th></th>
<th>HIV pos</th>
<th>HIV neg</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe PID</td>
<td>38%</td>
<td>24%</td>
<td>0.02</td>
</tr>
<tr>
<td>Need for surgery/</td>
<td>28%</td>
<td>21%</td>
<td>0.3</td>
</tr>
<tr>
<td>additional abs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery time</td>
<td>6-14d</td>
<td>3-9d</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Mugo NR et al *Obstet Gynecol* 2006; 107: 807-12

### Health promotion messages for patients

An explanation of what treatment is being given and its possible adverse effects

Following treatment fertility is usually maintained but there remains a risk of future infertility, chronic pelvic pain or ectopic pregnancy

Clinically more severe disease is associated with a greater risk of sequelae

Repeat episodes of PID are associated with an exponential increase in the risk of infertility

The earlier treatment is given the lower the risk of future fertility problems

Future use of barrier contraception will significantly reduce the risk of PID

The need to screen her sexual contacts for infection to prevent her becoming re-infected

(UK national guidelines)
Additional management

- Rest, analgesia
- **Contact tracing** - current/recent male partners MUST be treated, even if no primary organism identified
- **Sexual abstinence** until both partners have finished antibiotics
- Health promotion / safer sex messages
- Information leaflet

BASHH PID leaflet
Follow-up

- In moderate-severe disease - review in 48-72 hours
- In mild disease - review at 2-4 weeks
  - adequate clinical response (bimanual)
  - adherence to antibiotics
  - sexual partners treated
  - sexual abstinence
  - awareness of significance of PID
Sequelae / long term outcomes

- Infertility
- Ectopic pregnancy
- Chronic pelvic pain (defined as pain lasting >6 months)

Duration symptoms major factor
- <3 days to presentation: infertility 8.3%
- >3 days to presentation: infertility 19.7%


Weström et al

- 1,844 women with abnormal laparoscopy; 13,400 women-yrs
- 657 with normal laparoscopy; 3,958 women-yrs

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed to conceive</td>
<td>16%</td>
<td>2.7%</td>
</tr>
<tr>
<td>TFI</td>
<td>10.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>9.1%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

Each repeated episode doubled rate TFI
- 1 episode 8%; 2 episodes 19.5%; 3 episodes 40%

Prevention - chlamydia screening

- Scholes et al 1996
  - Women randomised to screening or usual care - followed for 12 months
  - Screening group 56% lower incidence PID (RR 0.44 (0.2-0.9))

- Danish study 2000
  - Home sampling vs standard of care - 43 infections vs 5 identified
  - 2.1% students treated for PID vs 4.2% in standard of care (Wilcoxon exact value, P=0.045)

- POPI trial (Prevention Of Pelvic Infections)
  - 1.3% (15/1191) in screened compared with 1.9% (23/1186) in controls
  - stored sample tested for CT at 1 year (RR 0.65, 95% CI 0.34 to 1.22)


Take Home Messages

- The more you know the more questions you have...
- Difficult area to research, but worthwhile
- Know you local GC rates
- Test PID cases for MG and treat appropriately
- Use anaerobic cover until we know more
- Don’t need to take out IUDs immediately
- Use opportunities for health promotion wherever possible
  (women with lower abdominal pain need better advice on when to seek early medical attention – this will avoid risk of reproductive damage)