Treatment of Pelvic Inflammatory Disease and *Neisseria gonorrhoeae*: Systematic Review of Efficacy and Antibiotic Resistance Trends

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INTRODUCTION

Pelvic Inflammatory Disease (PID) and related infections, including salpingitis and endometritis, remain significant causes of reproductive morbidity. *Neisseria gonorrhoeae* (Ng) is the second most common reported notifiable infection and a primary etiologic agent of PID. Active duty military women face disproportionately higher sexually transmitted infection (STI) rates compared to civilian counterparts. This is likely driven by demographics, behavioral and operational factors, underscoring the need for targeted research within this unique population. Antibiotic regimens for treating gonorrhea have evolved in response to rapidly changing genetic profiles and emerging resistance patterns in Ng. However, current clinical practice guidelines must be continually re-evaluated as global antimicrobial resistance (AMR) threatens existing protocols.

RESULTS

The six included RCTs encompassed sample sizes that ranged from 72 to 831 participants for a total of 2,489 participants, with geographic representation across the United States, Asia and a multinational study representing Europe and South Africa.

- Treatments demonstrated generally high efficacy using clinical outcomes for improvement or resolution of infection-related symptoms: pelvic pain, cervical motion tenderness, fever, abnormal discharge, or other indicators of inflammation
- Ages of participants varied by study with overall ranges between 13-38 years old
- 422 participants with PID had Ng as a causal agent
- One case of high-level resistance for Doxycycline was reported in the Wendel (1991) study and four treatment failures were reported in the Ross (2006) study with use of Ofloxacin and Metronidazole
- In the (2010) Judlin study the standard treatment of Levofloxacin + Metronidazole was tested against Moxifloxacin and neither MIC exceeded 2 mg/L in any isolates tested
    - Ceftriaxone was added to the treatment plan for all participants with a positive test for Ng

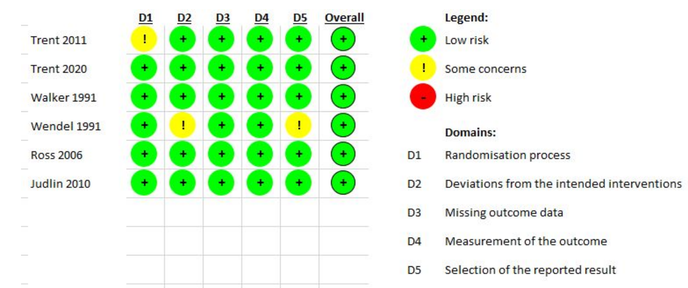

Figure 2. Cochrane Risk of Bias Assessment (RoB2) Traffic Light Plot.

PURPOSE

Antimicrobial resistance in *Neisseria gonorrhoeae* is rising globally, threatening the management of gonococcal infections. Because PID is the primary driver of morbidity and long-term sequelae in infected individuals, evaluating whether standard empiric regimens effectively clear ascending infections is critical. This systematic review evaluates the efficacy and safety of antibiotic regimens for PID and related STIs using evidence from RCTs, while characterizing longitudinal trends in treatment strategies and pathogen clearance

Year & Author	Drugs Studied	Study Outcomes	Ng / PID Standard Treatment for Period
1991 *(Walker et al.)*	**Cefotetan (IV)** **Cefoxitin (IV)** **Doxycycline (PO)**	**PID Cure:** 94% cure rate overall	**Ng:** Ceftriaxone (IM) + Doxycycline/Tetracycline **PID Outpatient:** Cephalosporin + Doxycycline **OR** Ofloxacin ± Clindamycin
1991 *(Wendell et al.)*	**Ofloxacin (PO)** *vs.* **Cefoxitin (IM) + Probenecid (PO) + Doxycycline (PO)**	**PID Cure:** 95% (Ofloxacin) *vs.* 97% (Cefoxitin combo) **Ng Cure:** 100% in both arms	**Ng:** Ceftriaxone (IM) + Doxycycline/Tetracycline **PID Outpatient:** Cephalosporin + Doxycycline **OR** Ofloxacin ± Clindamycin
2006 *(Ross et al.)*	**Moxifloxacin (PO)** *vs.* **Ofloxacin (PO) + Metronidazole (PO)**	**Ng Cure:** 100% (Moxifloxacin) *vs.* 82% (Ofloxacin combo) *High overall bacterial vaginosis (BV) failure rates (~80%) in both arms*	**Ng:** Fluoroquinolone resistance rising; Ceftriaxone (IM) **OR** Cefixime increasingly preferred over options like Ciprofloxacin/Ofloxacin **PID Outpatient:** Ceftriaxone (IM) **OR** Cefoxitin (IM) + Probenecid followed by Doxycycline ± Metronidazole
2010 *(Judlin et al.)*	**Moxifloxacin (PO)** *vs.* **Levofloxacin (PO) + Metronidazole (PO)**	**Clinical Cure:** 78.4% (Moxifloxacin) *vs.* 81.6% (Combo) **Ng Cure:** 100% (Moxifloxacin) *vs.* 50% (Levofloxacin combo)	**Ng:** Dual therapy standard: Ceftriaxone (IM) **OR** Cefixime + Azithromycin **OR** Doxycycline **PID Outpatient:** Ceftriaxone + Doxycycline ± Metronidazole **OR** Cefoxitin + Probenecid + Doxycycline ± Metronidazole
2011 *(Trent et al.)*	**Cefoxitin (IV) + Doxycycline (PO)**	Evaluated long-term relationship between subsequent STIs and Chronic Pelvic Pain (CPP) or infertility Recurrent PID associated with 1.8 times higher infertility rates and more than 4.2 times higher rates off CPP Subsequent LRT STI associated with 2.3 times more likely to have CPP	**Ng:** Ceftriaxone (IM) + Azithromycin **OR** Doxycycline **PID Outpatient:** Ceftriaxone (IM) + Doxycycline + Metronidazole **PID Inpatient:** Cefoxitin/Cefotetan (IV) + Doxycycline (IV or PO) **OR** Clindamycin (IV) + Gentamicin (IV or IM)
2020 *(Trent et al.)*	***RCT for educational intervention efficacy***	271 Ng cases; noted clearance of Ct/Ng but high persistence/reinfection of *M. genitalium* and *T. vaginalis*	**Ng:** Shifted to Ceftriaxone (IM) monotherapy (if Ct ruled out) for antibiotic stewardship; add Doxycycline if Ct suspected **PID Outpatient:** Ceftriaxone (250mg IM) + Doxycycline + Metronidazole

Table 1. Study & Treatment Evolution
***Note: The standard inpatient PID treatment did not change across the period of time covered by included studies**. Inpatient IV antibiotics are most often reserved for treatment of patients considered to have severe PID, have tubo-ovarian abscess, be pregnant or those who have previously failed treatment. Two regimens are used: Cefoxitin/Cefotetan (IV) + Doxycycline (IV or PO) **OR** Clindamycin (IV) + Gentamicin (IV or IM).*

Drug MoA Reference

- Cephalosporins/Cephamycins (Cefoxitin, Cefotetan, Ceftriaxone): Inhibits PBPs, halting cell wall synthesis causing lysis
- Probenecid is added to slow renal clearance and extend half-life
- Tetracyclines (Doxycycline): Binds to 30S ribosomal subunit, halting protein translation
- Fluoroquinolones (Ofloxacin, Moxifloxacin, Levofloxacin): Inhibits DNA gyrase & topoisomerase IV, halting DNA replication
- Nitroimidazoles (Metronidazole): Forms toxic free radicals that disrupt bacterial DNA

METHODS

- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Guidelines
- Databases: PubMed and ClinicalTrials.org
- Search Strategy: terms related to *N. gonorrhoeae,* Pelvic inflammatory Disease, and Randomized Clinical Trials
- Search Period: 1984 – Sept 2025 (ClinicalTrials.gov) and March up to 2026 (PubMed)
- Cochrane risk-of-bias (RoB2) tool
- Inclusion Criteria: biological female, clinical diagnosis of PID and gonorrhea, and RCT study design

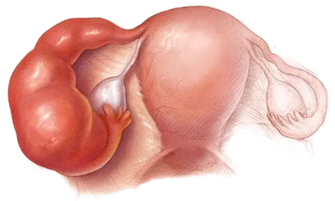

Figure 3. Visual diagram of a normal upper female reproductive tract (right) and with PID (left)

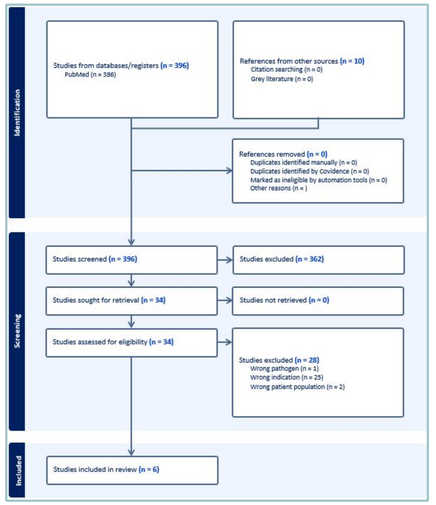

Figure 1. PRISMA Flow Diagram.

DISCUSSION

- PID in the included studies were annotated as complicated/severe or uncomplicated; however, as an ascended upper reproductive tract infection all PID for this review is considered a complicated infection
- Most PID cases are caused by polymicrobial agents making combination therapy most effective
- Future research should prioritize modern RCTs that evaluate current standard-of-care therapies, incorporate test-of-cure protocols and consider longer follow-up to assess long-term reproductive outcomes
- Future research should integrate pharmacokinetics and pharmacodynamics especially in ascending infections to optimize dosing strategies and improve therapeutic outcomes
    - diagnosis and treatment may need non-human studies to assess microbiological cure due to the anatomical location of ascending infections

References available upon request