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(REVIEW ARTICLE)

Antimicrobial resistance in sexually transmitted infections: Emerging therapeutic challenges and the need for updated treatment strategies

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Abstract

Sexually transmitted infections (STIs) continue to represent a global health crisis, with more than one million curable cases diagnosed daily. Bacterial STIs, including *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, *Chlamydia trachomatis*, and *Treponema pallidum*, were historically treatable, but are now increasingly resistant to first- and second-line antibiotics. Antimicrobial resistance (AMR) in these pathogens threatens the efficacy of established treatment regimens and poses a serious risk to global STI control strategies. This review synthesizes high-quality peer-reviewed research on resistance mechanisms, epidemiological trends, treatment failures, and diagnostic limitations across the four pathogens. We also examine current global surveillance efforts, limitations of syndromic management, and the urgent need for novel therapeutics. Understanding the evolving resistance patterns and their clinical implications is essential to prevent returning to the pre-antibiotic era in STI management.

Keywords: Antimicrobial resistance; Sexually transmitted infections; *Neisseria gonorrhoeae*; *Mycoplasma genitalium*; *Chlamydia trachomatis*; *Treponema pallidum*; Treatment failure; Resistance surveillance

1. Introduction

Sexually transmitted infections (STIs) remain among the most common communicable diseases worldwide. The World Health Organization (WHO) estimates over 374 million new cases of chlamydia, gonorrhea, syphilis, and trichomoniasis occur annually, predominantly in low- and middle-income countries (WHO, 2023). While many STIs are bacterial and curable with antibiotics, rising antimicrobial resistance (AMR) now compromises treatment efficacy. The threat is severe in *Neisseria gonorrhoeae*, which has progressively acquired resistance to every class of antimicrobial agents used against it (Unemo & Shafer, 2014). More recently, *Mycoplasma genitalium* has emerged as another pathogen with high-level resistance to both macrolides and fluoroquinolones (Machalek et al., 2020).

In the case of *Chlamydia trachomatis*, treatment failures are reported despite a lack of confirmed genetic resistance, while macrolide-resistant *Treponema pallidum* strains have spread globally, undermining oral syphilis treatment options (Lukehart et al., 2004; Stamm, 2010).

This literature review presents a pathogen-specific analysis of resistance mechanisms, epidemiological trends, diagnostic challenges, and emerging therapeutic strategies. The aim is to support the design of resistance-informed clinical guidelines and stimulate investment in diagnostic and pharmaceutical innovations.

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2. Neisseria gonorrhoeae

2.1. Pathogenesis and Clinical Burden

Neisseria gonorrhoeae, a Gram-negative diplococcus, infects mucosal surfaces including the urethra, endocervix, pharynx, rectum, and conjunctiva. Untreated infections can lead to pelvic inflammatory disease, infertility, and increased HIV transmission risk. The CDC reported over 700,000 gonorrhea cases in the U.S. in 2022, marking a 118% increase since 2009 (CDC, 2023). Globally, the disease burden is highest in sub-Saharan Africa and Southeast Asia (Rowley et al., 2019).

2.2. Historical Treatment Timeline and Resistance Evolution

Gonorrhea's history with antimicrobial treatment illustrates one of the most aggressive AMR trajectories. Resistance emerged in the following sequence:

- **Sulfonamides (1930s–40s)**: Resistance quickly emerged due to chromosomal mutations.
- **Penicillin (1940s–1980s)**: β-lactamase-producing plasmids (e.g., *blaTEM*) rendered penicillin ineffective (Whiley et al., 2018).
- **Tetracycline and fluoroquinolones (1990s–2000s)**: Resistance developed via ribosomal protection (*tetM*) and QRDR mutations in *gyrA/parC*.
- **Cephalosporins and macrolides (2010s–present)**: Mosaic *penA* alleles and 23S rRNA mutations compromised dual therapy regimens (Unemo et al., 2016).

2.3. Molecular Mechanisms of Resistance

- **β-lactam resistance**: Alterations in *penA* lead to reduced PBP2 binding affinity. Mosaic *penA* alleles (e.g., *penA XXXIV*) are associated with decreased ceftriaxone and cefixime susceptibility (Ohnishi et al., 2011).
- **Macrolide resistance**: High-level resistance is linked to mutations (A2059G) in the 23S rRNA gene and overexpression of the MtrCDE efflux pump, driven by *mtrR* promoter mutations or gene deletions (Fifer et al., 2016).
- **Fluoroquinolone resistance**: Caused by mutations in *gyrA* (S91F, D95G) and *parC* (S87R), leading to reduced drug binding to DNA gyrase and topoisomerase IV (Deguchi et al., 2016).
- **Efflux and permeability**: Porin mutations (*porB1b*) reduce permeability, while overactive efflux pumps decrease intracellular drug concentrations.

2.4. Treatment Challenges and Surveillance

The CDC now recommends high-dose ceftriaxone (500 mg IM) monotherapy for uncomplicated infections (CDC, 2021). However, treatment failures have been reported in Japan, the UK, and Australia (Eyre et al., 2019; Whiley et al., 2018). WHO's Gonococcal Antimicrobial Surveillance Programme (GASP) has documented resistance in >70 countries but lacks consistent data from Africa and Southeast Asia (Wi et al., 2017).

New drugs in development include:

- **Zoliflodacin** (a spiropyrimidinetrione)
- **Gepotidacin** (a novel topoisomerase inhibitor)Both show promise against multidrug-resistant strains (Taylor et al., 2018).

3. Mycoplasma genitalium

3.1. Overview and Clinical Relevance

Discovered in 1981, *Mycoplasma genitalium* is a fastidious, cell wall–lacking bacterium increasingly recognized as a major cause of non-gonococcal urethritis (NGU) in men and cervicitis and pelvic inflammatory disease (PID) in women (Taylor-Robinson & Jensen, 2011). Due to its intracellular lifestyle and small genome (~580 kbp), it evades host immunity and is difficult to culture in standard diagnostic settings. Prevalence estimates range from 1–3% in the general population to over 10% in high-risk groups, particularly among men who have sex with men (MSM) (Soni et al., 2019).

3.2. Diagnostic and Treatment Challenges

Culture is impractical; diagnosis relies on nucleic acid amplification tests (NAATs), which are not universally available. Initially treated with single-dose azithromycin, *M. genitalium* has developed significant resistance due to genetic mutations and inappropriate macrolide use, particularly in syndromic STI management (Read et al., 2017). Doxycycline, while partially effective, has low microbiological cure rates (~30%) (Bissessor et al., 2015).

Resistance-guided therapy is the current gold standard in Australia and the UK, where clinicians initiate treatment with doxycycline to reduce organism load, then adjust based on detected resistance mutations (Jensen et al., 2016; Tabrizi et al., 2020).

3.3. Molecular Mechanisms of Resistance

- **Macrolide resistance**: Point mutations at positions A2058 or A2059 in the 23S rRNA gene (homologous to *E. coli*) disrupt azithromycin binding to the 50S ribosomal subunit. These mutations are now present in >50% of global isolates, with higher prevalence in Australia and Japan (Hamasuna et al., 2018; Machalek et al., 2020).
- **Fluoroquinolone resistance**: Mutations in the quinolone resistance–determining regions (QRDRs) of *parC* (S83I, D87N) and, less commonly, *gyrA*, reduce fluoroquinolone activity (e.g., moxifloxacin). Dual resistance (macrolide + fluoroquinolone) is now seen in ~15% of clinical isolates in some settings (Read et al., 2019).

3.4. Clinical and Public Health Impact

Dual-class resistance significantly limits treatment options. Alternative agents like pristinamycin, sitafloxacin, and minocycline are not widely accessible. WHO surveillance of *M. genitalium* resistance is limited, and no globally harmonized treatment guidelines exist. As a result, many low-income settings use empirical regimens, accelerating resistance development (Bradshaw et al., 2017).

4. Chlamydia trachomatis

4.1. Epidemiological Burden and Clinical Manifestations

C. trachomatis is the most common bacterial STI globally, with an estimated 129 million new cases in 2020 (WHO, 2023). It is an obligate intracellular pathogen that infects epithelial cells of the urogenital tract, rectum, conjunctiva, and pharynx. Clinical outcomes include urethritis, cervicitis, PID, ectopic pregnancy, and infertility. Asymptomatic infections are common, particularly in women, complicating detection and control (Geisler, 2012).

4.2. Treatment Efficacy and Resistance Concerns

Unlike gonorrhea and *M. genitalium*, *C. trachomatis* has not demonstrated confirmed genetic antimicrobial resistance. First-line treatments are oral doxycycline (100 mg twice daily for 7 days) or azithromycin (1 g single dose). However, recent evidence indicates doxycycline is more effective, especially for rectal infections, with azithromycin failure rates up to 30% (Kong et al., 2014; Lau et al., 2021).

4.3. Hypotheses for Treatment Failure

- **Persistent infection**: Some strains enter a viable but non-culturable (VBNC) state or an aberrant "persistent" form when exposed to stress, such as sub-lethal antibiotic levels. These forms can survive treatment and later reactivate (Wyrick, 2010; Dean & Suchland, 2019).
- **Limited drug penetration**: Azithromycin may not reach effective concentrations in rectal or pharyngeal tissues.
- **High reinfection rates**: Reinfection rather than true resistance may explain some treatment failures, particularly in populations with limited partner notification and retesting.
- **Immunological evasion**: *C. trachomatis* modulates host immune responses and antigen presentation, potentially enabling prolonged intracellular survival (Rank & Yeruva, 2014).

4.4. Mass Drug Administration and Bystander Resistance

Mass azithromycin use in trachoma elimination programs raises concerns about promoting resistance in off-target organisms, including *Streptococcus pneumoniae* and *Shigella* (Doan et al., 2019). There is also concern that such campaigns might reduce azithromycin effectiveness for chlamydia treatment in co-endemic regions.

5. Treponema pallidum

5.1. Clinical Background and Global Burden

Treponema pallidum subsp. *pallidum*, the etiologic agent of syphilis, is a spirochete transmitted primarily through sexual contact. Infections can progress through primary, secondary, latent, and tertiary stages, and vertical transmission leads to congenital syphilis, a major cause of perinatal mortality and morbidity worldwide (Gomez et al., 2013). Despite decades of decline, syphilis incidence has resurged globally, particularly in men who have sex with men (MSM), persons living with HIV, and heterosexual populations in low-resource settings (Kojima et al., 2018).

5.2. Historical Treatment and Current Standards

Benzathine penicillin G remains the gold standard for all stages of syphilis, with no documented resistance. Alternative regimens include doxycycline (for non-pregnant penicillin-allergic patients) and azithromycin. However, azithromycin has been removed from many treatment protocols due to rising resistance (CDC, 2021).

5.3. Resistance Mechanisms

- **Macrolide resistance**: The primary mechanism of resistance in *T. pallidum* is via mutations in the *23S rRNA* gene, specifically A2058G and A2059G mutations leading to reduced macrolide binding to the 50S ribosomal subunit (Lukehart et al., 2004). These mutations are homologous to those found in other resistant bacteria, such as *M. genitalium* and *N. gonorrhoeae*.
- **Epidemiological spread**: Macrolide-resistant strains are now endemic in the U.S., China, and parts of Europe and Africa. A study in Shanghai, China, reported macrolide resistance rates exceeding 90% among *T. pallidum* isolates (Zhou et al., 2010; Peng et al., 2012).

5.4. Diagnostic Limitations

The inability to culture *T. pallidum* in vitro hinders phenotypic resistance testing. Surveillance relies on molecular methods such as PCR amplification and sequencing of the 23S rRNA gene from clinical specimens (Stamm, 2010). However, these tools are not routinely available in many high-burden countries.

5.5. Public Health and Therapeutic Implications

- **Penicillin shortages**: Despite the drug's continued efficacy, global shortages of benzathine penicillin G, due to manufacturing limitations, jeopardize syphilis control efforts, particularly in maternal and neonatal care (WHO, 2016).
- **Congenital syphilis**: Inadequate treatment access in pregnancy has led to an alarming increase in congenital syphilis in several countries, including Brazil, India, and Nigeria (Korenromp et al., 2019).

There is a clear need for global investment in penicillin production and for robust resistance monitoring, especially where azithromycin is still used as an alternative.

6. Diagnostic and Surveillance Challenges

6.1. Limitations of Syndromic Management

Many low-resource settings use syndromic management for STIs, in which treatment is based solely on symptoms and signs, without etiologic confirmation. While useful in high-prevalence settings, this approach has several limitations:

- Fails to identify asymptomatic infections, especially in women (Peeling et al., 2021)
- Leads to overuse of antibiotics, increasing resistance pressure
- Provides no resistance data to inform future treatment guidelines
- This model remains dominant across sub-Saharan Africa, South Asia, and parts of Latin America.

6.2. Resistance Testing: Access and Equity

Molecular resistance detection assays, such as the ResistancePlus MG assay (for *M. genitalium*) and NG-STAR typing (for *N. gonorrhoeae*), have revolutionized care in high-income settings. However, such tools are:

- Expensive
- Require infrastructure (NAAT platforms, trained personnel)
- Largely unavailable in countries with the highest STI burdens (Tabrizi et al., 2020)

Thus, resistance-guided therapy remains aspirational rather than standard in most of the world.

6.3. Global Surveillance Efforts

The WHO's Gonococcal Antimicrobial Surveillance Programme (GASP) monitors global *N. gonorrhoeae* resistance patterns. As of 2022:

- 74 countries submitted data
- Only 34 had complete data for ceftriaxone, cefixime, and azithromycin (WHO, 2023)

There is no global surveillance system for *M. genitalium* or *T. pallidum* resistance, leaving large knowledge gaps.

6.4. Policy Limitations and Research Gaps

- No unified global policy requires routine resistance testing before STI treatment.
- Most national STI programs do not have laboratory-based resistance monitoring.
- Real-time surveillance data is lacking, delaying updates to clinical guidelines.

The integration of resistance diagnostics into point-of-care platforms (e.g., GeneXpert) could democratize access, but political and financial commitment are required.

7. Future Therapeutic Directions

7.1. Novel Antimicrobial Agents

With resistance compromising current treatment regimens, multiple investigational drugs are in development:

- **Zoliflodacin**: A spiropyrimidinetrione targeting DNA gyrase, active against resistant *N. gonorrhoeae*, including strains resistant to ceftriaxone. Phase III trials are ongoing with promising results in Phase II (Taylor et al., 2018).
- **Gepotidacin**: A novel triazaacenaphthylene that inhibits bacterial DNA gyrase and topoisomerase IV via a mechanism distinct from fluoroquinolones. It has shown efficacy in preliminary trials for gonorrhea (Scangarella-Oman et al., 2018).
- **Pristinamycin, Minocycline, Sitafloxacin**: All show variable activity against *M. genitalium*, but are limited by regulatory approval status, cost, and geographic availability (Read et al., 2019).

7.2. Resistance-Targeted Diagnostic Innovation

Development of NAAT-based diagnostics that detect both pathogen and resistance markers is central to improving care:

- **Resistance Plus MG**: Simultaneously identifies *M. genitalium* and macrolide resistance mutations (Tabrizi et al., 2020).
- **NG-STAR**: A genotyping platform for characterizing AMR determinants in *N. gonorrhoeae* (Demczuk et al., 2017).

Efforts are also underway to adapt these into multiplex platforms for broader point-of-care use.

7.3. Non-antibiotic Strategies

- **Bacteriophage therapy**: Research on phages specific to *N. gonorrhoeae* is ongoing, though no clinical candidates exist yet.
- **Antimicrobial peptides**: These molecules disrupt bacterial membranes and may offer a resistance-proof mechanism.
- **CRISPR-Cas antimicrobials**: Engineered nucleases are being developed to target resistance genes directly (Bikard et al., 2014).

- **Microbiome modulation**: Manipulating the vaginal or urethral microbiome to promote colonization with protective species may red`uce STI risk and recurrence.

7.4. Global Policy and Investment Needs

International agencies must:

- Ensure equitable access to benzathine penicillin and new therapeutics
- Fund diagnostic scale-up in LMICs
- Integrate AMR surveillance into existing health information systems
- Incentivize pharmaceutical R&D for STI-specific antibiotics through push-and-pull models (Miethke et al., 2021)

8. Conclusion

The rise of antimicrobial resistance in bacterial STIs signals a major threat to global sexual and reproductive health. Gonorrhea, once easily curable, may soon become untreatable in many parts of the world. *Mycoplasma genitalium* already shows dual-class resistance, while treatment failures in *Chlamydia trachomatis* and macrolide-resistant *Treponema pallidum* are increasing. Diagnostic and surveillance infrastructure remains grossly inadequate, especially in the highest-burden regions.

There is still an opportunity to avert this crisis, but only with decisive global action. Investment in novel therapeutics, rapid diagnostics, and resistance-guided treatment must be prioritized alongside improved public health policy and equitable access to care. Without these measures, the world risks re-entering an era where the most common STIs are once again incurable.

Compliance with ethical standards

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Conflict of Interest

The author declares no conflict of interest.

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