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REVIEW

Safety Aspects and Rational Use of Single Intramuscular Dose Ceftriaxone: Clinical Insights on the Management of Uncomplicated Gonococcal Infections

George P Allen, Haley L Morrill

School of Pharmacy, Westbrook College of Health Professions, University of New England, Portland, ME, USA

Correspondence: George P Allen, School of Pharmacy, Westbrook College of Health Professions, University of New England, 716 Stevens Avenue, Portland, ME, 04103, USA, Tel +1 207-221-4075, Fax +1 207-523-1927, Email gallen3@une.edu

Abstract: Gonorrhea, a sexually transmitted infection caused by *Neisseria gonorrhoeae*, is a grave public health concern. Gonorrhea is the second most reported sexually transmitted infection worldwide. The treatment of uncomplicated gonococcal infections has evolved dramatically in response to the emergence of antimicrobial resistance. Multiple resistance mechanisms (for example, beta-lactamase production, antimicrobial efflux, and target site modification) exist, some of which may cause multidrug-resistance. Ceftriaxone was first recommended as an option for uncomplicated gonococcal infections in 1985, and it is now a mainstay of therapy in all clinical practice guidelines. Ceftriaxone has consistently shown high microbiologic cure rates in clinical trials, and it has demonstrated an excellent safety profile. Although its use may be limited in patients with hypersensitivity to penicillins, the risk of using ceftriaxone in such patients is overestimated. The emergence of reduced ceftriaxone susceptibility in *N. gonorrhoeae*, coupled with a lack of diverse treatment alternatives and the limited pipeline of new antimicrobials, is a significant threat to the treatment of gonorrhea.

Keywords: antimicrobial resistance, ceftriaxone, gonorrhea, *Neisseria gonorrhoeae*

Introduction

Gonorrhea, a sexually transmitted infection caused by the Gram-negative bacterium *Neisseria gonorrhoeae*, is a grave public health concern. While chlamydia is the most commonly reported sexually transmitted infection, gonorrhea is the second most reported sexually transmitted infection worldwide and rates of reported gonococcal infections have continued to increase in many geographic areas, including Asia, Europe, and North America. The World Health Organization (WHO) has estimated that there were 82.4 million new cases of gonorrhea in 2020 in adolescents and adults aged 15–49 years worldwide.[1] In 2021, a total of 710,151 cases of gonorrhea were reported to the Centers for Disease Control and Prevention (CDC), representing a 4.6% increase from 2020 to 2021, and rates of reported cases have increased by 118% since a historical low rate in 2009.[2] These increased rates in 2021 were noted in both males and females and in most age and racial groups. Social determinants of health, including socioeconomic status and lack of access to health care (including reduced access to testing and/or treatment), have been shown to influence the transmission of gonorrhea.[3]

The development of significant antimicrobial resistance in *N. gonorrhoeae* is a particular concern, as the organism has developed reduced susceptibility to most antimicrobials.[4] The CDC developed a report of notable antimicrobial-resistant microbes in 2013 and that report listed antimicrobial-resistant *N. gonorrhoeae* as one of the three organisms designated an urgent threat, the highest threat level.[5] A list of priority antimicrobial-resistant pathogens developed by the WHO in 2017 included *N. gonorrhoeae* as one of six bacteria in the high priority category, the second-highest priority.[6] A 2019

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update of the 2013 CDC report maintained antimicrobial-resistant *N. gonorrhoeae* as an organism (now, one of five) in the urgent threat category.[7] In fact, the possibility of the emergence of untreatable gonorrhea has been raised.[4]

N. gonorrhoeae may infect several anatomic sites in both males and females. Anatomic sites affected are the rectum, urogenital tract, oropharynx, and eye. From these sites, dissemination may occur if left untreated. Uncomplicated infection has been defined as infection that results in neither bacteremia nor disseminated infection.[8] In females, symptomatic gonococcal infections of the urogenital tract may present as vaginal discharge, vaginal pruritus, or abnormal vaginal bleeding. These may also be accompanied by abdominal pain or dyspareunia, alluding to the possible presence of pelvic inflammatory disease. Males with symptomatic urogenital infections may present with urethral discharge or dysuria. Infections of the urogenital tract are often asymptomatic in both sexes. In females, urogenital infections may be asymptomatic in 86.4% to 92.6% of cases.[9] The rate of asymptomatic urogenital infections in males is less defined, but one study predicts that 55.7% to 86.8% of cases may be asymptomatic.[9] Those with gonococcal proctitis may present with anorectal discharge, bleeding, tenesmus, and/or pain. Gonococcal conjunctivitis occurs due to autoinoculation in adults and occurs in infants born to infected mothers. Pharyngitis secondary to gonococcal infection may result in sore throat, pharyngeal exudates, or cervical lymphadenitis when symptomatic. However, like urogenital gonococcal infections, pharyngeal gonococcal infections are usually asymptomatic. A longitudinal study of men who have sex with men (MSM) revealed that within this population 92% of pharyngeal gonorrhea cases were asymptomatic.[10] Disseminated gonococcal infection typically presents as septic arthritis, dermatitis, or tenosynovitis.[11] In rarer cases other disseminated gonococcal infections have been observed, including endocarditis, osteomyelitis, myositis, and meningitis.[11] It is important to recognize and treat uncomplicated gonococcal infections in order to prevent adverse sequelae such as pelvic inflammatory disease and infertility and to reduce transmission.

Ceftriaxone is currently a core component of the preferred treatment regimens for uncomplicated genital, anorectal, and pharyngeal infections. However, recent decreases in ceftriaxone susceptibility in *N. gonorrhoeae* have raised concerns regarding the long-term viability of this agent for gonococcal infections. The following is a focused review of key aspects of the use of ceftriaxone for uncomplicated gonococcal infections.

Treatment of Uncomplicated Gonococcal Infections - Historical Perspective

Figure 1 includes notable historical events related to the management of uncomplicated gonococcal infections. The sulfonamide antimicrobials, first made available in the 1930s, were the first class of antimicrobials recommended for the treatment of gonorrhea. However, resistance in *N. gonorrhoeae* became widespread by 1945, and the use of sulfonamides for gonococcal infections was no longer recommended.[12,13] Penicillin was, however, found to display activity against sulfonamide-resistant *N. gonorrhoeae* and was used successfully to treat infections caused by sulfonamide-resistant strains.[14,15] Penicillin became the preferred therapy for many years, but ongoing, progressive reductions in penicillin susceptibility, as well as associations with penicillin treatment failure, were noted.[16–18] This development led to the use of escalating doses of procaine penicillin G until a dose of 4.8 million units intramuscularly was recommended in the 1972 CDC guidelines.[19] The concomitant administration of probenecid, which inhibits the renal tubular secretion of penicillin and displays synergistic in vitro antibacterial activity with penicillin, was also recommended.[20,21]

In 1985, in light of increasing penicillin resistance, ceftriaxone (administered as a single intramuscular dose of 250 mg) was added for the first time as a recommended treatment option.[22] The 1985 treatment guideline notably added concomitant administration of tetracycline, doxycycline, or erythromycin (the latter in those unable to receive tetracyclines) in order to provide activity against *Chlamydia trachomatis*, which often co-infects individuals with gonorrhea. Tetracycline and doxycycline were also included as alternative agents for gonorrhea in patients with hypersensitivity to penicillins or cephalosporins.[22] In 1986, the Gonococcal Isolate Surveillance Project (GISP), a national surveillance program that evaluates antimicrobial susceptibility in the United States, was developed. Initial findings from the GISP included increases in plasmid-mediated, penicillinase-producing *N. gonorrhoeae* and isolates with plasmid-mediated tetracycline resistance.[23] As resistance continued to emerge, in 1989 the CDC published revised guidelines that no longer included penicillin or tetracycline as a recommended therapy, and the combination of ceftriaxone (still at a dose of

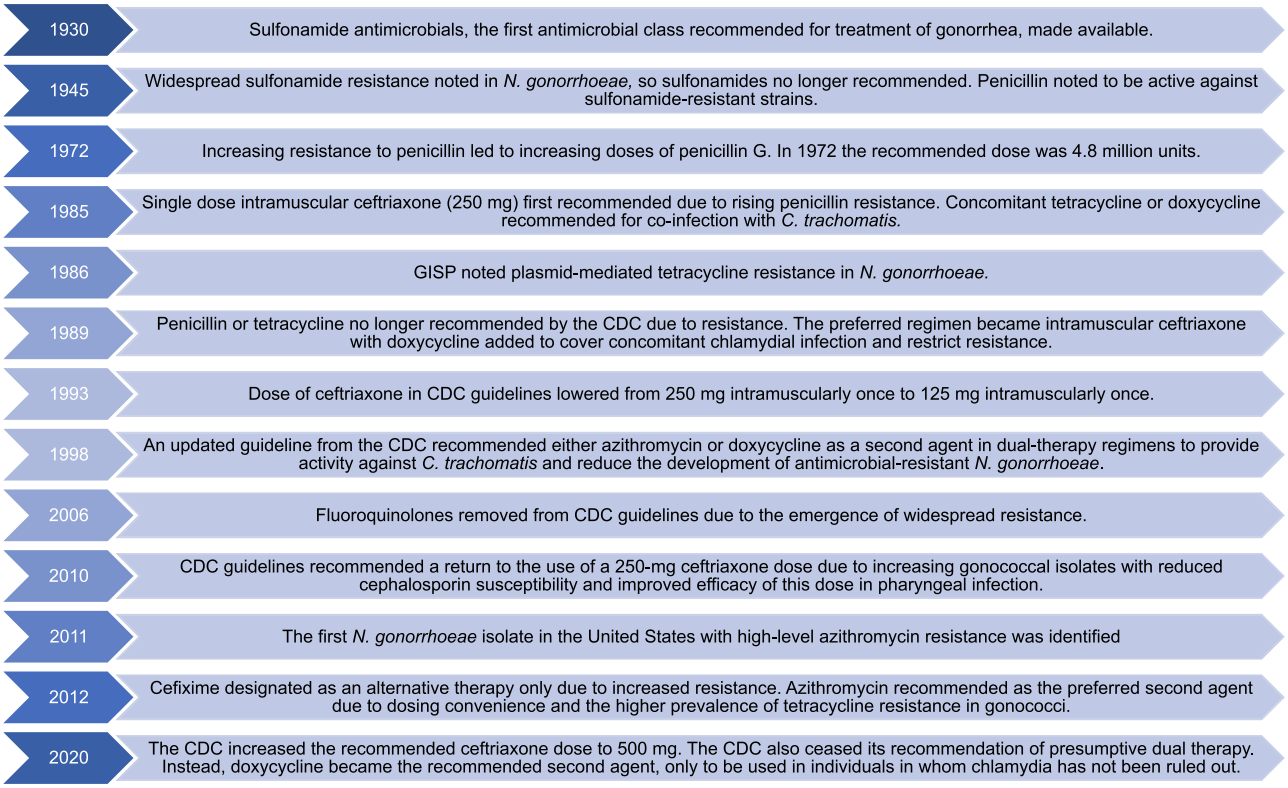

Figure 1 Timeline of Notable Events in the Treatment of Uncomplicated Gonococcal Infections.

250 mg intramuscularly) and doxycycline became the preferred regimen.[24] The addition of doxycycline was once again intended to treat concomitant chlamydial infection, but also to restrict the emergence of antimicrobial resistance in *N. gonorrhoeae*.

Updated guidelines in 1993 from the CDC continued to include ceftriaxone as the preferred therapy, but the recommended dose was lowered to 125 mg based on ceftriaxone's antimicrobial activity against *N. gonorrhoeae*, its pharmacokinetic profile, and results of published clinical trials.[25] Alternative recommended regimens included the oral cephalosporin cefixime or fluoroquinolones (ciprofloxacin or ofloxacin). Dual therapy with the addition of an agent displaying activity against *C. trachomatis*, including oral doxycycline or oral azithromycin, continued to be recommended. An updated guideline from the CDC in 1998 specifically recommended either azithromycin or doxycycline as a second agent in dual-therapy regimens to provide activity against *C. trachomatis* and reduce the development of antimicrobial-resistant *N. gonorrhoeae*.[26]

Fluoroquinolones offered several advantages for the treatment of gonorrhea, including availability as single-dose, oral regimens. However, decreased susceptibility to fluoroquinolones first emerged in Asia, and was later noted in Hawaii and California.[27–30] Fluoroquinolones were thus no longer recommended for gonococcal infections acquired in these geographic areas.[31] Later, the recommendation to avoid fluoroquinolones was expanded to include the MSM population because of reported increases in fluoroquinolone resistance in this population.[32] Finally, fluoroquinolones were removed from the CDC's treatment guidelines after widespread distribution of fluoroquinolone-resistant strains was noted in the United States.[33] Thus, cephalosporins remained the only preferred agents for gonorrhea.

The 2010 CDC guidelines recommended a return to the use of a 250-mg ceftriaxone dose because of wider distribution of gonococcal isolates with reduced cephalosporin susceptibility, reports of treatment failures in individuals who received ceftriaxone and improved efficacy of this dose in pharyngeal infection, which often goes undiagnosed.[34] In 2012, the CDC provided an update to its guidelines in which cefixime was no longer considered a recommended agent and was designated as an alternative treatment.[35] This recommendation was made because of noted increases in the distribution of gonococcal isolates with

reduced susceptibility to cefixime. In this same update azithromycin was recommended as the preferred second agent (rather than doxycycline) because of dosing convenience and the higher prevalence of tetracycline resistance in gonococci.[35] However, reduced susceptibility to azithromycin in *N. gonorrhoeae* was increasingly reported. The first *N. gonorrhoeae* isolate in the United States with high-level azithromycin resistance was identified in 2011, and the dissemination of strains with high-level azithromycin resistance and concomitant reduced cephalosporin susceptibility was reported.[36,37] At the same time, findings from the GISP showed that the ceftriaxone minimum inhibitory concentration (MIC) that inhibited 50% and 90% of gonococcal strains had increased by only one dilution when comparing data from 2014–2015 and 1992–1995.[38] Nonetheless, a pharmacodynamic analysis found that previously recommended doses of ceftriaxone and cefixime would not achieve an adequate time during which antimicrobial concentrations exceed the MIC for gonococcal isolates with elevated MIC values.[39] Since the pharmacokinetic/pharmacodynamic parameter that predicts the efficacy of beta-lactams is the time (percentage of the dosage interval) that concentrations exceed the MIC of a bacterium, the authors of this analysis suggested the use of higher cephalosporin doses (eg, ceftriaxone 500 mg or 1 gm) as one possible strategy for the treatment of gonococci with reduced susceptibility.[39] In a significant update in 2020, the CDC increased the recommended ceftriaxone dose to 500 mg (1 g in individuals weighing ≥ 150 kg) and increased the recommended dose of cefixime (still considered an alternative agent) to 800 mg.[40] The CDC also ceased its recommendation of presumptive dual therapy with the addition of azithromycin in light of continued reductions in azithromycin susceptibility and antimicrobial stewardship concerns. Instead, doxycycline became the recommended second agent, only to be used in individuals in whom chlamydia has not been ruled out.[40]

The recommendations described in this 2020 update are included in the current CDC guideline, published in 2021.[41] Australian guidelines recommend the combination of ceftriaxone 500 mg intramuscularly and azithromycin 1 g orally (2 g for oropharyngeal infection).[42] In Canadian guidelines, the combination of ceftriaxone 250 mg or cefixime 400 mg and azithromycin 1 g is recommended for anogenital infection, while cefixime is not included in the preferred regimen for oropharyngeal infection.[43] European guidelines recommend the combination of ceftriaxone 1 g intramuscularly and azithromycin 2 g orally based in part on documented efficacy of the combination and potential positive impacts on the development of antimicrobial resistance.[44] The use of ceftriaxone monotherapy is recommended only in particular circumstances, and only if local susceptibility testing has demonstrated that resistance to ceftriaxone is not present.[44] UK guidelines recommend monotherapy with ceftriaxone 1 g intramuscularly.[45] Azithromycin is not recommended as an additional agent in the UK guidelines because of antimicrobial stewardship concerns, increasing rates of resistance, inconclusive evidence of in vitro synergy between azithromycin and cephalosporins, and concerns regarding clinical efficacy.[45] Current WHO guidelines (published in 2016) recommend the combination of ceftriaxone 250 mg intramuscularly or cefixime 400 mg orally with azithromycin 1 g orally for genital and anorectal gonococcal infections, and monotherapy using ceftriaxone, cefixime, or spectinomycin is recommended as an alternative only if recent susceptibility has been noted in local surveillance data.[46] Monotherapy with cefixime or spectinomycin is not recommended for oropharyngeal infection.[46]

Antimicrobial Resistance in *Neisseria gonorrhoeae*

Resistance in *N. gonorrhoeae* develops rapidly through gene transfer (transformation/recombination) as well as through chromosomal mutations. Gonococci can mutate their genome and the bacterium is naturally competent for transformation throughout its life cycle.[47,48] Mutations occur particularly in response to selective pressures, such as antimicrobial exposure. Through these mechanisms, *N. gonorrhoeae* has acquired or evolved to have all four known physiological antimicrobial resistance mechanisms. These mechanisms are: i) enzymatic degradation or modification of antimicrobials, ii) target site modification to decrease affinity for antimicrobials, iii) decreased influx of antimicrobials, and iv) increased efflux of antimicrobials.[47] Acquisition of a single determinant of resistance does not appear to result in clinically significant increases in the MIC, but cumulative effects and interactions between several resistance determinants result in increases in the MIC that are of clinical significance.[47] Antimicrobial-resistant strains of *N. gonorrhoeae* do not exhibit significantly lower biological fitness (for example, lower rates of growth) compared to non-resistant strains, which may result in the persistence of resistant strains even in the absence of antimicrobial exposure.[47]

Sulfonamides inhibit the dihydropteroate synthase (DHPS) enzymes of bacteria, thus inhibiting folic acid synthesis. Resistance to sulfonamides in *N. gonorrhoeae* may be due to either overproduction of *p*-aminobenzoic acid or through alterations of DHPS encoded by the *folP* gene.[49] The addition of trimethoprim to sulfonamides expands their spectrum of

activity. Trimethoprim targets dihydrofolate reductase (DHFR), another enzyme involved in the folic acid synthesis pathway. However, the addition of trimethoprim does not overcome resistance in *N. gonorrhoeae* as gonococcal DHFR exhibits low affinity for trimethoprim.[50]

Resistance to penicillins in *N. gonorrhoeae* is multifaceted and may be either chromosomally- or plasmid-mediated. Penicillin and its derivatives inhibit peptidoglycan cross-linking through the binding of the beta-lactam ring to penicillin-binding proteins (PBPs). Chromosomally mediated penicillin resistance in gonococci is due to mutations that modify the target proteins (PBPs), increased expression of the efflux-pump encoding gene *mtrCDE*, and decreased influx through modification of genes encoding porin PorB.[48] There is also at least one known untransformable resistance determinant, "factor x", that has yet to be elucidated fully.[48] Plasmid-mediated resistance to penicillin in gonococcal strains typically consists of TEM-1 or TEM-135 type beta-lactamases (encoded by $bla_{TEM\text{-}1}$ and $bla_{TEM\text{-}135}$ respectively).[48] These enzymes hydrolyze the beta-lactam ring of beta-lactamase-susceptible penicillins, rendering them inert.

Tetracycline resistance in *N. gonorrhoeae* may also be either chromosomally- or plasmid-mediated. Tetracyclines inhibit protein synthesis by binding to the 30S ribosomal subunit and blocking aminoacyl-tRNA from binding the mRNA-ribosome complex. Chromosomally mediated resistance to tetracyclines in *N. gonorrhoeae* includes the same mutations in *mtrCDE* (resulting in increased efflux), and genes encoding porin PorB (resulting in decreased influx) that confer penicillin resistance.[47] This means that strains exhibiting chromosomally mediated resistance to penicillin through these genes will exhibit cross-resistance to tetracyclines. Chromosomally mediated resistance to tetracyclines may also occur due to mutations in the *rpsJ* gene, which encodes ribosomal protein S10, the binding target of tetracyclines.[47] Plasmid-mediated resistance to tetracyclines occurs due to the presence of a *tetM*-containing conjugative plasmid and results in high-level tetracycline resistance.[48] TetM binds to the bacterial ribosome and leads to the release of tetracyclines, allowing protein synthesis to resume.[48]

Resistance to macrolides in *N. gonorrhoeae* is solely chromosomally mediated. Macrolides inhibit protein synthesis by binding the 50S ribosomal subunit and preventing translocation of peptidyl-tRNa, resulting in blockage of the exit channel that forces the ribosome to release incomplete peptides. Gonococcal resistance to macrolides occurs through chromosomal modifications that result in alterations of the ribosomal target (blocking or reducing its affinity for macrolides) and/or overexpression of efflux pumps.[47] These efflux pumps include MtrCDE (the same pump that confers resistance to tetracyclines and penicillins) as well as the MacAB efflux pump.[48]

Gonococcal resistance to fluoroquinolones is also solely chromosomally mediated. Fluoroquinolones block bacterial DNA metabolism through inhibition of DNA gyrase and topoisomerase IV. Therefore, gonococcal resistance develops through mutations to the genes that encode these enzymes and resulting alteration of the binding of fluoroquinolones. DNA gyrase is encoded by *gyrA* and *gyrB* while topoisomerase IV is encoded by *parC* and *parE*.[48] The primary target gene for ciprofloxacin resistance is *gyrA* and isolates with higher levels of resistance have exhibited specific mutations in *parC*.[47] Fluoroquinolone susceptibility has been shown to be influenced by previous exposure to azithromycin.[51]

Cephalosporins bind to PBPs and inhibit peptidoglycan cross-linking and resulting cell wall synthesis in bacterial cells.[47] Unlike penicillins, however, they are not susceptible to degradation by penicillinases. Therefore, resistance to cephalosporins in *N. gonorrhoeae* is only chromosomally mediated. The cephalosporins most commonly used in the treatment of gonorrhea are the third generation extended-spectrum cephalosporins (ESCs) ceftriaxone (injectable) and cefixime (oral). Gonococcal resistance to cefixime hinges primarily on mutations to the *penA* gene encoding PBP2, with little resistance to cefixime seen from mutations to the genes encoding the efflux transporter MtrCDE or porin PorB.[52] Ceftriaxone resistance in gonococci, however, is equally weighted in mutations among *penA, mtrCDE*, and *penB* (which encodes PorB).[52] All of these resistance determinants are also seen in high-level penicillin-resistant strains of *N. gonorrhoeae*.[47] One distinct difference between penicillin resistance and ESC resistance in *N. gonorrhoeae* is that while mutations in the gene encoding PBP1 play a role in penicillin resistance, these mutations appear to minimally contribute to ESC resistance.[52] Reduced ceftriaxone susceptibility has also been associated with biofilm production and ceftriaxone tolerance, and ceftriaxone exposure has been shown to lead to ceftriaxone tolerance.[53,54]

There is significant overlap in resistance determinants in *N. gonorrhoeae* that confer resistance to several classes of medications. Overlap occurs in those determinants that are located chromosomally. Plasmid-mediated resistance shows no overlap, with resistance only to penicillins through bla_{TEM} and tetracyclines through *tetM*. Resistance determinants in

the MtrCDE efflux pump and porin PorB play a role in gonococcal resistance to penicillins, tetracyclines, and ESCs. This allows for the rapid development of extensively antimicrobial-resistant strains of *N. gonorrhoeae* through the development of a fewer number of mutations. When these resistance determinants are combined with those for sulfonamide resistance and tetracycline resistance, the emergence of strains for which there may be no current treatment occurs.

Evidence of Efficacy

When considering the acceptable efficacy of an antimicrobial for the treatment of gonorrhea, it has been proposed that a clinical cure rate of greater than 95%, with a lower limit of the 95% confidence interval for that cure rate of at least 90%, be required.[55] It was subsequently proposed that these criteria should be more stringent, with a clinical cure rate of at least 95% and a lower limit of the 95% confidence interval for clinical efficacy of at least 95%, which would potentially result in fewer therapeutic failures.[56] These more stringent criteria are now required for preferred regimens, but less stringent efficacy criteria are required for alternative regimens in order to lower the threshold for adoption of alternative regimens.[57] It has also been proposed that antimicrobials for the treatment of gonorrhea preferably be evaluated using prospective, randomized, double-blind, active-control studies, and that microbiologic eradication be the outcome that indicates efficacy.[55]

For many years dual therapy including ceftriaxone with either azithromycin or doxycycline has been recommended for the treatment of gonorrhea, and many clinical trials have included this dual-therapy regimen as a comparator. This practice unfortunately hinders assessment of the efficacy or safety of ceftriaxone alone.[58] Thus, in the current review, we have included only those studies that included ceftriaxone monotherapy as a comparator. We searched the PubMed database from its inception until June 1, 2023. Search terms (MeSH terms and keywords) included ceftriaxone, gonorrhea, and *Neisseria gonorrhoeae*. We included randomized, comparative trials with participants diagnosed with uncomplicated gonococcal infections. We did not include reviews, case reports, cohort studies, and studies published in languages other than English.

Table 1 includes efficacy results from randomized, controlled clinical trials.[59–67] All studies used microbiologic eradication as the primary outcome and indicator of cure. Some studies included only anogenital infections, but others included individuals with oropharyngeal infection. A beta-lactam or beta-lactam combination (ampicillin/sulbactam, cefotaxime, cefoxitin, ertapenem, aqueous procaine penicillin G, or procaine penicillin G plus benzylpenicillin) or spectinomycin was the most common comparator; some beta-lactams were combined with probenecid, which has no activity against *N. gonorrhoeae* but is used to increase concentrations of the beta-lactam with which it is combined. Ceftriaxone displayed high cure rates in all studies, with all cure rates exceeding the target of 95%.

Tolerability and Safety

Beta-lactams are among the safest of all antimicrobials, and serious adverse effects are generally uncommon. Table 1 includes safety results from randomized, controlled clinical trials.[59–67] Note that patients with a history of hypersensitivity to beta-lactams were excluded in seven trials. Ceftriaxone was generally associated with minor adverse events that resolved during each trial's study period. Injection site pain was reported in several studies, although two studies reported anecdotal commentary regarding the relative painlessness of ceftriaxone compared to other injections for gonorrhea.[61,64] The percentage of patients experiencing adverse events was generally comparable between treatments. For example, in a comparison with the combination of procaine penicillin plus benzylpenicillin, adverse events were reported in 16.8% of patients receiving procaine penicillin plus benzylpenicillin, 18% of patients receiving ceftriaxone 500 mg, and 11.8% of patients receiving ceftriaxone 250 mg.[64] In a comparison with cefotaxime, adverse events that were deemed possible or probably related to study drug were noted in 4.2% of individuals given cefotaxime and 7.3% of individuals given ceftriaxone.[66]

Some studies included laboratory analyses (for example, complete blood counts and measures of hepatic and renal function) as part of their assessment of adverse effects. Most such studies reported no significant laboratory abnormalities in patients given ceftriaxone. In one study that included four treatment arms, declines in glomerular filtration rate were noted in enrollees in all treatment arms, including 4% of ceftriaxone-treated individuals.[67] Patients experienced an improvement in their glomerular filtration rate to within 25% of baseline.

Table 1 Efficacy and Safety Results

Study	Study Population	Antimicrobials	Sample Size (Evaluable Patients)	Microbiologic Cure Rate	Adverse Effects
Handsfield et al[59]	Males aged 16 years or older	Ceftriaxone 125 mg or 250 mg IM Spectinomycin 2 g IM	Ceftriaxone: 59 Spectinomycin: 58	Ceftriaxone: 100% Spectinomycin: 97%	No serious adverse events were noted. No important laboratory abnormalities were noted.
Judson et al[60]	Females aged 18 years or older	Ceftriaxone 250 mg IM Aqueous procaine penicillin G 4.8×10^6 units IM x 2 doses	Ceftriaxone: 23 Penicillin G: 28	Ceftriaxone: 100% Penicillin G: 100%	Mild injection pain was noted by an unreported number of patients. No serious adverse events were noted. No important laboratory abnormalities were noted.
Zajdowicz et al[61]	Males; age limit not specified	Ceftriaxone 250 mg IM Cefoxitin 2 g IM plus probenecid 1 g PO	Ceftriaxone: 61 Cefoxitin: 67	Ceftriaxone: 100% Cefoxitin: 98.5%	All patients given ceftriaxone reported minimal or no injection pain. No serious adverse effects were noted.
Judson et al[62]	Males and females aged 18 years or older	Ceftriaxone 125 mg IM Spectinomycin 2 g IM	Ceftriaxone: 84 Spectinomycin: 23	Ceftriaxone: 97.6% Spectinomycin: 65.2%	Mild injection pain was noted by an unreported number of patients. One patient given ceftriaxone developed an erythematous maculopapular rash and slight facial swelling that resolved. No important laboratory abnormalities were noted.
Panikabutra et al[63]	Males; age limit not specified	Ceftriaxone 250 mg IM Spectinomycin 2 g IM	Ceftriaxone: 97 Spectinomycin: 93	Ceftriaxone: 100% Spectinomycin: 100%	No adverse effects to either treatment were noted.
Dixon et al[64]	Males and females; age limit not specified	Ceftriaxone 250 mg or 500 mg IM Procaine penicillin G 1.5 g plus Benzylpenicillin 300 mg IM	Ceftriaxone: 107 Procaine penicillin G plus Benzylpenicillin: 115	Ceftriaxone: 100% Procaine penicillin G plus Benzylpenicillin: 90–100% (across four experimental groups)	Mild injection pain was noted by an unreported number of patients. Transient gastrointestinal symptoms were the only other adverse events noted. No serious adverse events were noted.
Baddour et al[65]	Males and females aged 18 years or older	Ceftriaxone 250 mg IM Ampicillin/sulbactam 1 g/0.5 g IM plus Probenecid 1 g PO	Ceftriaxone: 97 Ampicillin/sulbactam plus Probenecid: 98	Ceftriaxone: 99% Ampicillin/sulbactam plus Probenecid: 94.9%	No serious adverse events were noted. One patient given ceftriaxone developed a rash.
McCormack et al[66]	Males and females; age limit not specified	Ceftriaxone 250 mg IM Cefotaxime 500 mg IM	Ceftriaxone: 223 Cefotaxime: 218	Ceftriaxone: 99.1% Cefotaxime: 97.7%	Injection pain was noted in 3.9% of patients given ceftriaxone. No serious adverse events were noted. No important laboratory abnormalities were noted.
de Vries et al[67]	Males and females aged 18 years or older	Ceftriaxone 500 mg IM Ertapenem 1 g IM Gentamicin 5 mg/kg IM Fosfomycin 6 g PO	Ceftriaxone: 93 Ertapenem: 87 Gentamicin: 85 Fosfomycin: 33	Ceftriaxone: 100% Ertapenem: 99% Gentamicin: 93% Fosfomycin: 12%	Adverse events were noted in 23% of individuals given ceftriaxone. Of these adverse events, 19% were mild and 2% were moderate.

Abbreviations: IM, intramuscularly; PO, orally.

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Alternative Therapies

Current clinical practice guidelines include several antimicrobials that are recommended as alternatives in individuals in whom preferred agents are contraindicated or unavailable. These include cefixime, ciprofloxacin, or the combination of azithromycin and gentamicin. Other antimicrobials that are not routinely included in current guidelines but that may offer promise for the treatment of gonorrhea exist, but there remains a need for additional antimicrobials for this infection.

Cefixime is not generally considered a first-line agent but is an alternative recommendation in certain situations (for example, in the CDC guidelines its use is recommended when ceftriaxone is not available).[41] Limitations to the use of cefixime include reduced efficacy in oropharyngeal infection and attainment of a lower time above the MIC than is achieved by ceftriaxone.[39,56] A higher dose of azithromycin (2 g) has been shown to be effective against urogenital gonococcal infections, but increasing resistance to this agent, reports of treatment failure, and significant gastrointestinal adverse effects may limit its use.[56] Spectinomycin is included in some clinical practice guidelines, but is not included in current CDC guidelines due to the unavailability of this agent in the United States. Spectinomycin has also demonstrated reduced efficacy in oropharyngeal infection.[56] Gentamicin is considered an alternative agent in certain scenarios, but two recent studies found that gentamicin failed to achieve non-inferiority to ceftriaxone, and it has shown poorer results in oropharyngeal infection.[67,68] Ciprofloxacin is considered an alternative treatment in some guidelines, but only in cases in which genetic testing to detect mutations in the gene *gyrA* is available.

Ertapenem, a parenteral carbapenem, has been used to treat highly resistant *N. gonorrhoeae*.[69,70] In a recent randomized, controlled, double-blind, non-inferiority trial ertapenem achieved microbiologic eradication in 86 of 87 patients with anorectal or urogenital infection and showed non-inferiority to a 500-mg dose of ceftriaxone.[68] Delafloxacin is a newer fluoroquinolone that has shown in vitro activity against *N. gonorrhoeae*. However, an open-label, multicenter study that compared a single 900-mg oral dose of delafloxacin and ceftriaxone 250 mg intramuscularly failed to show non-inferiority of delafloxacin.[71]

Gepotidacin is a novel triazaacenaphthylene antimicrobial that inhibits DNA gyrase and topoisomerase IV in a unique manner. A Phase 2, dose-ranging study found that microbiologic eradication was achieved in 97% and 95% of individuals who received a 1.5-g or 3-g dose, respectively.[72] Zoliflodacin is a novel spiropyrimidinetrione antimicrobial that inhibits DNA synthesis in a manner distinct to that of fluoroquinolones. In a multicenter, phase 2 trial, zoliflodacin (administered as a single 2-g or 3-g dose) was compared to ceftriaxone and displayed cure rates of 96% for anogenital infection but lower cure rates for oropharyngeal infection (50% with the 2-g dose and 82% with the 3-g dose).[73] Gepotidacin and zoliflodacin have not yet been approved for clinical use.

Rational Use of Ceftriaxone

Use in Patients with Uncomplicated Gonococcal Infections

Ceftriaxone is the primary component of all currently recommended first-line regimens for individuals with uncomplicated gonococcal infections who lack contraindications to its use, including patients with concomitant HIV infection and other at-risk individuals. A major current concern is the emergence of reduced ceftriaxone susceptibility in *N. gonorrhoeae*. In the United States, the Clinical and Laboratory Standards Institute has not established resistance breakpoint MIC values for ceftriaxone, but an elevated MIC value (a so-called "alert" value) is defined as an MIC $\geq$ 0.125 mg/L.[74] In the most recent GISP report, susceptibility information is reported between 2016 and 2020. It was noted that approximately 90% of isolates displayed ceftriaxone MIC values $\leq$0.015 mg/L, while approximately 0.2% of isolates displayed elevated MIC values.[74] In some years, isolates with elevated MIC values have been noted more frequently in the MSM population.[74] Certain geographic regions, such as Denmark, France, Japan, Thailand, and the United Kingdom, have also noted more substantial MIC elevations.[75] Pharmacodynamic analyses suggest that current recommended ceftriaxone doses may fail to attain the pharmacokinetic/pharmacodynamic target (a time above the MIC of 20–24 hours) as ceftriaxone MIC values continue to increase, although most current circulating gonococcal strains should be successfully inhibited.[39]

Nonetheless, ceftriaxone resistance in *N. gonorrhoeae* has been described. In 2011, an isolate with the then-highest reported MIC value, 2 mg/L, was cultured from a single individual.[76] Further genetic examination of this strain revealed

that it had developed resistance through a unique *penA* mosaic allele, $penA_{H041}$, and susceptibility testing showed extensive antimicrobial resistance.[77] Other case reports of multidrug-resistant strains and geographic dissemination of such strains have been published.[69,70,78,79] These reports of resistance highlight the need for further delineation of the most appropriate ceftriaxone dose and determination of the merits of dual therapy versus ceftriaxone monotherapy.

Use in Patients with Hypersensitivity to Beta-Lactams

Beta-lactams are the most commonly reported antibiotics that cause hypersensitivity reactions, with penicillins being the most prevalent beta-lactam to which allergy is reported.[80] Approximately 6 to 10% of the general population reports having a penicillin allergy; however, upwards of 90% of these reports are not true allergies.[81] This means that the true incidence of penicillin allergy amongst the general population is approximately 1%. A thorough patient history can be a tool used to detect allergies. Complete allergy histories should include, at a minimum, the reaction type and date of occurrence. Another important issue is the safety of ceftriaxone in a patient with an allergy to penicillin. The cross-reactivity between penicillins and cephalosporins is 3 to 5% in patients with a true penicillin allergy, with a benign cutaneous reaction being most common.[82] Ceftriaxone in particular has been found to have an approximate 2.1% cross-reactivity rate in penicillin allergic patients.[80] Therefore, the risk of reaction must be weighed against the benefits of optimal antibiotic therapy in patients exhibiting hypersensitivity to beta-lactams. This risk to benefit ratio may be skewed in favor of ceftriaxone's use in particular disease states where ceftriaxone is the treatment with the most documented efficacy, such as in pharyngeal infections.[41]

Current CDC guidelines recommend the combination of azithromycin 2 g orally and gentamicin 240 mg intramuscularly in those with IgE-mediated cephalosporin or penicillin allergy.[41] An alternative is oral ciprofloxacin, but only when patients are asymptomatic and it is possible to verify ciprofloxacin susceptibility.[41] Note that the CDC guidelines recommend no alternative agents for pharyngeal gonorrhea, and so consultation with an infectious diseases specialist is recommended.[41] The Australian guidelines do not recommend a specific therapy in patients with beta-lactam hypersensitivity.[42] Canadian guidelines recommend the combination of azithromycin 2 g orally and gentamicin 240 mg intramuscularly in those with cephalosporin allergy or a history of a severe non-IgE-mediated reaction to penicillins.[43] European guidelines recommend azithromycin 2 g orally plus spectinomycin 2 g intramuscularly in individuals with a history of severe hypersensitivity (for example, anaphylaxis) to beta-lactams.[44] In those same individuals, UK guidelines recommend the combination of azithromycin 2 g orally and gentamicin 240 mg intramuscularly or azithromycin 2 g orally plus spectinomycin 2 g intramuscularly.[45] Current WHO guidelines do not provide a specific recommendation for the treatment of gonorrhea in patients with beta-lactam hypersensitivity.[46]

Conclusion

Ceftriaxone as a single intramuscular dose is currently the mainstay of the treatment of uncomplicated gonococcal infections. Ceftriaxone has demonstrated high clinical response rates, albeit in a limited number of randomized controlled clinical trials. Ceftriaxone has also demonstrated a favorable safety profile, although hypersensitivity may somewhat limit use of the agent. There is some disagreement among current clinical practice guidelines regarding the preferred ceftriaxone dose and the advisability of combination therapy that encompasses the addition of azithromycin or doxycycline. The ongoing evolution of reduced susceptibility to ceftriaxone in *N. gonorrhoeae* constitutes the primary threat to ceftriaxone's place in the therapy of uncomplicated gonococcal infections. Therefore, the development of alternative antimicrobials for gonococcal infections is an essential need.

Disclosure

All authors report no conflicts of interest in this work.

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