E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.02.845

Systematic Review

Antibiotic Regimens for Uncomplicated Urogenital Gonorrhoea, with a Focus on Urethral Infection, in the Era of Emerging Resistance: A Systematic Review and Network Meta-Analysis of Randomised Trials Including Zoliflodacin and Gepotidacin

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ABSTRACT
Background/Objectives: Zoliflodacin and gepotidacin, two first-in-class oral agents, have recently been approved for uncomplicated urogenital gonorrhoea, but they have not been compared with each other or with all contemporary alternatives. We compared the efficacy and safety of current antibiotic regimens, with a focus on urethral infection.
Methods: We searched PubMed, Cochrane CENTRAL, Google Scholar and trial registries (January 2010 to September 2026) for randomised controlled trials. The primary outcome was microbiological cure at test of cure. We performed a frequentist random-effects network meta-analysis with ceftriaxone plus azithromycin as the reference, derived absolute risk differences, assessed risk of bias with RoB 2 and graded certainty with CINeMA (PROSPERO CRD420261529486).
Results: Nine trials (2533 participants; 13 regimens) formed one connected network. Against ceftriaxone plus azithromycin (pooled cure 95.3%), zoliflodacin 3 g had lower cure (risk ratio [RR] 0.945, 95% confidence interval 0.910–0.981; risk difference −5.3 percentage points, −8.6 to −1.8; high certainty), within the 10% non-inferiority margin. Gepotidacin was similar (RR 1.015, 0.958–1.076; high certainty). Gentamicin plus azithromycin was marginally lower (RR 0.955, 0.914–0.999; moderate certainty); gentamicin 5 mg/kg and single-dose fosfomycin 6 g were inferior. Indirectly, gepotidacin achieved higher cure than zoliflodacin (RR 1.075, 1.003–1.151; low certainty). Adverse events were more frequent with gepotidacin (RR 2.24, 1.89–2.66) but not with zoliflodacin 3 g (RR 1.00, 0.86–1.15). Heterogeneity and inconsistency could not be estimated.
Conclusions: Ceftriaxone-based therapy remains the most reliable treatment. Gepotidacin matches its cure rate but causes more gastrointestinal adverse events; zoliflodacin is better tolerated but has a small absolute cure deficit. Evidence is sparse and limited to ceftriaxone-susceptible infections.

Keywords: Gonorrhoea, *Neisseria gonorrhoeae*, Network meta-analysis, Zoliflodacin, Gepotidacin, Ceftriaxone, Urethritis, Antimicrobial resistance

INTRODUCTION

Gonorrhoea is one of the most common bacterial sexually transmitted infections, with an estimated 86.9 million new infections among adults worldwide in 2016.[1] Untreated urogenital infection causes urethritis and cervicitis and can lead to pelvic inflammatory disease, infertility and increased HIV transmission.[2] *Neisseria gonorrhoeae* has acquired resistance to every antimicrobial class used for first-line treatment, leaving extended-spectrum cephalosporins as the last widely recommended empirical option.[2] Current guidelines recommend a single intramuscular dose of ceftriaxone, given alone or with azithromycin depending on the setting, and reserve alternatives such as gentamicin, cefixime or spectinomycin for specific situations.[3,4] The spread of ceftriaxone-resistant strains and the need for an injection have made new oral agents a priority.

Two first-in-class oral agents have now completed phase 3 trials. Zoliflodacin, a spiropyrimidinetrione that inhibits bacterial GyrB, met its 12% non-inferiority margin against ceftriaxone plus azithromycin, but its urogenital cure rate was lower (90.9% vs. 96.2%).[5] Gepotidacin, a triazaacenaphthylene topoisomerase inhibitor given as two 3000 mg doses, met a −10% margin (92.6% vs. 91.2%) but caused more gastrointestinal adverse events.[6] Both were approved by the US Food and Drug Administration on 12 December 2025 for uncomplicated urogenital gonorrhoea in patients aged 12 years or older.[7] Clinicians now need to know how these agents compare with each other and with older alternatives, yet no trial has compared them directly.

Existing evidence syntheses do not answer this question. The most comprehensive network meta-analysis (NMA) of gonorrhoea treatment searched to March 2019, before either phase 3 trial, and included historical regimens that are no longer used.[8] Recent pairwise meta-analyses pooled zoliflodacin and gepotidacin together as oral topoisomerase inhibitors[9] or examined gepotidacin across urinary and gonococcal infections,[10,11] which hides differences between the two drugs and cannot place them alongside gentamicin, ertapenem or cefixime-based regimens. None interpreted the pooled estimates against the absolute non-inferiority margins used in the trials.

We therefore performed a systematic review and frequentist NMA of randomised controlled trials (RCTs) of contemporary regimens for uncomplicated urogenital gonorrhoea, giving priority to urethral data where available. We aimed to estimate the relative and absolute microbiological cure of each regimen compared with ceftriaxone plus azithromycin, to provide an indirect comparison of zoliflodacin with gepotidacin, and to compare their safety.

MATERIALS AND METHODS

Protocol and Registration

The review followed a protocol written before data extraction, which defined eligibility, outcomes, node definitions and the analysis plan. The review was registered in PROSPERO (CRD420261529486). Reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and its extension for network meta-analyses[12,13]; the completed checklist is provided in the Supplementary Materials (File S1).

Eligibility Criteria

We included parallel-group RCTs (phase 2 to 4) that randomised adolescents or adults (aged 12 years or older, mostly adults) with laboratory-confirmed uncomplicated urogenital gonorrhoea to at least two eligible regimens and reported microbiological cure or adverse events. Recruitment had to start on or after 1 January 2010, to reflect current resistance patterns. Eligible regimens were ceftriaxone (any intramuscular dose) with or without azithromycin, cefixime-based regimens, spectinomycin, gentamicin, and investigational agents tested against a current regimen (zoliflodacin, gepotidacin, solithromycin, delafloxacin, ertapenem and fosfomycin).

We excluded historical regimens (fluoroquinolones as the active treatment, penicillins, tetracycline or azithromycin monotherapy, older cephalosporins, kanamycin and thiamphenicol), complicated or disseminated infection, trials of pharyngeal or rectal infection only, non-randomised designs, and trials whose regimens could not be connected to the network. Because most trials enrolled several anatomical sites, we extracted site-specific data using a pre-specified hierarchy: urethral data first; the male subgroup as a proxy second; and urogenital (urethral and cervical) data third.

Information Sources and Search Strategy

We searched PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform from 1 January 2010 to 3 September 2026. PubMed was searched with strategies: a condition search combined with the Cochrane sensitivity-maximising RCT filter. We also screened the reference lists of included trials and related reviews. Full search strings are given in Table S1.

Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts and then full texts, resolving disagreements by discussion or with a third reviewer. Reports of the same trial were linked by registration number. Two reviewers extracted data using a piloted form covering design, setting, recruitment period, population, regimens and doses, test-of-cure timing, diagnostic method, analysis population, and arm-level outcome counts. All numbers were checked against the full text and supplementary appendices.

Outcomes

The primary outcome was microbiological cure of urogenital infection at the test-of-cure visit, defined by culture or, where culture was not the primary method, by nucleic acid amplification testing (NAAT). We used the trial's microbiological intention-to-treat or modified intention-to-treat population where available, and per-protocol data only when no other urogenital data were reported. Secondary outcomes were any adverse event, gastrointestinal adverse events, serious adverse events, discontinuation because of adverse events, and emergence of resistance. Clinical cure was pre-specified but was not synthesised, because timing and definitions differed markedly between trials.

Risk of Bias and Certainty of Evidence

Two reviewers assessed risk of bias for each trial and outcome with the Cochrane RoB 2 tool.[14] Because microbiological cure is a laboratory outcome, open-label administration was not judged high risk by default; each domain was assessed on its own merits. We graded confidence in each network estimate using the six domains of Confidence in Network Meta-Analysis (CINeMA): within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence.[15,16] Imprecision was judged against the −10% absolute non-inferiority margin.

Network Geometry and Node Definition

In the primary analysis, ceftriaxone doses were pooled within two separate nodes: ceftriaxone plus azithromycin (ceftriaxone 250 to 1000 mg with azithromycin 1 to 2 g) and ceftriaxone alone (250 to 500 mg). Different doses or schedules of the same new agent were kept as separate nodes (zoliflodacin 2 g and 3 g; gentamicin 240 mg plus azithromycin and gentamicin 5 mg/kg alone; fosfomycin 3 g on days 1, 3 and 5 and fosfomycin 6 g as a single dose). In a sensitivity analysis every ceftriaxone dose was treated as a separate node. We assessed transitivity by tabulating potential effect modifiers across comparisons (Table S2).

Statistical Analysis

We performed a frequentist random-effects NMA with the graph-theoretical method in the netmeta package (version 3.7-0) in R 4.3.3.[17] Effects are risk ratios (RR) with 95% confidence intervals (CI), with ceftriaxone plus azithromycin as the reference. Multi-arm trials were handled within the model. For trials with a zero cell, 0.5 was added to events and non-events in every arm of that trial, which keeps multi-arm trials internally consistent. Absolute risk differences (RD) were calculated as $p_0 \times (RR - 1)$, where p_0 is the pooled cure proportion in the reference arms, estimated with a random-effects logistic model. We compared the lower confidence limit of each RD with the −10% and −12% margins used in the trials. This is an interpretive comparison, not a formal non-inferiority test. Treatments were ranked with P-scores,[18] which we interpret only alongside the effect estimates and their certainty.

Heterogeneity was to be estimated with τ^2 and inconsistency with the design-by-treatment interaction test and node-splitting. Pre-specified sensitivity analyses were: strict dose-specific nodes; treatment failure as the outcome; NABOGO anogenital instead of urogenital data; exclusion of per-protocol analyses; restriction to culture-defined cure; exclusion of the phase 2 trial; odds ratios; and a common-effect model. A Mantel–Haenszel NMA for sparse data was planned. Male-subgroup (proxy urethral) estimates were extracted where reported. Any adverse event was analysed by NMA with the same methods, and gastrointestinal adverse events as direct pairwise comparisons because that network was disconnected. Network meta-regression and small-study bias were not assessed, because fewer than ten trials were available. The arm-level dataset and R code are available from the corresponding author (see Data Availability Statement).

Use of Generative Artificial Intelligence

The authors confirm that no artificial intelligence (AI), language models, or machine learning tools were used in any stage of this research, including literature screening, data extraction, data analysis, coding, or drafting of this manuscript.

RESULTS

Study Selection

The database and register searches identified 5994 records (PubMed 1680; Cochrane CENTRAL 1887; Google Scholar 2420; trial registers 7). Before screening, 1002 records were removed (2 duplicates and 1000 records marked as ineligible by automation tools). Of 4992 records screened, 2393 were excluded. Of 2599 reports sought for retrieval, 12 could not be obtained in full text; of the 2587 reports assessed for eligibility, 2578 were excluded (wrong population, n = 787; wrong intervention or comparator, n = 1781; wrong outcome or study design, n = 3; language, n = 7). Nine RCTs were included in the review and in the network meta-analysis[5,6,19–25] (Figure 1).

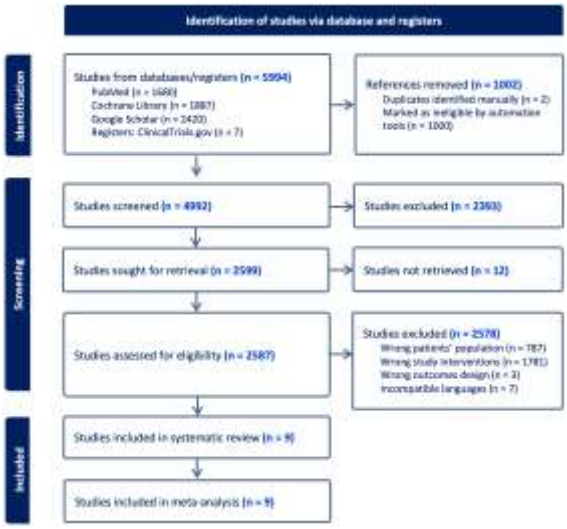


Figure 1: PRISMA 2020 flow diagram of study selection.

Characteristics of Included Trials

The nine trials randomised 3839 participants between 2013 and 2023 in Australia, Belgium, China, the Czech Republic, Germany, Mexico, the Netherlands, South Africa, Spain, Thailand, the UK and the USA (Table 1). Between 80% and 100% of participants were male. One trial enrolled only men with gonococcal urethritis.[22] Microbiological cure was defined by culture in six trials, by NAAT in two[20,25] and by both in one.[23] Test of cure took place 4 to 21 days after treatment. One trial was double-blind,[25] one masked participants and outcome assessors,[20] and seven were open-label. Six trials had low risk of bias for the primary outcome and three had some concerns: two because of per-protocol analyses[22,25] and two because of retrospective or local-only registration[22,23] (Figure 2; Table S3).

Table 1: Characteristics of the nine included randomised controlled trials.

Trial	Design; Setting; Recruitment	Randomised (*n*); Male (%)	Intervention(s)	Comparator	Test of Cure; Method	Urogenital Data Used	Cured/Analysed, Intervention vs. Comparator	RoB 2
Yuan 2016[22]	Open-label RCT; 1 centre, China; 2013–2015	152; 100	Fosfomycin trometamol 3 g PO days 1, 3, 5	CRO 250 mg IM + AZM 1 g	Day 7; smear and culture	Urethral; per protocol	60/62 vs. 61/64	Some concerns
Taylor 2018[24]	Phase 2 open-label; 5 US sites; 2014–2015	180; 93	Zoliflodacin 2 g or 3 g PO	CRO 500 mg IM	Day 6 ± 2; culture	Urethral/cervical; micro-ITT	2 g 55/57; 3 g 54/56 vs. 28/28	Low
Chen 2019 (SOLITAIRE-U)[19]	Phase 3 open-label; Australia, USA; 2014–2015	262; 94	Solithromycin 1000 mg PO	CRO 500 mg IM + AZM 1 g	Day 7 ± 2; culture	Genital; mITT	99/123 vs. 109/129	Low
Hook 2019[21]	Phase 3 open-label; 25 US sites; 2014	460; 80	Delafloxacin 900 mg PO	CRO 250 mg IM	Day 7 ± 3; culture	Urogenital; mITT	194/228 vs. 91/100	Low
Ross 2019 (G-ToG)[20]	Pragmatic RCT, participants and assessors masked; 14 clinics, England; 2014–2016	720; 81	Gentamicin 240 mg IM + AZM 1 g	CRO 500 mg IM + AZM 1 g	2 weeks; NAAT	Genital subgroup	163/174 vs. 151/154	Low
de Vries 2022 (NABOGO)[25]	Double-blind RCT; 1 centre, the Netherlands; 2017–2020	346; 95	Ertapenem 1 g IM; gentamicin 5 mg/kg IM; fosfomycin 6 g PO	CRO 500 mg IM	7–14 days; NAAT	Urethral + cervicovaginal; per protocol	Ertapenem 32/33; gentamicin 29/34; fosfomycin 2/13 vs. 31/31	Some concerns
Bížová 2024[23]	Open-label RCT; 2 sites, Czech Republic; 2021–2022	161; 95	Cefixime 800 mg PO + doxycycline 100 mg twice daily for 7 days	CRO 1 g IM + AZM 2 g	1 and 3 weeks; culture and NAAT	Urogenital; per protocol	48/48 vs. 49/49	Some concerns
Ross 2025 (EAGLE-1)[6]	Phase 3 open-label, sponsor-blinded; 6 countries; 2019–2023	628; 89	Gepotidacin 3000 mg PO × 2 (10–12 h apart)	CRO 500 mg IM + AZM 1 g	Day 4–8; culture	Urogenital; micro-ITT	187/202 vs. 186/204	Low
Luckey 2026[5]	Phase 3 open-label; 5 countries; 2019–2023	930; 88	Zoliflodacin 3 g PO	CRO 500 mg IM + AZM 1 g	Day 6 ± 2; culture	Urogenital; micro-ITT	460/506 vs. 229/238	Low

AZM, azithromycin; CRO, ceftriaxone; IM, intramuscular; micro-ITT, microbiological intention-to-treat; mITT, modified intention-to-treat; NAAT, nucleic acid amplification test; PO, oral; RCT, randomised controlled trial; RoB 2, overall risk of bias for microbiological cure. Recruitment years are the start and end of enrolment.



Figure 2: Risk of bias (RoB 2) for microbiological cure in each included trial, by domain. D1, randomisation process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the

outcome; D5, selection of the reported result; +, low risk; −, some concerns.

Network Structure

The primary network included 2533 participants and 13 regimens, with 16 direct pairwise comparisons from 9 designs (Figure 3). Six trials compared a regimen with ceftriaxone plus azithromycin, and three compared regimens with ceftriaxone alone. The two parts of the network were connected only through zoliflodacin 3 g, which was tested against ceftriaxone plus azithromycin in the phase 3 trial[5] and against ceftriaxone alone in the phase 2 trial.[24] Every comparison was informed by a single trial, and the only closed loops were within multi-arm trials. Heterogeneity (τ^2) and inconsistency therefore could not be estimated (Q = 0, 0 degrees of freedom), and the random-effects and common-effect results were identical.

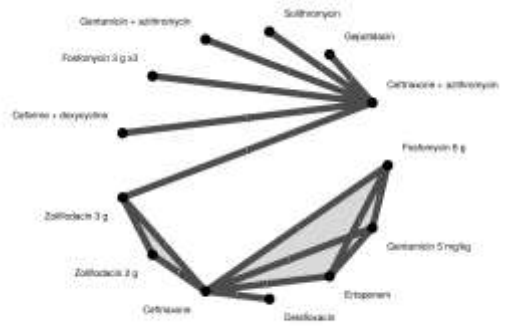


Figure 3: Network of regimens compared for microbiological cure. Nodes are regimens; lines are direct comparisons (numbers indicate trials). Shaded areas are multi-arm trials (Taylor 2018, three arms; NABOGO, four arms).

Microbiological Cure

The pooled cure proportion with ceftriaxone plus azithromycin was 95.3%. Compared with this reference, zoliflodacin 3 g had a lower cure rate (RR 0.945, 95% CI 0.910 to 0.981), equal to 5.3 fewer cures per 100 treated (95% CI 1.8 to 8.6 fewer); the certainty of evidence was high (Table 2; Figure 4). The lower confidence limit remained within both the −10% and −12% margins. Gepotidacin had a cure rate similar to the reference (RR 1.015, 0.958 to 1.076; RD +1.5 percentage points, −4.0 to +7.2; high certainty). Gentamicin 240 mg plus azithromycin, analysed with genital-site data, was marginally lower (RR 0.955, 0.914 to 0.999; RD −4.3, −8.2 to −0.1; moderate certainty).

Table 2: Microbiological cure of urogenital gonorrhoea: network estimates versus ceftriaxone plus azithromycin (random-effects model; 9 trials, 2533 participants).

Regimen	Direct Evidence vs. Reference	Cured/Analysed (All Arms)	RR (95% CI)	RD per 100 Treated (95% CI)	P-Score	Certainty (CINeMA)
Ceftriaxone + azithromycin (reference)	6 trials	785/838	1 (reference)	0 (reference)	0.78	—
Gepotidacin	Ross 2025	187/202	1.015 (0.958 to 1.076)	1.5 (−4.0 to 7.2)	0.85	High
Fosfomycin 3 g × 3	Yuan 2016	60/62	1.015 (0.946 to 1.090)	1.5 (−5.2 to 8.6)	0.83	Low
Cefixime + doxycycline	Bížová 2024	48/48	1.000 (0.961 to 1.040)	0.0 (−3.7 to 3.9)	0.77	Low
Ceftriaxone	Indirect	150/159	0.971 (0.894 to 1.055)	−2.8 (−10.1 to 5.2)	0.61	Low
Solithromycin	Chen 2019	99/123	0.953 (0.850 to 1.068)	−4.5 (−14.3 to 6.5)	0.49	Moderate
Gentamicin + azithromycin	Ross 2019	163/174	0.955 (0.914 to 0.999)	−4.3 (−8.2 to −0.1)	0.47	Moderate
Ertapenem	Indirect	32/33	0.943 (0.838 to 1.061)	−5.4 (−15.4 to 5.8)	0.45	Very low
Zoliflodacin 2 g	Indirect	55/57	0.946 (0.867 to 1.031)	−5.2 (−12.7 to 2.9)	0.44	Low
Zoliflodacin 3 g	Luckey 2026	514/562	0.945 (0.910 to 0.981)	−5.3 (−8.6 to −1.8)	0.40	High
Delafloxacin	Indirect	194/228	0.908 (0.808 to 1.020)	−8.8 (−18.3 to 1.9)	0.28	Low
Gentamicin 5 mg/kg	Indirect	29/34	0.832 (0.701 to 0.986)	−16.1 (−28.5 to −1.3)	0.13	Very low
Fosfomycin 6 g	Indirect	2/13	0.176 (0.057 to 0.544)	−78.5 (−89.9 to −43.5)	0.00	Low

CI, confidence interval; CINeMA, Confidence in Network Meta-Analysis; RD, risk difference calculated from the pooled reference-arm cure proportion (95.3%); RR, risk ratio (RR < 1 favours the reference). Indirect, no trial compared the regimen directly with ceftriaxone plus azithromycin. P-scores (0–1) rank regimens by certainty of higher cure and should be read alongside effect estimates. Heterogeneity and inconsistency could not be estimated (each comparison informed by one trial).

Single-dose fosfomycin 6 g (2 of 13 cured; RR 0.176, 0.057 to 0.544) and gentamicin 5 mg/kg (29 of 34; RR 0.832, 0.701 to 0.986) were clearly inferior. Estimates for solithromycin, delafloxacin, ertapenem, zoliflodacin 2 g and ceftriaxone alone had confidence intervals that included no difference but extended beyond a 10% absolute deficit. Fosfomycin 3 g on days 1, 3 and 5 (RR 1.015, 0.946 to 1.090) and cefixime plus doxycycline (RR 1.000, 0.961 to 1.040) came from single small trials with low certainty.

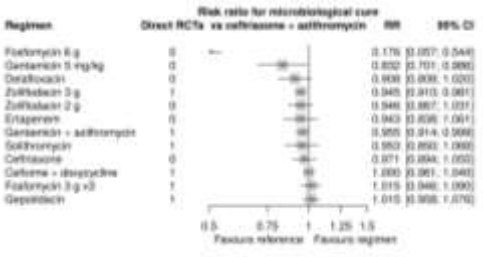


Figure 4: Microbiological cure of each regimen versus ceftriaxone plus azithromycin (random-effects network meta-analysis). Risk ratios below 1 favour the

reference. Direct RCTs, number of trials directly comparing the regimen with the reference; CI, confidence interval; RCT, randomised controlled trial.

In the indirect comparison, gepotidacin had a higher cure rate than zoliflodacin 3 g (RR 1.075, 1.003 to 1.151). We rated this finding low certainty because it is an anchored indirect estimate from two trials with different test-of-cure windows and its lower confidence limit is close to 1. Gepotidacin had the highest P-score (0.85), followed by fosfomycin 3 g on three days (0.83), ceftriaxone plus azithromycin (0.78) and cefixime plus doxycycline (0.77). Zoliflodacin 3 g scored 0.40. The full league table is in Table S4, and certainty ratings for every comparison are in Table S5.

Sensitivity and Subgroup Analyses

With strict dose-specific nodes, the trials of delafloxacin, fosfomycin 3 g and cefixime plus doxycycline became disconnected, and all remaining estimates were unchanged (Table S6). Using NABOGO anogenital instead of urogenital data gave similar conclusions (ertapenem RR 0.960, 0.879 to 1.048; gentamicin 5 mg/kg RR 0.903, 0.814 to 1.001; fosfomycin 6 g RR 0.129, 0.054 to 0.307). Excluding per-protocol analyses, restricting to culture-defined cure or using a common-effect model did not change the estimates for the remaining regimens. With treatment failure as the outcome, zoliflodacin 3 g had a higher failure risk (RR 2.40, 1.20 to 4.83), consistent with the primary analysis. The Mantel–Haenszel model could not be estimated, because the ceftriaxone-alone arms had no failures and dropping them disconnected the network. In male participants (proxy urethral data), the direction of effect was the same: zoliflodacin 3 g RR 0.933 (0.898 to 0.970), delafloxacin RR 0.924 (0.841 to 1.016), and fosfomycin 3 g on three days RR 1.015 (0.946 to 1.090) in the urethritis-only trial (Table S7).

Safety

Any adverse event was reported in seven trials (3411 participants; 11 regimens; Figure S1). Compared with ceftriaxone plus azithromycin, adverse events were more frequent with fosfomycin 6 g (RR 5.08, 2.77 to 9.34), ertapenem (RR 3.02, 1.61 to 5.66), gepotidacin (RR 2.24, 1.89 to 2.66), delafloxacin (RR 1.91, 1.10 to 3.33) and solithromycin (RR 1.55, 1.16 to 2.06) (Table 3; Figure 5). Zoliflodacin 3 g did not increase adverse events (RR 1.00, 0.86 to 1.15), and neither did gentamicin plus azithromycin (RR 0.85, 0.57 to 1.26). Gastrointestinal adverse events were four times more frequent with gepotidacin (206 of 309 vs. 49 of 313; RR 4.26, 3.25 to 5.57) and nearly twice as frequent with solithromycin (RR 1.85, 1.29 to 2.67) (Table 4). They were not significantly increased with zoliflodacin in the phase 2 trial (RR 1.59, 0.45 to 5.66). Diarrhoea affected half of those given ertapenem and 87% of those given fosfomycin 6 g in NABOGO.[25]

Table 3: Any adverse event: network estimates versus ceftriaxone plus azithromycin (7 trials, 3411 participants).

Regimen	Trials	Events/Participants (All Arms)	RR (95% CI)	*p*
Ceftriaxone + azithromycin (reference)	4	340/1072	1 (reference)	—
Zoliflodacin 3 g	2	310/686	0.995 (0.859 to 1.153)	0.948
Zoliflodacin 2 g	1	18/72	0.695 (0.407 to 1.184)	0.180
Gepotidacin	1	230/309	2.240 (1.890 to 2.656)	<0.001
Solithromycin	1	69/130	1.545 (1.160 to 2.058)	0.003
Gentamicin + azithromycin	1	38/298	0.850 (0.573 to 1.262)	0.421
Ceftriaxone	3	92/297	1.250 (0.765 to 2.044)	0.373
Delafloxacin	1	151/304	1.913 (1.100 to 3.327)	0.022
Ertapenem	1	58/103	3.021 (1.614 to 5.657)	<0.001
Gentamicin 5 mg/kg	1	22/102	1.157 (0.570 to 2.349)	0.686
Fosfomycin 6 g	1	36/38	5.083 (2.766 to 9.339)	<0.001

CI, confidence interval; RR, risk ratio (RR > 1 indicates more adverse events than the reference).

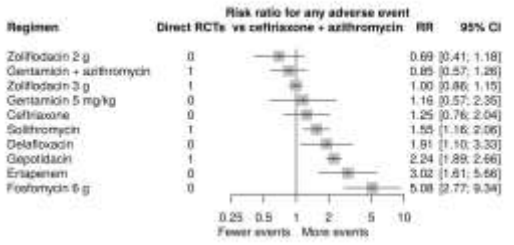


Figure 5: Any adverse event for each regimen versus ceftriaxone plus azithromycin (random-effects network meta-analysis, seven trials). Risk ratios above 1 indicate more adverse events. CI, confidence interval.

Table 4: Gastrointestinal adverse events: direct pairwise comparisons.

Trial	Comparison	Events	RR (95% CI)	*p*
Ross 2025[6]	Gepotidacin vs. ceftriaxone 500 mg + azithromycin 1 g	206/309 vs. 49/313	4.259 (3.254 to 5.573)	<0.001
Chen 2019[19]	Solithromycin vs. ceftriaxone 500 mg + azithromycin 1 g	57/130 vs. 31/131	1.853 (1.288 to 2.666)	<0.001
Taylor 2018[24]	Zoliflodacin 3 g vs. ceftriaxone 500 mg	8/67 vs. 3/40	1.592 (0.448 to 5.657)	0.472
Taylor 2018[24]	Zoliflodacin 2 g vs. ceftriaxone 500 mg	5/72 vs. 3/40	0.926 (0.233 to 3.674)	0.913

CI, confidence interval; RR, risk ratio (RR > 1 indicates more adverse events than the comparator). Gastrointestinal adverse events could not be analysed by network meta-analysis because the available

trials did not form a connected network; in the phase 2 zoliflodacin trial the comparator was ceftriaxone 500 mg alone.

Serious adverse events were rare in the trials that reported them (no more than one per arm) and were judged unrelated to treatment, except for one episode of stridor after ertapenem.[25] Three participants discontinued gepotidacin because of adverse events,[6] and three discontinued delafloxacin because of early vomiting.[21] No zoliflodacin recipient in the phase 3 trial discontinued because of adverse events.[5] No trial detected emergent resistance to the study drug. Zoliflodacin minimum inhibitory concentrations (MICs) did not shift between baseline and test of cure,[5] and gepotidacin produced no reduction in susceptibility.[6]

DISCUSSION

This NMA of nine RCTs provides, to our knowledge, the first joint comparison of zoliflodacin and gepotidacin with all contemporary alternatives for urogenital gonorrhoea. Three findings stand out. First, ceftriaxone-based therapy remains the benchmark: no regimen cured more infections than ceftriaxone plus azithromycin. Second, the two new oral agents differ. Gepotidacin matched the reference but doubled adverse events, whereas zoliflodacin 3 g was as well tolerated as ceftriaxone but cured about five fewer infections per 100 treated, a deficit that was statistically robust yet within the margins regulators accepted. Third, several alternatives that are still sometimes considered, such as gentamicin 5 mg/kg alone and single-dose fosfomycin, performed poorly.

Our results add to, rather than contradict, recent pairwise reviews. A 2026 meta-analysis of three RCTs found no significant difference between oral topoisomerase inhibitors and ceftriaxone-based therapy (urogenital cure 92% vs. 94%).[9] Pooling the two drugs, however, averages a small deficit for zoliflodacin with a null effect for gepotidacin. When the drugs are separated, as in our network, the zoliflodacin difference becomes apparent (RD −5.3 percentage points). Reviews of gepotidacin alone likewise reported similar microbiological success,[10,11] and the review that assessed tolerability found more gastrointestinal adverse events,[10] which agrees with our safety estimates. The 2019 NMA predates both phase 3 trials and was dominated by regimens that are now obsolete.[8]

The zoliflodacin deficit needs careful interpretation. In the phase 3 trial, whole-genome sequencing showed that 23% of zoliflodacin microbiological failures involved a different strain at test of cure, suggesting reinfection rather than treatment failure. No failure isolate carried mutations associated with raised zoliflodacin MICs, and 59% of failures had no clear microbiological explanation.[26] Part of the observed difference may therefore reflect reinfection or measurement rather than lower drug activity, but this cannot be confirmed from aggregate data. For patients, a 95% cure rate after a single oral dose without excess adverse events may be acceptable when injection is not feasible, provided test of cure is performed.

Gepotidacin achieved cure rates comparable to ceftriaxone plus azithromycin, and a NAAT-based analysis of the same trial showed high concordance with culture (98.4%) and similar NAAT-confirmed success.[27] Its main drawback is tolerability: two-thirds of recipients had gastrointestinal adverse events, mostly diarrhoea and nausea. The two-dose schedule 10 to 12 h apart also depends on adherence outside the clinic. The indirect comparison favouring gepotidacin over zoliflodacin is plausible but fragile. It rests on two trials with different test-of-cure windows (4 to 8 days vs. 6 ± 2 days) and a lower confidence limit close to no difference, so it should generate hypotheses for a head-to-head trial rather than guide practice.

Among older alternatives, gentamicin 240 mg plus azithromycin achieved 94% genital cure, slightly below the reference, consistent with the G-ToG conclusion that it is an alternative when ceftriaxone cannot be used.[20] Gentamicin 5 mg/kg without azithromycin and single-dose fosfomycin 6 g should not be used for urogenital gonorrhoea. By contrast, fosfomycin 3 g given on three days achieved 97% cure in Chinese men with urethritis,[22] a signal that deserves confirmation in a larger trial with modern methods. Ertapenem cured all urethral infections in NABOGO,[25] but its network estimate was imprecise and it caused frequent diarrhoea.

These findings are relevant to Indonesia and other settings in the WHO South-East Asia and Western Pacific regions. WHO surveillance of isolates collected in 2021 to 2024 in eight countries, including Indonesia, showed high *in vitro* susceptibility to both zoliflodacin and gepotidacin. However, 35.5% of isolates carried the ParC D86N substitution, which can predispose to gepotidacin resistance at suboptimal drug concentrations, and two isolates carried a GyrB D429N mutation associated with raised zoliflodacin MICs.[28,29] Introducing either drug should therefore be accompanied by susceptibility surveillance and, ideally, test of cure.

This review has limitations. First, the network is sparse: each comparison rests on one trial, so heterogeneity and inconsistency could not be assessed, and P-scores are unstable. Second, the two halves of the network are linked only through zoliflodacin 3 g, so estimates for ceftriaxone alone, delafloxacin, ertapenem and NABOGO regimens depend on one phase 2 trial with 141 evaluable participants. Third, pooling ceftriaxone doses assumes that doses of 250 to 1000 mg are equally effective against susceptible urogenital infection, although the strict-dose sensitivity analysis gave unchanged results for the connected regimens. Fourth, truly urethral data were available from only one trial, and most estimates relate to urogenital infections in predominantly male populations. Fifth, the phase 3 trials enrolled only ceftriaxone-susceptible infections, so no conclusion can be drawn about ceftriaxone-resistant gonorrhoea. Sixth, three trials contributed per-protocol data and test-of-cure timing varied from 4 to 21 days. Finally, we lacked access to Embase and Scopus, which we partly mitigated with CENTRAL, registries and citation searching.

CONCLUSIONS

Ceftriaxone-based therapy remains the most effective and best-tolerated option for uncomplicated urogenital gonorrhoea. Both new oral agents achieve cure rates within accepted non-inferiority margins. Gepotidacin matches ceftriaxone but causes frequent gastrointestinal adverse events, while zoliflodacin is well tolerated but carries a small absolute cure deficit. A direct comparison of the two agents, trials in women and in ceftriaxone-resistant infection, and routine genomic confirmation of failures are the most pressing research needs.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/doi/s1, Table S1: Search strategies, dates and numbers of records; Table S2: Distribution of potential effect modifiers across trials (transitivity assessment); Table S3: RoB 2 judgements for microbiological cure, with supporting information; Table S4: League table for microbiological cure; Table S5: Confidence in network estimates for microbiological cure (CINeMA); Table S6: Sensitivity analyses for microbiological cure; Table S7: Male-subgroup (proxy urethral) direct estimates; Figure S1: Network of regimens for any adverse event; File S1: PRISMA 2020 checklist with PRISMA-NMA items.

Author Contributions: Conceptualization, N.M.W. and K.K.W.; methodology, N.M.W. and K.K.W.; investigation (literature search, study selection, data extraction and risk-of-bias assessment), N.M.W. and K.K.W.; formal analysis, N.M.W. and K.K.W.; validation, K.K.W.; writing—original draft preparation, N.M.W.; writing—review and editing, N.M.W. and K.K.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable. This study analysed published aggregate data only and did not involve new data collection from human participants.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article and its Supplementary Materials. The arm-level dataset and R analysis code are available from the corresponding author on reasonable request.

Acknowledgments: The authors would like to thank the Faculty of Medicine and Health Sciences, Universitas Warmadewa, for academic support during the preparation of this study.

Conflicts of Interest: The authors declare no conflicts of interest.

ABBREVIATIONS

The following abbreviations are used in this manuscript:

AZM	azithromycin
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CINeMA	Confidence in Network Meta-Analysis
CRO	ceftriaxone
IM	intramuscular
micro-ITT	microbiological intention-to-treat
MIC	minimum inhibitory concentration
mITT	modified intention-to-treat
NAAT	nucleic acid amplification test
NMA	network meta-analysis
PO	oral (per os)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomised controlled trial
RD	risk difference
RoB 2	Cochrane risk-of-bias tool for randomised trials, version 2
RR	risk ratio
WHO	World Health Organization

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