

Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials

Angela Huttner^{1*}, Els M. Verhaegh², Stephan Harbarth¹, Anouk E. Muller³, Ursula Theuretzbacher⁴ and Johan W. Mouton^{5,6}

¹Infection Control Program, Geneva University Hospitals and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4, Geneva, Switzerland;

²Laboratory of Medical Microbiology and Immunology, St Elisabeth Hospital, Tilburg, The Netherlands; ³Department of Medical Microbiology, Medical Centre Haaglanden, The Hague, The Netherlands; ⁴Center for Anti-infective Agents, Eckpergasse 13, Vienna, Austria;

⁵Department of Medical Microbiology, Radboudumc, Nijmegen, The Netherlands; ⁶Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands

*Corresponding author. Tel: +41-79-553-3396; Fax: +41-22-372-3987; Email: angela.huttner@hcuge.ch

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Objectives: Nitrofurantoin's use has increased exponentially since recent guidelines repositioned it as first-line therapy for uncomplicated lower urinary tract infection (UTI). We conducted a systematic review and meta-analysis to assess nitrofurantoin's efficacy and toxicity in the treatment of lower UTI.

Methods: We performed a systematic review of all human controlled clinical trials published from 1946 to 2014 and assessing short-term (≤ 14 days) nitrofurantoin for lower UTI. Meta-analyses assessing efficacy and adverse events were conducted on randomized trials.

Results: Twenty-seven controlled trials including 4807 patients fulfilled entry criteria; most were conducted between the 1970s and 1990s and were at increased risk for various biases. Nitrofurantoin appears to have good clinical and microbiological efficacy for UTI caused by common uropathogens, with clinical cure rates varying between 79% and 92%. The most methodologically robust studies surveyed indicate overall equivalence between nitrofurantoin when given for 5 or 7 days and trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin. Meta-analyses of randomized controlled trials confirmed equivalence in clinical cure, but indicated a slight advantage to comparator drugs in microbiological efficacy (risk ratio 0.93, 95% CI 0.89–0.97). If given for only 3 days, nitrofurantoin's clinical efficacy was diminished (61%–70%). Toxicity was infrequent (5%–16% in the 17 reporting studies), mild, reversible and predominantly gastrointestinal; meta-analyses confirmed no difference between nitrofurantoin and comparators. Hypersensitivity reactions such as pulmonary fibrosis and hepatotoxicity were not observed. Acquisition of resistance to nitrofurantoin is still relatively rare.

Conclusions: When given short term for lower UTI, nitrofurantoin has good clinical and microbiological efficacy; toxicity is mild and predominantly gastrointestinal.

Keywords: urinary tract infections, antibiotic, antibacterial, efficacy, toxicity

Introduction

The nitration of heterocyclic compounds in the 1940s led to the creation of thousands of nitrofurans,¹ among which the best clinically known is nitrofurantoin. Approved by the FDA in 1953 for the treatment of lower urinary tract infection (UTI), nitrofurantoin was prescribed widely for the next two decades, until its popularity waned in the 1970s with the advent of trimethoprim/sulfamethoxazole and the β -lactam antibiotics. Recently, however, increasing resistance to trimethoprim/sulfamethoxazole and fluoroquinolones along with a near absence of novel oral antibiotics in the anti-infective arsenal have led to renewed interest in

this old drug. Beginning in the late 2000s—and coincident with the rise in ESBL-producing and carbapenem-resistant bacteria—several guidelines were revised to reposition nitrofurantoin as first-line therapy for uncomplicated lower UTI.^{2–5} Since then, its consumption has increased exponentially (Figure 1). Indeed, large population-level datasets point to a significant reliance on nitrofurantoin even in patient groups for whom this drug has historically been discouraged, such as men and the elderly.^{6,7}

Nitrofurantoin possesses several mechanisms of antimicrobial action, none of which is fully understood. It is known that intracellular nitroreductases produce the active form of the drug via reduction of the nitro group; resultant intermediate metabolites

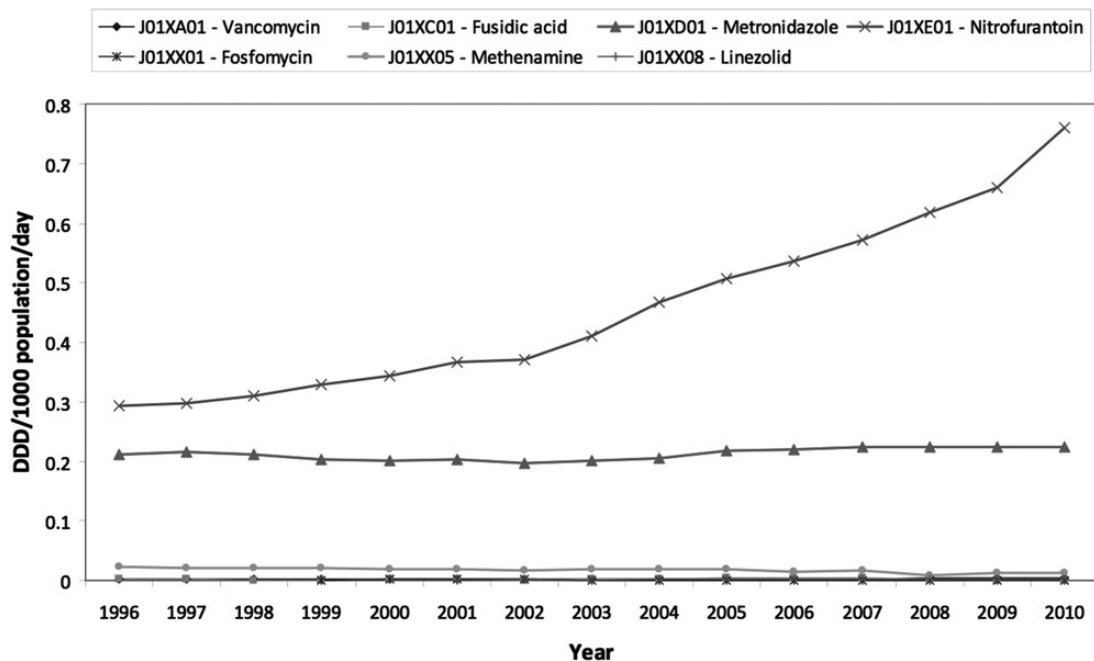


Figure 1. Trends in nitrofurantoin consumption in recent years. Nitrofurantoin's DDDs per 1000 inhabitants per day are shown. The data from British Columbia³⁵ are representative of many regions and countries today.^{36,37} Consumption is increasing in some countries (Nordic countries except Finland, Germany, Austria, Belgium, Poland), decreasing in France and still low in southern countries. Reproduced with permission from BC PharmaNet.

are highly active, binding to bacterial ribosomes and inhibiting several bacterial enzymes involved in the synthesis of DNA, RNA and other metabolic enzymes.⁸

The current body of pharmacokinetic knowledge regarding nitrofurantoin in both healthy subjects and patients with UTI is suboptimal and based mainly on decades-old studies using comparatively archaic laboratory and analytical techniques.⁹ Bioavailability is thought to be 80%.¹⁰ Except in patients with severe renal failure, serum concentrations are almost undetectable, with peak levels of 1 mg/L.^{10,11} Indeed, nitrofurantoin achieves therapeutically active concentrations only in the lower urinary tract.¹² For this reason it is recommended neither for treatment of upper UTI nor for men with UTI and possible concomitant prostatitis.

Nitrofurantoin was commercialized in an era predating requirements for robust methodology in drug development. Despite the drug's remarkable post-market resurgence and widespread consumption, uncertainties persist regarding its true efficacy and toxicity. For this reason we performed a structured, systematic review and meta-analysis of controlled clinical trials to evaluate nitrofurantoin's efficacy and toxicity when given short term (≤ 14 days) for the treatment of UTI.

Methods

Using the MeSH descriptor 'nitrofurantoin', two reviewers (A. H. and E. V.) searched the MEDLINE, EMBASE and Cochrane Library databases for all published material from 1946 to December 2014. There were no language restrictions. For the systematic review of nitrofurantoin's efficacy and toxicity when given for treatment of UTI, Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.¹³

Entry criteria for the systematic review on efficacy and toxicity

For the systematic review of nitrofurantoin's efficacy and toxicity when given for UTI, only human controlled clinical studies, whether randomized or not, were included. Studies evaluating nitrofurantoin as prophylaxis for UTI were not included. Table 1 describes these entry criteria in detail.

Outcomes

This review's primary outcome of interest is nitrofurantoin's clinical efficacy, as defined in the respective studies, for therapy of acute UTI at short-term follow-up (≤ 6 weeks post-treatment completion). Secondary outcomes, also assessed according to the definitions used in the studies, are the incidence of nitrofurantoin-related adverse events when given short term (≤ 14 days), short-term microbiological cure after nitrofurantoin therapy, patient-reported outcomes (symptoms, quality of life) and economic outcomes. All adverse events were evaluated, but emphasis was placed on data specifically pertaining to gastrointestinal events (nausea, vomiting, abdominal pains, diarrhoea), skin findings (including severe reactions such as Stevens-Johnson syndrome), haematological and neurological events, pulmonary and hepatic fibrosis and other reactions, and hospital admissions and death. When available, results of ITT analyses were preferentially extracted over those of per-protocol analyses.

Data extraction for the systematic review of efficacy and toxicity

All article abstracts and/or main texts were reviewed independently by A. H. and E. V. against the inclusion and exclusion criteria for the review's primary and secondary outcomes of nitrofurantoin efficacy and toxicity, respectively. Both authors then independently conducted data abstraction of the final sample, examining and recording the trial characteristics and

Table 1. Inclusion criteria for studies considered for the review of nitrofurantoin's efficacy and toxicity for therapy of lower UTI

Study design	
Included:	Excluded:
<ul style="list-style-type: none"> controlled clinical trials 	<ul style="list-style-type: none"> uncontrolled trials
Participants	
Included:	Excluded:
<ul style="list-style-type: none"> human patients of all ages and both genders in all settings 	<ul style="list-style-type: none"> animal studies <i>in vitro</i> studies
Interventions	
Included:	Excluded:
<ul style="list-style-type: none"> oral nitrofurantoin at any dose ≤ 14 days for treatment of UTI^a 	<ul style="list-style-type: none"> nitrofurantoin combined with another antibacterial targeting uropathogens nitrofurantoin for prostatitis nitrofurantoin for prophylactic purposes nitrofurantoin for treatment of conditions outside the urinary tract
Comparators	
Included:	Excluded:
<ul style="list-style-type: none"> placebo no treatment a different drug nitrofurantoin at a different dose, frequency or duration 	<ul style="list-style-type: none"> nitrofurantoin with another antibacterial targeting uropathogens

^aIn literature published before 1990, asymptomatic bacteriuria was often considered sufficient for a diagnosis of UTI.

outcomes using a pre-designed data abstraction form for information pertaining to trial demographics, intervention, comparator(s), methodology, outcomes and overall quality. Both reviewers' results were then cross-checked for reliability. Disagreements were resolved between the two reviewers by discussion and consensus among all authors.

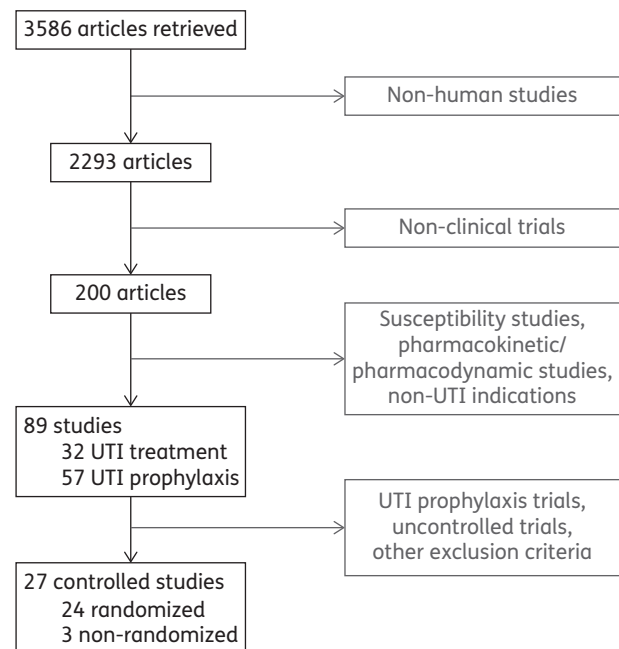
Risk of bias and quality assessment

A. H. and E. V. independently assessed the quality of studies using the Cochrane Collaboration's tool for assessing risk of bias.¹⁴ Inter-rater reliability was assessed by means of inter-rater agreement percentages and κ values. While all studies meeting the inclusion criteria for efficacy and toxicity evaluation were included in the review regardless of quality, studies of stronger design and increased relevance to the primary aims of the review were given more weight in the reporting of results.

Meta-analyses of randomized controlled trials

Meta-analyses were performed using Review Manager (version 5.3, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen 2014). Risk ratios (RRs) for dichotomous data (microbiological cure, clinical cure and adverse effects) were calculated for individual trials with 95% CIs. Heterogeneity in trial results was assessed using the I^2 measure of inconsistency. When I^2 was $\leq 30\%$ of the total analysis we used a fixed-effects model; otherwise a random-effects model was used.¹⁴

Initially all randomized controlled trials were included, independent of the antibiotic used as comparator and of respective dosing regimens; we

**Figure 2.** Flow chart for the retrieval of studies evaluated in the review of nitrofurantoin's efficacy and toxicity.

then excluded studies that: (i) did not disclose the exact number of patients in the treatment arms; (ii) included men or children; (iii) compared nitrofurantoin with placebo, drugs not used for UTI or a comparator administered for < 3 days (excluding fosfomycin); and (iv) used an exclusively microcrystalline nitrofurantoin formulation (currently out of use). Sensitivity analyses were performed based on various selections of randomized controlled trials in separate analyses.

Results

Figure 2 shows the results of the systematic search of the literature for trials on nitrofurantoin's efficacy and toxicity when given as treatment for UTI. Of 3586 articles on nitrofurantoin, 200 were clinical trials. Of these, the majority were UTI prophylaxis studies, pharmacokinetic/pharmacodynamic studies or investigations on nitrofurantoin's potential non-UTI uses. Ultimately, 27 studies, 24 of which were randomized, fulfilled entry criteria for the systematic review; these were subject to independent evaluation for their content (Table S1, available as Supplementary data at JAC Online) as well as their risk of bias and overall quality (below and Table S2). Recent susceptibility studies were reviewed more generally to provide the profile described below.

Risk-of-bias assessments and inter-rater agreement

Inter-rater agreement was strong, with 100% agreement (κ 1.00) in overall quality assessments and 89%–100% agreement (κ 0.36–1.00) in risk-of-bias assessments (Table S2). While studies predating 1990 fared significantly worse in both quality and risk-of-bias assessments, neither reviewer considered any study to be of high or excellent quality. Only a minority of studies (12/27, 44%) were deemed to be of fair quality; the rest were considered to be of poor quality. All studies were judged to be at high

risk for at least one major type of bias; most were at risk for several types of bias. Thirteen (48%) were deemed at risk for all major biases evaluated.

Clinical and microbiological efficacy of nitrofurantoin for UTI

One of the first antibiotics available, nitrofurantoin was not subject to controlled trials before or in the two decades following its release. The first trials date from the 1970s, when nitrofurantoin, by then considered the gold standard for UTI therapy, was used as the comparator for several emerging antibiotics: trimethoprim/sulfamethoxazole in the 1970s, then aminopenicillins, cephalosporins and fluoroquinolones in the 1980s (Table S1). Twenty-four studies (89%) were randomized; 10 (37%) were either single or double blind. The main patient population was adult women, but six (22%) studies included both men and women, and three (11%) included both adults and children. Many data were either not presented or missing altogether; ITT analyses were rarely done. In addition, before 1990, bacteriuria was often sufficient for a diagnosis of UTI, whether symptomatic or not. Efficacy outcomes were thus not always clinical, but rather microbiological in patients who may not have been bothered by their bacteriuria.

The methodologically strongest studies date from the late 1990s and 2000s; these demonstrate overall equivalence between nitrofurantoin when given for 5 or 7 days and trimethoprim/sulfamethoxazole,^{15–19} ciprofloxacin,^{16–19} amoxicillin²⁰ and fosfomicin,^{18,21} with clinical cure rates for the former varying between 79% and 92% in the different studies' final follow-up.

Of note, nitrofurantoin appears to lose efficacy if given for only 3 days. In an open-label, randomized controlled trial, Hooton *et al.*²⁰ compared 3 day regimens of high-dose nitrofurantoin (100 mg four-times daily), trimethoprim/sulfamethoxazole, cefadroxil and amoxicillin; 6 weeks post-therapy, nitrofurantoin's clinical efficacy was only 61%. Similarly, a 2002 trial by Christiaens *et al.*²² comparing 3 days of nitrofurantoin with placebo in young women with symptoms of UTI and pyuria found clinical cure rates of 70% versus 42%, respectively, 7 days after the start of therapy.

A meta-analysis for clinical cure and including all randomized controlled trials (802 and 1345 patients receiving nitrofurantoin and one of seven comparators, respectively) showed no significant difference between nitrofurantoin and comparator (RR 0.99, 95% CI 0.96–1.02), with moderate heterogeneity ($I^2=35\%$). The nitrofurantoin dosing regimens comprised five different schedules in dose, frequency and duration (Figure 3). Indeed, the diversity in outcomes was wide and the high risk of bias likely significant; a funnel plot could not be drawn. Further analyses including only double-blind randomized controlled trials or only studies deemed fair in the quality assessment also showed no superiority of either treatment (not shown).

Courses of 5 or 7 days of nitrofurantoin yielded microbiological cure rates varying between slightly below 80% and 92%. Nine studies including 15 comparisons fulfilled criteria for the meta-analysis assessing microbiological cure, with 616 patients receiving nitrofurantoin and 1046 patients receiving one of eight comparators (Figure 4). Overall, the use of the comparator was more likely to result in microbiological cure than nitrofurantoin (RR 0.93, 95% CI 0.89–0.97), with little heterogeneity ($I^2=16\%$). When only double-blind randomized controlled trials were included (results not shown), the comparator still emerged with a more favourable

outcome, although the difference was not significant. A further analysis including only studies deemed 'fair' in the risk-of-bias and overall quality assessments yielded the same results, but with no statistical significance.

The incidence of nitrofurantoin resistance among uropathogens in patients failing therapy was not systematically assessed as an outcome in the controlled studies. Gupta *et al.*¹⁸ evaluated the emergence of antibiotic resistance among intestinal flora after therapy with nitrofurantoin, ciprofloxacin or trimethoprim/sulfamethoxazole. Four weeks after completing therapy, there was no nitrofurantoin or trimethoprim/sulfamethoxazole resistance in intestinal *Escherichia coli* isolates in women taking either of these antibiotics, but of the 25 women taking ciprofloxacin, one harboured two newly ciprofloxacin-resistant *E. coli* strains.¹⁸

Nitrofurantoin is not universally recommended for men with UTI because of the possibility of concomitant infection of the prostate, where the drug does not achieve therapeutic concentrations. While six of the controlled trials included some male patients, baseline demographics by study arm were rarely disclosed and results were not stratified by gender; thus, no appraisal of nitrofurantoin's clinical or microbiological efficacy in men can be made.

Toxicity

In all studies reporting adverse event outcomes, toxicity was generally mild, reversible and predominantly gastrointestinal. No study documented any severe or irreversible adverse outcome.

Microcrystalline versus macrocrystalline nitrofurantoin

Two of the earliest trials assessed compared nitrofurantoin monohydrate with macrocrystalline nitrofurantoin for occurrence of side effects.^{23,24} Both studies demonstrated a roughly 50% reduction in the occurrence of gastrointestinal side effects with the macrocrystalline formulation, with comparable microbiological efficacy. The clinical trials following these two studies used a macrocrystalline formulation.

Toxicity of short-term nitrofurantoin

Seventeen of the 27 controlled trials measured the occurrence of side effects due to nitrofurantoin as an outcome. In most of the studies, nitrofurantoin was given for 5 or 7 days, but in 10 studies conducted before 1983, it was given for either 10 or 14 days. The prevalence of participants with side effects attributed to nitrofurantoin in the 17 studies generally ranged from 5% to 16%; nausea, abdominal discomfort and headaches were described. An exception was an open-label randomized controlled trial whose primary outcome was quality of life.¹⁷ Side effects due to nitrofurantoin were reported by 49% of the women taking it, while 45% and 62% of women taking trimethoprim/sulfamethoxazole and ciprofloxacin, respectively, also reported side effects of a similar intensity. Indeed, in all of the studies, the comparator drugs, most often trimethoprim/sulfamethoxazole and ciprofloxacin, fared similarly or worse, with reported side effect frequencies often twice that of nitrofurantoin. A meta-analysis assessing adverse effects (Figure 5) did not show a significant difference between nitrofurantoin and any of seven comparators (RR 1.05, 95% CI 0.91–1.22), with no heterogeneity ($I^2=0\%$).

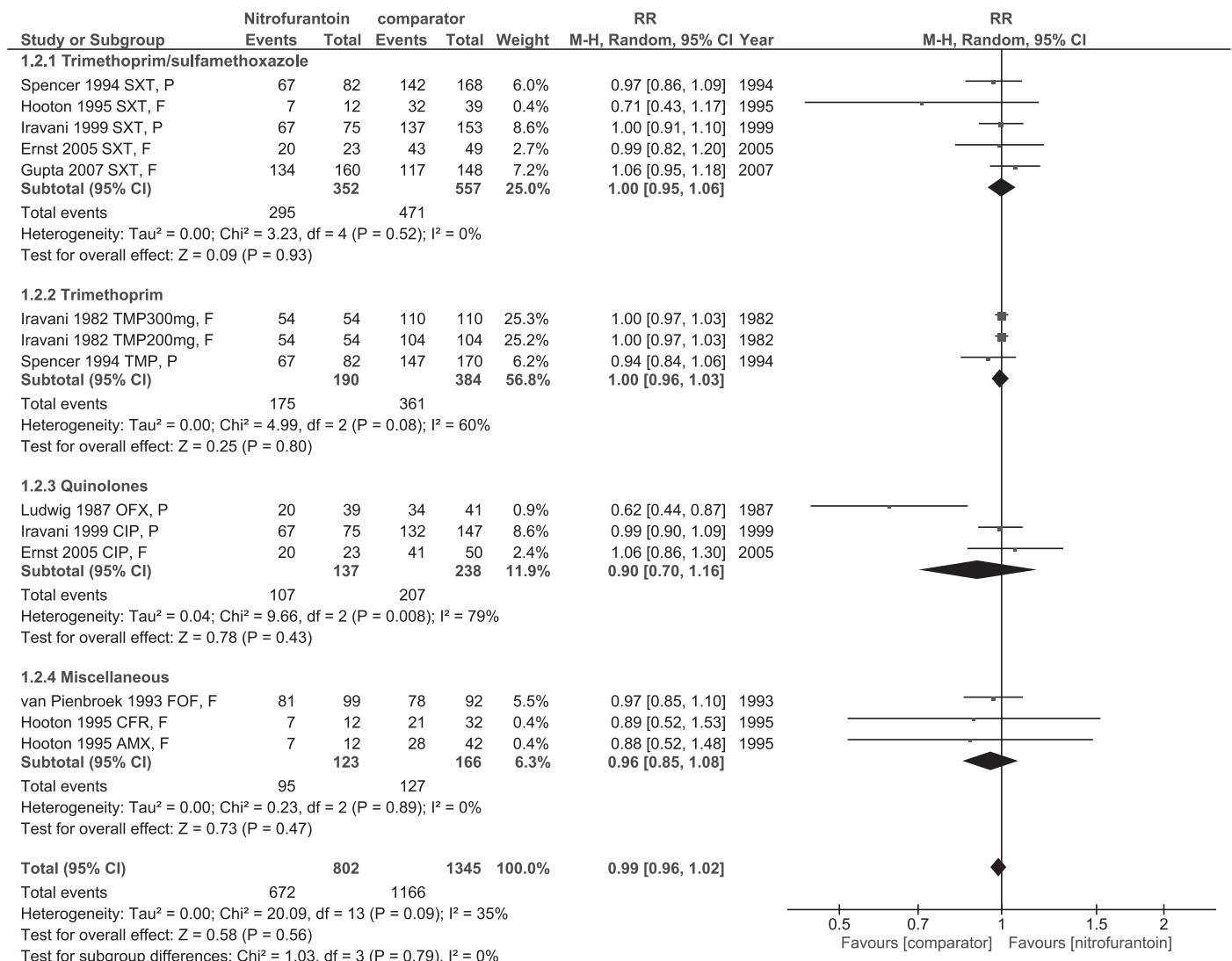


Figure 3. Results of the meta-analysis for clinical efficacy. F, fair; P, poor (no studies were deemed to be of high or excellent quality); AMX, amoxicillin; CFR, cefadroxil; CIP, ciprofloxacin; FOF, fosfomycin; NAL, nalidixic acid; OFX, ofloxacin; PMA, pipemidic acid; TMP, trimethoprim; SXT, trimethoprim/sulfamethoxazole.

Other outcomes

Quality of life

In an open-label, randomized controlled trial comparing quality-of-life outcomes for women taking either nitrofurantoin for 5 days or trimethoprim/sulfamethoxazole or ciprofloxacin for 3 days, there were no significant differences reported in quality of life in any of the three treatment groups.¹⁷

Discussion

Nitrofurantoin’s clinical efficacy appears to be on par with that of more contemporary antibiotics. The studies dating from the late 1990s and 2000s generally demonstrate the most robust methodology with more favourable risk-of-bias assessments, as well as increased transparency regarding funding and potential conflicts of interest. These studies indicate an overall equivalence between

nitrofurantoin when given for 5 or 7 days and trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin, with clinical cure rates for the former varying between 79% and 92% in the different studies’ final follow-up. Meta-analyses for clinical cure confirmed overall equivalence between nitrofurantoin and comparators.

Meta-analyses for microbiological cure, however, consistently showed a slightly more favourable effect for comparators. The practical significance of this finding is unclear, as almost none of the studies addressed the emergence of post-treatment resistance. In addition, the meta-analyses suffer from important limitations such as the large variation and debatable quality of the study designs. Comparisons were made against at least seven antibiotics, with dosing regimens differing among them. Independent quality assessments indicate that many of the randomized controlled trials were likely biased; their use in the analyses is questionable and thus no firm conclusions can be drawn from them.

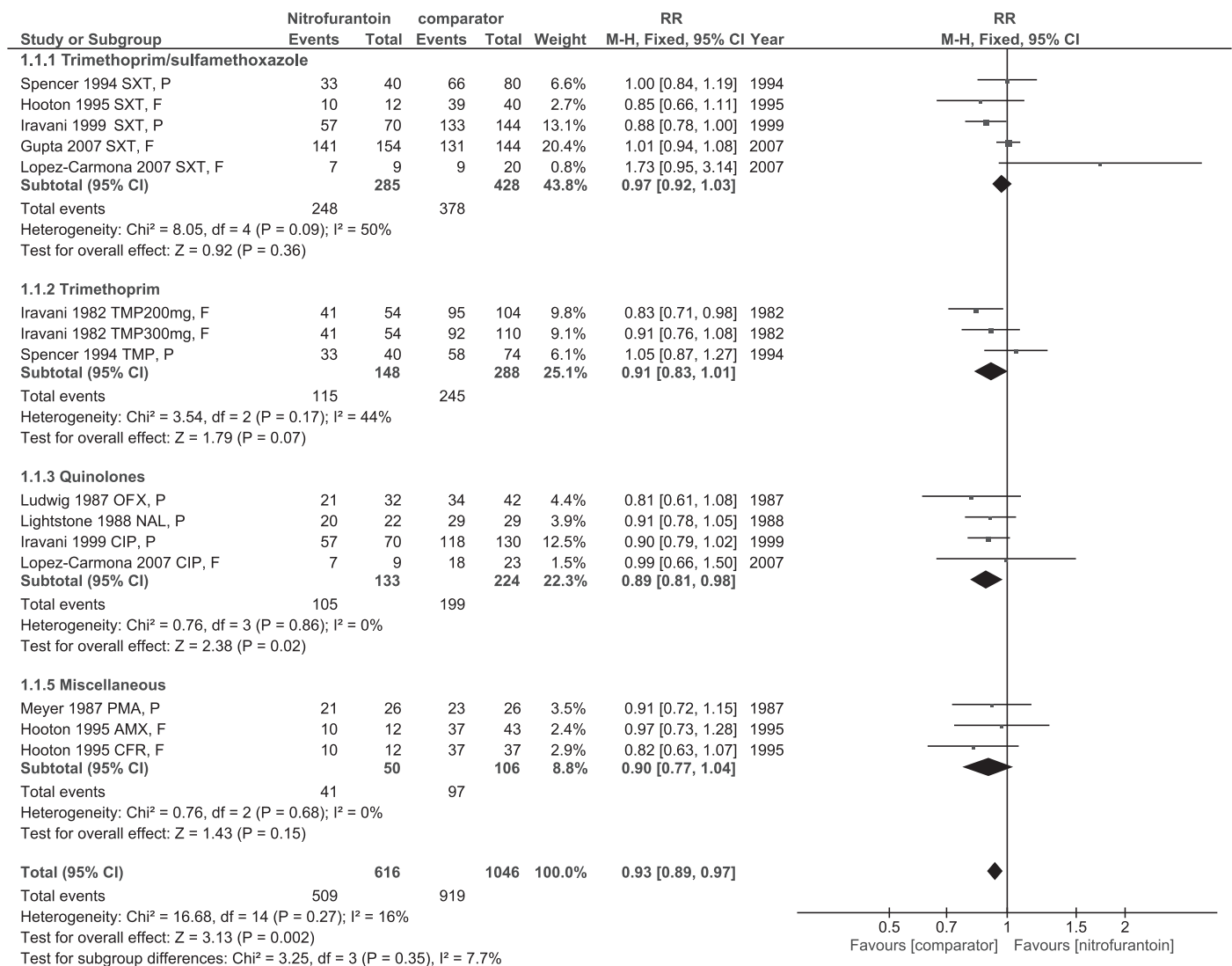


Figure 4. Results of the meta-analysis for microbiological cure. F, fair; P, poor; AMX, amoxicillin; CFR, cefadroxil; CIP, ciprofloxacin; FOF, fosfomycin; NAL, nalidixic acid; OFX, ofloxacin; PMA, pipemidic acid; TMP, trimethoprim; SXT, trimethoprim/sulfamethoxazole.

In these studies, toxicity was minor, reversible and overall less frequent than that of comparator drugs. Severe adverse drug reactions were not observed. Indeed, the most feared side effects of nitrofurantoin, pulmonary fibrosis and hepatotoxicity, have been documented overwhelmingly in patients receiving nitrofurantoin prophylaxis for several months or years.⁹ These autoimmune-like phenomena are generally reversible when a prompt diagnosis is made and nitrofurantoin immediately discontinued,²⁵ but fatalities have been described.²⁶ Other serious side effects such as erythema multiforme, erythema nodosum, agranulocytosis, megaloblastic anaemia and optic neuritis have been described anecdotally,¹ but were not reported in any of the trials surveyed. Side effects, including the more common mild gastrointestinal manifestations, appear to be an intrinsic property of the nitrofurantoin molecule itself, in particular the 5-nitrofuram moiety, although the switch from nitrofurantoin monohydrate to predominantly macrocrystalline nitrofurantoin formulations in the 1960s led to improved tolerance. The accumulation of toxic

nitrofurantoin-derived metabolites was not observed in these trials, as patients with renal insufficiency were excluded.

A strong publication bias likely contributes to the misperception that nitrofurantoin hypersensitivity reactions are numerous.²⁷ In 1985 at the height of its use, D'Arcy⁹ reviewed the major adverse drug reactions to nitrofurantoin from published reports as well as information submitted worldwide to the developers of the drug, Norwich-Eaton Pharmaceuticals, by all manufacturers from all sources. Calculated frequencies for all pulmonary reactions combined and hepatic toxicity were 0.001% and 0.0003% of courses of therapy, respectively. Other severe reactions were similarly rare, with calculated frequencies for combined neurological and haematological events at 0.0007% and 0.0004%, respectively.⁹

Antibacterial activity and resistance

Only 11 (41%) of the trials reported baseline resistance rates to nitrofurantoin and comparators (Table S1), and only one

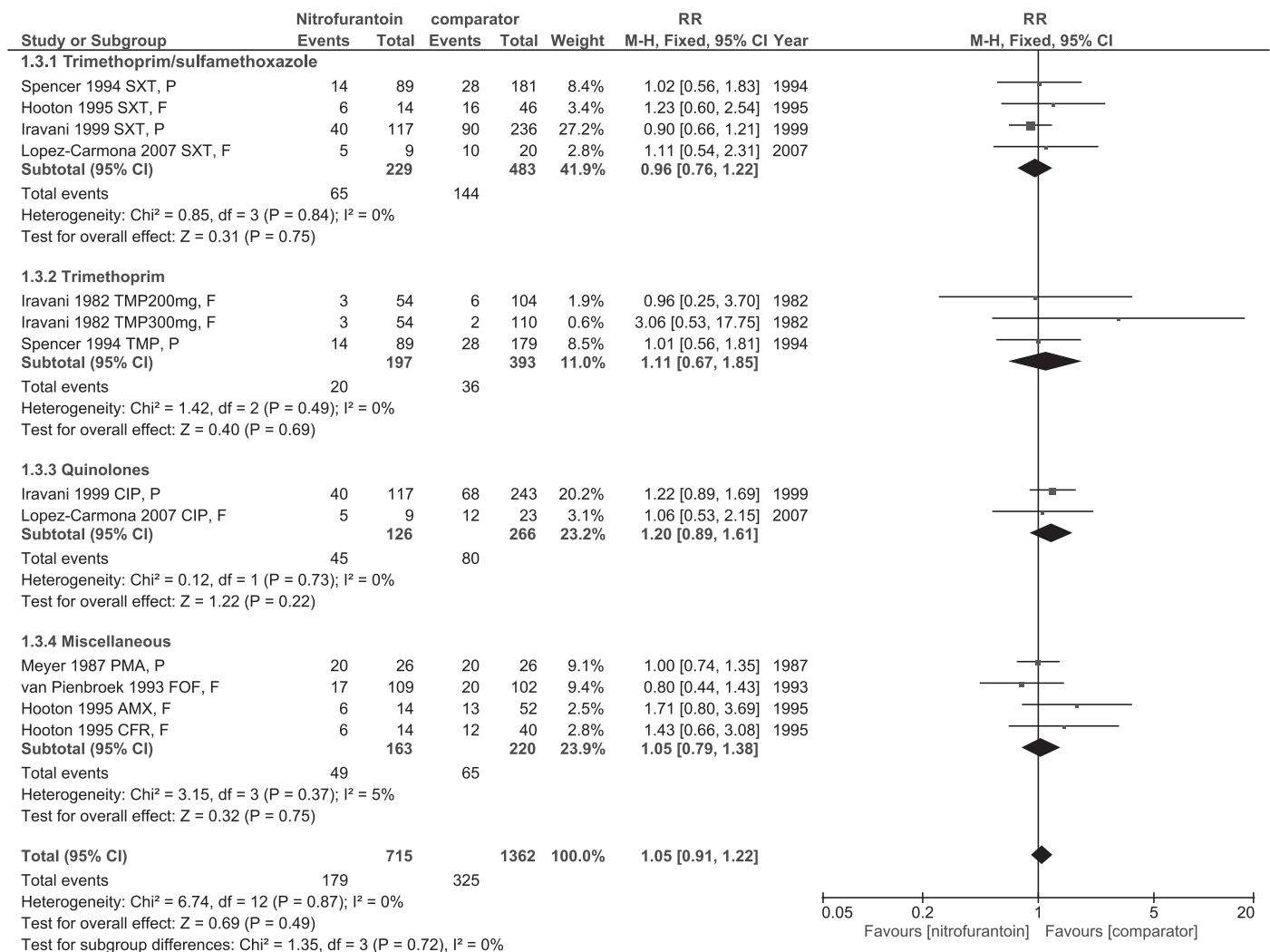


Figure 5. Results of the meta-analysis for adverse effects. F, fair; P, poor; AMX, amoxicillin; CFR, cefadroxil; CIP, ciprofloxacin; FOF, fosfomycin; NAL, nalidixic acid; OFX, ofloxacin; PMA, pipemidic acid; TMP, trimethoprim; SXT, trimethoprim/sulfamethoxazole.

underpowered study¹⁸ assessed emergence of resistance as a formal outcome. Baseline resistance was low (0%–5%) even in earlier eras of widespread use. Likely because of nitrofurantoin's multiple modes of action, acquisition or emergence of resistance is relatively infrequent. When it does occur, resistance is thought to be due to loss of intracellular nitroreductase activity via sequential mutations in the DNA regions encoding these enzymes.^{28,29} Indeed, despite several decades of use, much of it prolonged and at lower doses in the context of UTI prophylaxis, nitrofurantoin has generally retained its broad-spectrum activity against Gram-negative and Gram-positive bacteria, including most enterococci, but with the important exception of some *Klebsiella* strains, *Pseudomonas aeruginosa* and the Proteae (e.g. *Proteus*, *Morganella* and *Providencia* spp.), which carry intrinsic resistance.⁸

In Western countries, resistance is still rare in *E. coli* and most other ESBL-producing Enterobacteriaceae. A recent population-based survey of *in vitro* antimicrobial resistance of urinary *E. coli* isolates among US outpatients from 2000 to 2010 showed an increase in nitrofurantoin resistance from 0.8% to 1.6%, while increases in ciprofloxacin and trimethoprim/sulfamethoxazole

resistance were more marked, from 3% to 17.1% and from 17.9% to 24.2%, respectively.³⁰ The most recent susceptibility data from *E. coli* community-acquired UTIs in Europe point to a similarly low resistance prevalence (<2% from isolates in 2007–08).³¹ Nonetheless, nitrofurantoin resistance will likely increase with its reintroduction as first-line therapy for uncomplicated UTI.⁴ Indeed, resistance rates among uropathogens in non-Western countries are higher, with recent prevalence documented at 34.3%, 10.1% and 8.3% in India,³² Senegal³³ and South Africa,³⁴ respectively.

Conclusions

Once again recommended as first-line therapy for UTI, nitrofurantoin appears to have clinical efficacy equivalent to that of trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin, although meta-analyses for microbiological cure indicate a slightly more favourable effect for comparators. Nitrofurantoin appears to achieve therapeutic concentrations only in the lower urinary tract, restricting its indication to the treatment of lower

UTI. Toxicity of short-term (≤ 14 days) nitrofurantoin is generally mild and predominantly gastrointestinal. Hypersensitivity reactions such as pulmonary fibrosis and hepatotoxicity were not observed in persons taking short-term nitrofurantoin. Acquisition of resistance to nitrofurantoin is still relatively rare, although is likely to rise given recent increases in consumption. Of note, treatment durations of at least 5 days appear to optimize efficacy.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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