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Nitroxoline: A "Re-Emerging" Antibacterial Agent in the Prevention of Recurrent Urinary Tract Infection Based on Updated Worldwide Guidelines

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ABSTRACT

Introduction. Urinary tract infections (UTIs) represent a critical global healthcare challenge, impacting over 404 million individuals annually. Escalating antimicrobial resistance among primary uropathogens, particularly to fluoroquinolones and broad-spectrum beta-lactams, has driven a critical paradigm shift toward antibiotic-sparing agents. Nitroxoline (5-nitro-8-hydroxyquinoline), an oral uroantiseptic, has re-emerged as a promising therapeutic alternative.

Material and methods. This narrative review synthesizes current clinical and microbiological evidence regarding nitroxoline's mechanism of action, pharmacokinetics, safety profile, and resistance rates. Furthermore, it evaluates the drug's therapeutic positioning across updated international clinical guidelines published up to May 2026.

Results. Nitroxoline exhibits broad-spectrum activity against Enterobacterales (including ESBL strains), urogenital mycoplasmas, and *Candida* species. Its antimicrobial effect is driven by the chelation of essential divalent metallic cations, which inhibits bacterial RNA polymerase, reduces biofilm synthesis, inhibits metallo-beta-lactamases, and impairs mucosal adhesion. Oral nitroxoline achieves rapid, high urinary concentrations with low disruption to native intestinal microflora. Clinical data demonstrate high tolerability (~96%) and a minimal discontinuation rate (~1.3%). Major European consensus guidelines (EAU, AWMF, SSGO) recommend nitroxoline as a first-line oral agent for acute localized cystitis and prophylaxis where available. Guidelines in non-registered regions omit the drug solely due to regional market unavailability.

Conclusions. Nitroxoline is a potent, safe, and antibiotic-sparing uroantiseptic that aligns with global antimicrobial stewardship principles. Future efforts should focus on expanding

clinical trials and clarifying its pharmacokinetics in renal impairment to fully utilize its therapeutic potential against resistant uropathogens.

Keywords: “nitroxoline," "urinary tract infection," "recurrent UTI," "antimicrobial resistance," "guidelines," and "uropathogens."

INTRODUCTION

The diagnosis of urinary tract infections (UTIs) relies on a combination of clinical presentation and laboratory findings [1]. Accurate assessment of global UTI prevalence remains challenging due to widespread self-medication, non-specific symptoms in older adults, and diagnostic hurdles in pediatric populations [1,2]. Nonetheless, global epidemiological data indicate that over 404.6 million individuals were diagnosed with UTIs in 2019 alone [2]. Women aged 25–35 years exhibit the highest incidence, driven by anatomical, physiological, and behavioral risk factors such as sexual activity, menstruation, and pregnancy [2,3].

UTIs encompass a broad clinical spectrum, ranging from asymptomatic bacteriuria and localized cystitis to severe ascending pyelonephritis [1,4]. Common manifestations include dysuria, urinary frequency, suprapubic pressure, fever, and nausea [1]. Complicated or untreated cases can progress to bacteremia, severe sepsis, septic shock, and death, resulting in prolonged hospitalizations and frequent readmissions [2,4]. High-risk populations, including pregnant women, postmenopausal women, elderly individuals, patients with diabetes mellitus, and those with structural or functional urinary abnormalities (e.g., vesicoureteral reflux or bladder and bowel dysfunction) face an elevated likelihood of ascending infection

and associated adverse outcomes [1,3]. Notably, UTIs during pregnancy pose significant risks to both mother and fetus, strongly correlating with preterm birth and small-for-gestational-age infants [3].

Nitroxoline (5-nitro-8-hydroxyquinoline) is a synthetic, broad-spectrum antimicrobial agent first synthesized in 1964 [1,5]. Despite a long clinical history as an effective oral uroantiseptic, general awareness of the drug among primary care physicians remains limited [1,6]. Furthermore, its commercial availability is largely restricted to select European nations, including Germany, Poland, Croatia, Bulgaria, Romania, Bosnia and Herzegovina, and Montenegro [1,5]. However, in light of escalating uropathogen resistance to commonly prescribed agents, particularly fluoroquinolones, nitroxoline is gaining renewed clinical and research interest worldwide [1,5,7].

MATERIALS AND METHODS

This narrative review synthesizes current evidence regarding the therapeutic role of nitroxoline and evaluates its positioning across updated global clinical guidelines for the management and prevention of UTIs [1]. A systematic literature search was conducted in PubMed and Google Scholar for relevant studies published up to May 2026 [1,5]. Search strategies utilized combinations of keywords related to: *"nitroxoline," "urinary tract infection," "recurrent UTI," "antimicrobial resistance," "guidelines,"* and *"uropathogens."* Only English-language and Polish-language full-text articles were included [1]. Eligible studies comprised randomized controlled trials, observational studies, systematic reviews, meta-analyses, relevant experimental research (in vitro and animal models), and official guidelines [1,5,6].

MECHANISM OF ACTION

Nitroxoline possesses a unique chemical structure as an 8-hydroxyquinoline derivative, setting it apart from traditional antibiotic classes [1,4,8]. Its antimicrobial mechanism is driven primarily by the chelation of essential divalent metallic cations, specifically iron Fe (2+), zinc Zn (2+), and magnesium Mg(2+) [1,8,9]. As uropathogens rely heavily on these metal ions as vital enzymatic cofactors to sustain metabolic pathways and structural integrity, cation depletion exerts a multi-faceted bactericidal and anti-virulence effect [1,8].

The chelation of iron and zinc inhibits bacterial RNA polymerase and significantly reduces biofilm formation [8,9]. Additionally, zinc depletion enables nitroxoline to function as an effective inhibitor of bacterial metallo-beta-lactamases (MBLs) [1,8]. Depletion of magnesium alters the hydrophobicity of the bacterial cell envelope, impairing the pathogen's ability to adhere to urothelial mucosal surfaces and urinary catheters [1,8,10]. Crucially, interaction with these divalent cations facilitates drug accumulation within bacterial cell walls (e.g., *Escherichia coli*), maintaining efficacy even at sub-inhibitory concentrations [8,10].

Through these distinct pathways, nitroxoline exhibits broad-spectrum activity against a wide array of uropathogens [1,5,11]: Gram-negative Enterobacterales (*Escherichia coli*, *Citrobacter* spp., *Enterobacter* spp., *Klebsiella oxytoca*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, and *Providencia* spp) [1,5,7,11]; Urogenital Mycoplasmas (*Mycoplasma hominis* and *Ureaplasma urealyticum*) [1,5]; and Fungal Pathogens (Opportunistic *Candida* species) [1,8,11].

PHARMACOKINETICS AND CLINICAL SAFETY PROFILE

Following oral administration, nitroxoline is rapidly absorbed, reaching high urinary concentrations within approximately 1 hour [1,5,19]. Elimination occurs primarily through the kidneys, with roughly 60% of the active compound excreted unchanged in the urine [1,5,19]. While impaired renal function reduces urinary drug concentration, the detailed

pharmacokinetic profile of nitroxoline across varying degrees of renal insufficiency requires further dedicated clinical research [1,19].

Nitroxoline demonstrates an exceptionally favorable safety profile in clinical practice [1,6,10]. In large-scale clinical evaluations, nearly 96% of patients rated overall drug tolerability as "good" or "very good" [1,10]. Treatment discontinuation rates due to drug toxicity remain minimal (~1.3%), matching the safety profiles of established controls such as norfloxacin [1,6,16]. Mild, transient adverse effects occur in approximately 9.4% to 12.9% of patients, predominantly presenting as self-limiting gastrointestinal complaints (e.g., nausea, mild abdominal discomfort, and diarrhea) [1,6,10]. Rare, isolated side effects include mild headaches, cutaneous pruritus, and benign, reversible yellow discoloration of the urine and hair [1,5]. Crucially, unlike broad-spectrum systemic antimicrobials, oral nitroxoline exerts negligible disruptive pressure on native intestinal microflora, significantly lowering the risk of secondary opportunistic infections and dysbiosis [1,8].

ANTIMICROBIAL RESISTANCE AND CLINICAL UTILITY

Bacterial resistance to nitroxoline remains low globally [1,5,7]. This durable susceptibility profile is attributed to its multi-target mechanism of action, historically restricted regional distribution, and selective prescribing practices [1,8,18]. Although comprehensive European-wide surveillance networks and specific regional registries (such as in Poland) lack extensive resistance data, decades of continuous clinical use in countries like Germany demonstrate persistently low resistance rates among key uropathogens, including extended-spectrum-beta-lactamase (ESBL)-producing strains [1,5,12,17,18].

In summary, nitroxoline represents an effective, safe, and currently underutilized antimicrobial option for the treatment and prophylaxis of lower urinary tract infections [1,5,10]. Despite restricted global availability, its unique mechanism and minimal

cross-resistance position it as a valuable therapeutic asset in modern urological practice [1,4,8].

POSITIONING IN RECENT GLOBAL GUIDELINES

In updated clinical guidelines, nitroxoline's therapeutic positioning is defined by its strong efficacy profile and geographic availability [1,5,13,14]. Under the European Association of Urology (EAU) guidelines; which distinguish "localised UTI" (cystitis) from "systemic UTI" (pyelonephritis/urosepsis); nitroxoline is recommended as a first-line oral antimicrobial for localized cystitis (250 mg three times daily for 5 days) in countries where it is commercially licensed [13]. Similarly, the German Interdisciplinary S3 Guideline (AWMF) and the Swiss Society of Gynecology and Obstetrics (SSGO) maintain nitroxoline as a primary first-line option alongside fosfomycin, nitrofurantoin, and pivmecillinam [14,15]. Furthermore, recent consensus data support its role as an effective option for long-term low-dose prophylaxis (250 mg once or twice daily) in managing recurrent UTIs [1,14]. Conversely, organizations in regions without regulatory registration—such as the Infectious Diseases Society of America (IDSA), the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), and the Mexican College of Specialists in Gynecology and Obstetrics (COMEGO)—do not include nitroxoline in their standard algorithms, prioritizing locally marketed alternatives [1,5,20]. Overall, international expert panels recognize nitroxoline as a valuable antibiotic-sparing agent that supports antimicrobial stewardship by demonstrating high activity against extended-spectrum-beta-lactamase producing uropathogens while limiting the use of fluoroquinolones and systemic broad-spectrum agents [1,5,13,14,20].

DISCUSSION

Therapeutic Value in the Era of Antimicrobial Resistance

The escalating global crisis of antimicrobial resistance (AMR), particularly among Gram-negative uropathogens producing extended-spectrum-beta-lactamases, necessitates a paradigm shift toward antibiotic-sparing strategies [1,5,6]. Nitroxoline represents a compelling "re-emerging" therapeutic option that directly aligns with modern antimicrobial stewardship principles [5]. Its distinct multi-target mechanism - driven by the chelation of essential divalent metallic cations Fe (2+), Zn (2+), MG(2+) - exerts concurrent bactericidal, anti-biofilm, and anti-adhesion effects [8,9]. Unlike classical antimicrobials that target single enzymatic pathways susceptible to point mutations or plasmid-mediated resistance, nitroxoline's cation-depletion pathway imposes a high genetic barrier to resistance [6,8]. Consequently, despite over five decades of clinical application in Central Europe, susceptibility rates among *Escherichia coli* and other Enterobacterales remain exceptionally high [1,7,12,17].

Guideline Divergence and Geographic Disparities

A central finding of this review is the sharp contrast between regional clinical guidelines regarding nitroxoline. Major European consensus bodies -including the European Association of Urology, the German Interdisciplinary S3 Guideline, and the Swiss Society of Gynecology and Obstetrics recommend nitroxoline as a first-line oral agent for acute localized cystitis [13,14]. Conversely, guidelines from regions where the drug is not commercially registered (such as IDSA in North America, SEIMC in Spain, and COMEGO in Mexico) omit nitroxoline entirely from their treatment algorithms [1,20]. This divergence is not driven by clinical inferiority or safety concerns, but rather by regulatory history, market fragmentation, and a lack of pharmaceutical sponsorship for international multi-center trials [1,5]. Re-evaluating nitroxoline through expanded international clinical trials could facilitate

regulatory approvals outside Central Europe, offering clinicians a crucial alternative to fluoroquinolones and carbapenems.

Efficacy in Recurrent UTI Prevention and Biofilm Mitigation

Beyond acute localized cystitis, nitroxoline demonstrates significant potential in managing recurrent urinary tract infections [1,14]. The drug's ability to chelate iron and zinc suppresses biofilm formation and disrupts established bacterial matrix structures on urothelial mucosa and indwelling urinary catheters [8,9]. This anti-biofilm activity addresses a primary cause of persistent bacteriuria and treatment failure in recurrent lower UTIs [1,4]. Furthermore, long-term low-dose prophylactic regimens (250 mg once or twice daily) provide continuous uroantiseptic coverage without inducing significant bacterial cross-resistance [10,14].

Safety Profile and Microbiome Preservation

Nitroxoline's pharmacokinetic profile further reinforces its utility as an outpatient uroantiseptic [19]. Because it is rapidly excreted into the urinary tract with minimal systemic accumulation, it achieves high therapeutic concentrations in the urine while exerting negligible selective pressure on the native gut and vaginal microflora [3,8,19]. This minimal disruption of microflora minimizes secondary opportunistic infections (such as *Clostridioides difficile* colitis or vulvovaginal candidiasis) commonly associated with broad-spectrum oral agents [3,6]. Moreover, clinical safety data confirm an exceptionally low rate of serious adverse events and treatment discontinuations (~1.3%), making it well-tolerated across diverse patient cohorts [6,10].

Gaps in Evidence and Future Research Directions

Despite its therapeutic promise, several key clinical and scientific gaps remain to be addressed. Because nitroxoline relies predominantly on renal excretion to achieve therapeutic

urinary concentrations, well-designed pharmacokinetic studies are urgently needed to establish clear safety parameters and precise dosing adjustments in patients with impaired renal function [1,19]. Furthermore, the absence of centralized, pan-European surveillance databases limits the ability to continuously monitor nitroxoline resistance trends across different uropathogenic species [1,18]. Beyond its primary antimicrobial role, emerging pre-clinical data suggest that nitroxoline possesses distinct anti-angiogenic and anti-neoplastic properties, pointing to potential synergistic and adjunct applications in urological oncology that warrant further clinical exploration [4].

Closing these evidence gaps through prospective, multi-center trials and harmonized susceptibility testing will be essential to fully integrate nitroxoline into global UTI management pathways.

CONCLUSIONS

Nitroxoline represents a highly effective and safe therapeutic option in the era of escalating antimicrobial resistance. Its unique multi-target mechanism of action, driven by divalent cation chelation, accounts for persistently low global resistance rates and minimal disruption to the native intestinal microbiota. Backed by solid clinical efficacy and favorable tolerability, nitroxoline is rightfully positioned as a first-line agent for acute localized cystitis and a viable option for recurrent UTI prophylaxis in recent international guidelines. However, its restricted geographic availability currently limits wider clinical utility. Future research should focus on clarifying its pharmacokinetic profile in patients with renal impairment to fully unlock its global potential in modern urological practice.

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