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In Vitro Activity of Nitroxoline against *Escherichia coli* Urine Isolates from Outpatient Departments in Germany

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Increased acquired resistance to orally administered antibiotics in *Escherichia coli* has complicated the management of urinary tract infections (UTI) in outpatients (1–3). In this context, nitroxoline (5-nitro-8-hydroxyquinoline) (Fig. 1), an oral antibiotic, has received renewed attention in the management of UTI. Nitroxoline possesses activity *in vitro* against a variety of microorganisms, including *E. coli* and other uropathogens (4, 5). The mechanism of action is believed to be chelation of divalent cations required for bacterial RNA polymerase, leading to bacteriostatic activity in most cases (6, 7).

Nitroxoline has received marketing authorization for prophylaxis and treatment of acute and recurrent UTI in various European countries, including Germany. The standard daily dosage of nitroxoline is 250 mg administered every 8 h. The drug is heavily metabolized (>95%) into microbiologically active conjugated and nonconjugated derivatives. Urine recovery is >50% (30% microbiologically active) (7, 8). At subinhibitory concentrations, the drug inhibits the adhesion of uropathogenic *E. coli* to uroepithelial cells and urinary catheters (9–11). An individual-patient meta-analysis of four randomized controlled clinical trials comparing the safety and efficacy of nitroxoline versus cotrimoxazole or norfloxacin in 466 patients with uncomplicated UTI detected a microbiological eradication rate of >90% for nitroxoline (12).

We determined the *in vitro* activity of nitroxoline against 499 *E. coli* isolates recovered from urine samples of outpatients during a surveillance study conducted by the Antimicrobial Resistance Working Party of the Paul Ehrlich Society between October and December of 2010 (13). Twenty-five laboratories were requested each to collect 20 consecutive nonduplicate isolates. Species confirmation and susceptibility testing were performed in a central laboratory (Antiinfectives Intelligence). MICs were determined by the broth microdilution procedure as described in the ISO document ISO 20776-1:2006 (14).

The majority of isolates were obtained from women (85.9%), with approximately 35% of isolates from females aged >65 years. High rates of resistance were observed for amoxicillin (42.9%), cotrimoxazole (30.9%), and ciprofloxacin (19.8%). Two hundred fifty-two (50.5%) isolates were fully susceptible to amoxicillin, amoxicillin-clavulanate, cefuroxime, third-generation cephalosporins (cefixime and cefpodoxime), ciprofloxacin, cotrimoxazole, and fosfomycin, while 143 (28.7%) isolates met the criterion for multidrug resistance (resistance to at least three of the seven antibacterial drugs/drug subclasses). Nineteen (3.8%) isolates were resistant to all drugs/drug subclasses except for fosfomycin, and 1 strain (0.2%) was resistant to all antibiotics. Forty isolates (8%) showed an extended-spectrum β-lactamase phenotype (13).

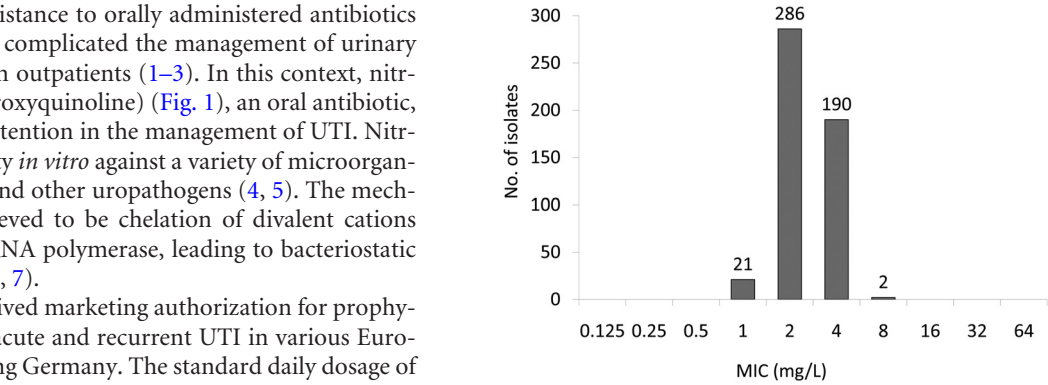

FIG 1 Chemical structure of nitroxoline.

FIG 2 Susceptibilities of 499 *E. coli* isolates to nitroxoline.

The nitroxoline MICs showed a normal (Gaussian) distribution, with values ranging from 1 to 8 mg/liter (Fig. 2). Based on the MIC_{50} and MIC_{90} values, there was no difference in activity between fully susceptible and multidrug resistant isolates (Table 1). The German breakpoint committee (Nationales Antibiotika-Sensitivitätstest-Komitee [NAK]) has recently established a clinical breakpoint (susceptible, ≤16 mg/liter, and resistant, >16 mg/liter) for nitroxoline against *E. coli* (15). Applying this breakpoint, all 499 isolates were rated susceptible to nitroxoline.

Although nitroxoline has been on the market for decades, resistance to nitroxoline in *E. coli* seems still to be very rare in Germany. This finding might be explained by the moderate consumption of nitroxoline in our country. In 2011, outpatient nitroxoline use was 1.0 million defined daily doses (DDD) (corresponding to 0.034 DDD per 1,000 inhabitants per day) (16).

Nitroxoline showed 100% *in vitro* activity against *E. coli* urine isolates, irrespective of their resistance profile. In a previous study, nitroxoline demonstrated the same *in vitro* activity against sulfonamide-susceptible and sulfonamide-resistant *E. coli* strains (5). In conclusion, nitroxoline should be equally effective against suscep-

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TABLE 1 *In vitro* activity of nitroxoline against subgroups of fully susceptible and multidrug-resistant *E. coli* isolates

Group (no. of isolates)	Nitroxoline MIC (mg/liter)	
	MIC_{50}	MIC_{90}
All isolates (499)	2	4
Susceptible isolates (252)[a]	2	4
Mutidrug-resistant isolates (143)[b]	2	4

[a] Isolates were susceptible to amoxicillin, amoxicillin-clavulanate, cefuroxime, third-generation cephalosporins (cefixime and cefpodoxime), ciprofloxacin, cotrimoxazole, and fosfomycin.

[b] Isolates were resistant to at least three of the seven antibacterial drugs/drug subclasses.

tible and multidrug-resistant *E. coli* bacteria causing acute or recurrent uncomplicated UTI.

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