Proposal for nitroxoline breakpoints for *Escherichia coli* from uncomplicated urinary tract infection

Listed below are proposals for nitroxoline breakpoints for *Escherichia coli* from uncomplicated urinary tract infection. The proposals are open for comment by 28th November 2015. Please send comments, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (derek.brown222@btinternet.com). Please use the attached form for your comments.

Background

Nitroxoline (5-nitro-8-hydroxyquinoline) is an oral agent which is different from any other antimicrobial drug class. The mechanism of action is believed to be chelation of divalent cations required for activity of bacterial RNA polymerase. There are some resistant isolates but the mechanisms of resistance have not yet been determined.

The antimicrobial spectrum of nitroxoline covers *Escherichia coli* and other uropathogens. *Pseudomonas* spp. are resistant. Nitroxoline has been shown to be effective against both fully susceptible and multiple drug-resistant *E. coli.*

Nitroxoline has marketing authorisation for prophylaxis and treatment of acute and recurrent UTI in Germany, Bulgaria, Croatia, Poland, Romania, Bosnia-Herzegovina and Montenegro.

Current clinical breakpoints

There are breakpoints for Enterobacteriaceae in Germany (S ≤16 mg/L, R >16 mg/L for *E. coli* only).

Dosage

The approved dosage is an oral dose of 250 mg three times daily.

MIC distributions

Organism	MIC (mg/L)												
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Escherichia coli	1	1	0	0	32	464	462	551	115	1	1	0	0
Citrobacter spp.	0	0	0	0	0	2	4	41	11	2	0	0	0
Klebsiella oxytoca	0	0	0	0	0	1	21	10	1	0	0	0	0
Klebsiella pneumoniae	0	0	0	0	1	13	46	29	4	4	0	0	0
Klebsiella spp.	0	0	0	0	2	1	8	57	58	17	3	0	0
Morganella morganii	0	0	0	0	0	3	14	45	17	0	0	0	0
Proteus mirabilis	0	0	0	0	2	12	99	221	42	1	1	0	0
Proteus vulgaris	0	0	0	0	0	2	36	61	18	0	0	0	0
Proteus spp. indole-positive	0	0	0	0	0	2	1	13	11	1	1	0	0
Serratia spp.	0	0	0	0	0	0	0	3	55	11	0	0	0
Enterobacter cloacae	0	0	0	0	1	1	4	27	4	0	0	0	0
Enterobacter spp.	0	0	0	0	0	2	12	25	49	8	1	0	0
Acinetobacter spp.	0	0	0	3	6	28	29	6	0	1	1	0	0
Pseudomonas aeruginosa	0	0	0	0	0	0	1	1	26	18	27	5	0
Pseudomonas spp.	0	0	0	0	0	0	0	0	0	27	57	23	3
Staphylococcus aureus	0	0	0	0	17	39	29	130	1	0	0	0	0
Staphylococcus epidermidis	0	0	0	0	0	1	36	113	21	0	0	0	0
Staphylococcus saprophyticus	0	0	0	0	0	0	0	30	0	1	0	0	0
Coagulase-negative staphylococci	0	0	0	1	10	35	9	8	2	0	0	0	0
Enterococcus faecalis	0	0	0	0	0	3	20	124	158	46	6	0	0
Enterococcus faecium	0	0	0	0	0	1	8	42	0	0	0	0	0

Pharmacokinetics

The Cmax in human serum is 6.-1-7.8 mg/L with a half life of about 2 h.

Concentrations (mg/L) in urine following a dose of 200 mg in one study (Bergogne-Berezin E *et al*, *Pathol Biol (Paris)* 1987; 35: 873-8) were 46±5 at 0-1 h, 216±137 at 1-2h, 187±134 at 2-3h, 220±131 at 3-4h, 105±83 at 4-6h, 84±71 at 6-8h, 59.5±34 at 8-10h.

Pharmacodynamic data are not available.

Clinical data

In a meta-analysis, published data from 26 uncontrolled studies were analysed (Naber KG *et al*. *BMC Infect Dis* 2014; 14:628-643). Studies included 1206 patients (947 adults and 259 children), two controlled studies included 148 patients (100 adults and 48 children) and one post-marketing observational study comprised 9,800 patients with uncomplicated and complicated UTI. Nitroxoline was mainly administered for treatment of uncomplicated and complicated UTI as well as for prophylaxis of recurrent UTI, with daily dosages mostly between 300 and 900 mg. The treatment duration varied between three and 10 days depending on the indication. Success rates varied from 66-100%, with most in the 70-90% range.

A total of 466 female patients with acute uncomplicated or recurrent cystitis were included in four unpublished prospective open randomized studies. Of these, 234 received 250 mg of nitroxoline orally three times daily and 232 either 960 mg of cotrimoxazole three times daily (n=178) or 400 mg norfloxacin twice daily (n=54) for 5-10 days. More than 90% of the patients showed eradication of bacteriuria with nitroxoline, meeting the statistical requirement of a 10% non-inferiority margin in eradication rates compared with the controls in all three evaluation sets. The clinical efficacy (reduction of symptoms, global assessment by patient and physician) was similar between the two treatment groups.

Data relating MIC to outcome are not available.

Proposed clinical breakpoints

Breakpoints of S ≤16 mg/L, R >16 mg/L are proposed for *E. coli* from uncomplicated UTI only.

For other Enterobacteriaceae, *S. saprophyticus* and *Enterococcus* spp. there is insufficient evidence to set breakpoints. Other organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints.