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Nationales Antibiotika-Sensitivitätstest-Komitee

Nitroxoline	Rationale for the NAK clinical breakpoints, version 1.0	31st January 2014

Foreword

NAK
The German Antimicrobial Susceptibility Testing Committee (NAK - Nationales Antibiotika-Sensitivitätstest -Komitee; German NAC) was founded the 14th of June, 2012. Major objectives are I) to establish EUCAST breakpoints and technical aspects of in vitro antimicrobial susceptibility testing in German laboratories, II) to adapt EUCAST breakpoint to local requirements, and (III) to evaluate breakpoints for antimicrobial agents that have not yet been considered by EUCAST.
The organizational structure largely follows that of EUCAST. The General Committee comprising representatives of national scientific societies and organizations in the fields of infectious diseases and patient safety decides on recommendations proposed by the Steering Committee. The Steering Committee currently consists of 15 experts having a background in clinical microbiology, infectious diseases or regulatory affairs. Both boards will meet at least once a year. Industry has an observational status only.

Information on NAK is available on the NAK website at http://www.nak-deutschland.org.

NAK rationale documents
NAK rationale documents summarise the information on which the NAK clinical breakpoints are based.

Availability of NAK document
All NAK documents are freely available from the NAK website at http://www.nak-deutschland.org.

Citation of NAK documents
This rationale document should be cited as: “NAK - Nationales Antibiotika-Sensitivitätstest -Komitee. Nitroxoline: Rationale for the clinical breakpoints, version 1.0, 2014.

Introduction

Nitroxoline (5-nitro-8-hydroxyquinoline) is an oral antibiotic which is different from any other antimicrobial drug class.

Following oral administration, the drug is heavily metabolized (>95%) into microbiologically active conjugated and non-conjugated derivatives, resulting in relatively low serum concentrations and high urinary concentrations. The drug is primarily used for oral therapy of acute cystitis. Its antimicrobial spectrum covers *Escherichia coli* and other uropathogens. *Pseudomonas* spp. are resistant.

The mechanism of action is chelation of divalent cations required for inhibition of RNA polymerase. At sub-inhibitory concentrations the drug inhibits the adhesion of *Escherichia coli* and other uropathogens to uroepithelial cells.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose				**250mg x 3**		
Maximum dose schedule				250mg x 3		
Available formulations				Oral		

2. MIC distributions[1] and epidemiological cut-off (ECOFF) values (mg/L)

Organism	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Escherichia coli - Kresken	0	0	0	0	0	0	0	0	0	21	286	190	2	0	0	0	0	0	0	
Escherichia coli - Marre	0	0	0	0	0	0	0	0	0	1	8	77	50	2	0	0	0	0	0	
Escherichia coli - Opferkuch	0	0	0	0	0	0	0	0	0	0	12	117	463	112	0	0	0	0	0	
Escherichia coli - Pfister	0	0	0	0	0	1	1	0	0	5	158	74	12	1	0	1	0	0	0	
Escherichia coli	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**0**	**27**	**464**	**458**	**527**	**115**	**0**	**1**	**0**	**0**	**0**	**16**
Citrobacter spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	2	4	41	11	2	0	0	0	0	
***Citrobacter* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**4**	**41**	**11**	**2**	**0**	**0**	**0**	**0**	**ND**
Klebsiella oxytoca - Marre	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	
Klebsiella oxytoca - Pfister	0	0	0	0	0	0	0	0	0	0	1	20	8	1	0	0	0	0	0	
Klebsiella oxytoca	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**21**	**10**	**1**	**0**	**0**	**0**	**0**	**0**	**ND**
Klebsiella pneumoniae - Kresken	0	0	0	0	0	0	0	0	0	0	4	17	9	0	0	0	0	0	0	
Klebsiella pneumoniae - Marre	0	0	0	0	0	0	0	0	0	0	0	4	10	1	2	0	0	0	0	
Klebsiella pneumoniae - Pfister	0	0	0	0	0	0	0	0	0	1	9	25	10	3	2	0	0	0	0	
Klebsiella pneumoniae	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**13**	**46**	**29**	**4**	**4**	**0**	**0**	**0**	**0**	**16**
Klebsiella spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	6	52	47	5	2	0	0	0	
Klebsiella spp.	0	0	0	0	0	0	0	0	0	0	0	6	52	47	5	2	0	0	0	**ND**
Morganella morganii – Kresken	0	0	0	0	0	0	0	0	0	0	3	13	14	9	0	0	0	0	0	
Morganella morganii - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	1	31	8	0	0	0	0	0	
Morganella morganii	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**14**	**45**	**17**	**0**	**0**	**0**	**0**	**0**	**ND**
Proteus mirabilis - Kresken	0	0	0	0	0	0	0	0	0	0	0	34	67	0	0	0	0	0	0	
Proteus mirabilis - Marre	0	0	0	0	0	0	0	0	0	0	0	1	3	2	0	0	0	0	0	
Proteus mirabilis - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	37	90	31	1	0	0	0	0	
Proteus mirabilis - Pfister	0	0	0	0	0	0	0	0	0	1	12	26	57	3	0	1	0	0	0	
Proteus mirabilis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**12**	**98**	**217**	**36**	**1**	**1**	**0**	**0**	**0**	**16**
Proteus vulgaris – Kresken	0	0	0	0	0	0	0	0	0	0	0	20	30	9	0	0	0	0	0	
Proteus vulgaris - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	11	30	9	0	0	0	0	0	

Organism	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Proteus vulgaris - Pfister	0	0	0	0	0	0	0	0	0	0	2	5	1	0	0	0	0	0	0	
Proteus vulgaris	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**16**	**31**	**9**	**0**	**0**	**0**	**0**	**0**	**ND**
Serratia spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	0	3	55	11	0	0	0	0	
***Serratia* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**55**	**11**	**0**	**0**	**0**	**0**	**ND**
Enterobacter cloacae - Pfister	0	0	0	0	0	0	0	0	0	1	1	4	27	4	0	0	0	0	0	
Enterobacter cloacae	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**4**	**27**	**4**	**0**	**0**	**0**	**0**	**0**	**ND**
Enterobacter spp - Marre	0	0	0	0	0	0	0	0	0	0	0	1	4	0	0	0	0	0	0	
Enterobacter spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	7	18	49	6	1	0	0	0	
Enterobacter spp - Pfister	0	0	0	0	0	0	0	0	0	0	2	3	2	0	0	0	0	0	0	
***Enterobacter* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**11**	**24**	**49**	**6**	**1**	**0**	**0**	**0**	**ND**
Other Enterobacteriaceae - Pfister	0	0	0	0	0	0	0	0	0	0	3	9	6	14	1	0	0	0	0	
Other Enterobacteriaceae	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**9**	**6**	**14**	**1**	**0**	**0**	**0**	**0**	**ND**
Acinetobacter spp - Opferkuch	0	0	0	0	0	0	0	0	1	0	21	29	6	0	1	1	0	0	0	
Acinetobacter spp - Pfister	0	0	0	0	0	0	0	0	2	6	7	0	0	0	0	0	0	0	0	
***Acinetobacter* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**6**	**28**	**29**	**6**	**0**	**1**	**1**	**0**	**0**	**0**	**ND**
Pseudomonas aeruginosa - Marre	0	0	0	0	0	0	0	0	0	0	0	0	0	2	5	2	1	0	0	
Pseudomonas aeruginosa - Pfister	0	0	0	0	0	0	0	0	0	0	0	1	1	7	11	13	4	0	0	
Pseudomonas aeruginosa	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**9**	**16**	**15**	**5**	**0**	**0**	**ND**
Pseudomonas spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	0	0	0	27	57	23	3	0	
***Pseudomonas* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**27**	**57**	**23**	**3**	**0**	**ND**
Staphylococcus aureus - Marre	0	0	0	0	0	0	0	0	0	0	0	6	1	0	0	0	0	0	0	
Staphylococcus aureus - Opferkuch	0	0	0	0	0	0	0	0	0	0	1	18	102	0	0	0	0	0	0	
Staphylococcus aureus - Pfister	0	0	0	0	0	0	0	0	0	16	38	3	3	1	0	0	0	0	0	
Staphylococcus aureus	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**16**	**39**	**27**	**106**	**1**	**0**	**0**	**0**	**0**	**0**	**ND**
Staphylococcus epidermidis - Opferkuch	0	0	0	0	0	0	0	0	0	0	1	36	106	15	0	0	0	0	0	
Staphylococcus epidermidis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**36**	**106**	**15**	**0**	**0**	**0**	**0**	**0**	**ND**
CNS - Marre	0	0	0	0	0	0	0	0	0	0	0	1	3	1	0	0	0	0	0	
CNS - Pfister	0	0	0	0	0	0	0	0	1	10	35	8	5	1	0	0	0	0	0	
CNS	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**10**	**35**	**9**	**8**	**2**	**0**	**0**	**0**	**0**	**0**	**ND**

Organism	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Staphylococcus saprophyticus - Kresken	0	0	0	0	0	0	0	0	0	0	0	0	30	0	0	0	0	0	0	
Staphylococcus saprophyticus - Marre	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	
Staphylococcus saprophyticus	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**30**	**0**	**1**	**0**	**0**	**0**	**0**	**16**
Enterococcus faecalis - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	0	18	148	44	0	0	0	0	
Enterococcus faecalis - Pfister	0	0	0	0	0	0	0	0	0	0	3	20	106	8	1	0	0	0	0	
Enterococcus faecalis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**20**	**124**	**156**	**45**	**0**	**0**	**0**	**0**	**ND**
Enterococcus faecium - Pfister	0	0	0	0	0	0	0	0	0	0	1	8	42	0	0	0	0	0	0	
Enterococcus faecium	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**8**	**42**	**0**	**0**	**0**	**0**	**0**	**0**	**ND**
Enterococcus spp - Marre	0	0	0	0	0	0	0	0	0	0	0	0	6	7	7	0	0	0	0	
***Enterococcus* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**6**	**7**	**7**	**0**	**0**	**0**	**0**	**ND**
Streptococcus spp - Pfister	0	0	0	0	0	0	0	1	2	2	7	2	0	0	0	0	0	0	0	
***Streptococcus* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**2**	**2**	**7**	**2**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**ND**
Haemolytic streptococci - Opferkuch	0	0	0	0	0	0	0	0	3	8	6	20	15	0	0	0	0	0	0	
Haemolytic streptococci	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**8**	**6**	**20**	**15**	**0**	**0**	**0**	**0**	**0**	**0**	**ND**

[1] The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence (IE) no epidemiological cut-off has been determined (ND).

3. Breakpoints prior to harmonisation (mg/L) S≤ / R>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoints							
		≤1 / >32*					
Species-related breakpoints							
Enterobacteriaceae							
Pseudomonas spp.							
Acinetobacter spp.							
Staphylococcus spp.							
Streptococcus spp.							
Streptococcus pneumoniae							
Enterococcus spp.							
Haemophilus influenzae							
Moraxella catarrhalis							
Corynebacteria							
Neisseria meningitidis							
Neisseria gonorrhoeae							
Pasteurella multocida							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
Campylobacter spp.							
Helicobacter pylori							

*breakpoints published in 2013

4. Pharmacokinetics

Dosage (mg)	200 mg single dose orally	200 mg x 3 orally	250 mg x 3 orally	
Cmax (mg/L) HPLC	5.59 ± 3.15 after 1.75 ± 1.04 h	8.08 ± 4.42 after 1 h	6,09 – 7,78	
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	2.63 ± 2.66		ca. 2	
AUC (mg.h/L)	32.34 ± 11.34		15.11 – 17.68	
Fraction unbound (%)			90	
Volume of distribution (L/KG)				
Comments	• Two values are given where references differ. Cells are left empty when data are not readily available. • Oral absorption is almost 100%. • **Concentration in urine >200 mg/L (bioassay)**			
References	• Bergogne-Berezin et al Path Biol 1987; 35: 873-878 • Nitroxolin forte Fachinformation (SPC), March 2012			

5. Pharmacodynamics				
Dose				
*f*AUC/MIC for bacteriostasis				
*f*AUC/MIC for 2 log reduction				
*f*AUC/MIC from clinical data				
Comments	• Pharmacodynamics parameters for nitroxoline have not been determined. • Cells are left empty when data are not readily available. • Nitroxoline usually exerts bacteriostatic activity. Urinary inhibitory titers of nitroxoline for *E. coli, K. pneumoniae* and *S. saprophyticus* were higher at pH 5.5 than at pH 8.0.			
References	• Wagenlehner et al. Antimicrob Agents Chemother. 2014;58:713-21			

6. Monte Carlo simulations and Pk/Pd breakpoints

No data

7. Clinical data

Efficacy of nitroxoline has been studied in clinical trials for treatment of patients with acute cystitis and acute recurrent cystitis caused by bacteria categorized as wildtype.

8. Clinical breakpoints	
Non-species-related breakpoints	There is insufficient evidence to set a non-species related breakpoint.
Species-related breakpoints	For *E. coli* the breakpoint is 16/16 mg/L.
Species without breakpoints	All other species and bacterial groups.
Clinical qualifications	Nitroxoline is used only for uncomplicated UTI.
Dosage	The breakpoint applies to a daily oral dose of 250 mg x 3.
Additional comment	

9. Agent name - NAK clinical MIC breakpoints

These can be found at http://www.nak-deuschland.org.