

Impact of different urine pH levels on the pharmacodynamics of nitrofurantoin for pathogens involved in urinary tract infections

Fiona Fransen,¹ Claudia Lagarde,¹ Ria Melchers,¹ Joseph Meletiadis,^{2,3} Johan W.Mouton^{1,3}

¹Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands; ²Clinical Microbiology Laboratory, Attikon Hospital, University of Athens, Athens, Greece; ³Department of Medical Microbiology and Infectious Diseases, Erasmus Medical Center, Rotterdam, The Netherlands

Introduction

Nitrofurantoin has been used for treatment of urinary tract infection for over 50 years. However, as an old drug, the pharmacodynamics (PD) of nitrofurantoin under physiological conditions have hardly been studied and are poorly understood. Several factors may influence antimicrobial activity in urinary tract infections like urine pH,

Aim of the study

To determine the basic PD properties of nitrofurantoin in urine at different pH levels by in vitro time-kill assays.

Methods

Strains

Seven ESBL strains (4 *E. coli*, 2 *K. pneumoniae*, 1 *E. cloacae*) and two ESBL negative strains (1 *E. cloacae*, 1 *K. pneumoniae*) with nitrofurantoin MICs 8-32 mg/L.

Antibiotic and susceptibility testing

Nitrofurantoin (CAS 67-20-9), solvent dimethylsulfoxide, MIC determined by broth microdilution (ISO).

Time-Kill assay and Analysis

Time-kill assays were performed at 4 pH levels (5.5, 6.5, 7.5 and 8.5) in urine at 37°C during 24h at two-fold increasing concentrations from 0.125 up to 32xMIC.

The kill rate ($\log_{10}\text{CFU/ml} \times \text{h}^{-1}$) was determined by linear regression analysis of the $\log_{10}\text{CFU/ml}$ data for the time interval of 1-6h.

A sigmoidal Emax model with variable slope was used to fit the 6h kill rate-drug concentration data and the maximal kill-rate (Emax) as well as the concentration corresponding to 50% of Emax (EC50) was determined for each strain and pH.

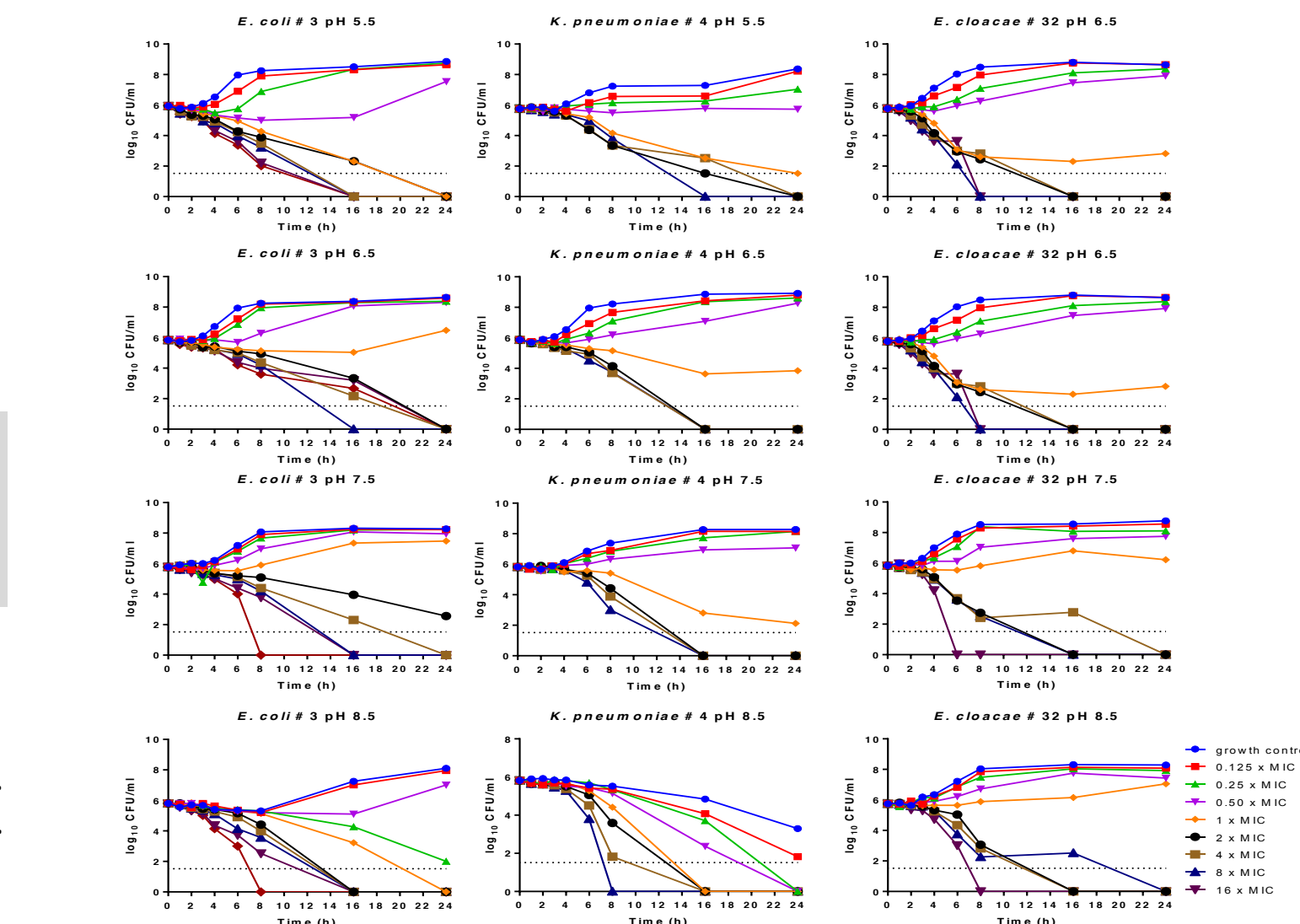


Fig 1. Growth curves of nitrofurantoin at different pH levels. Cell viability ($\log_{10}\text{CFU/ml}$) plotted for cultures grown at different concentrations of nitrofurantoin.

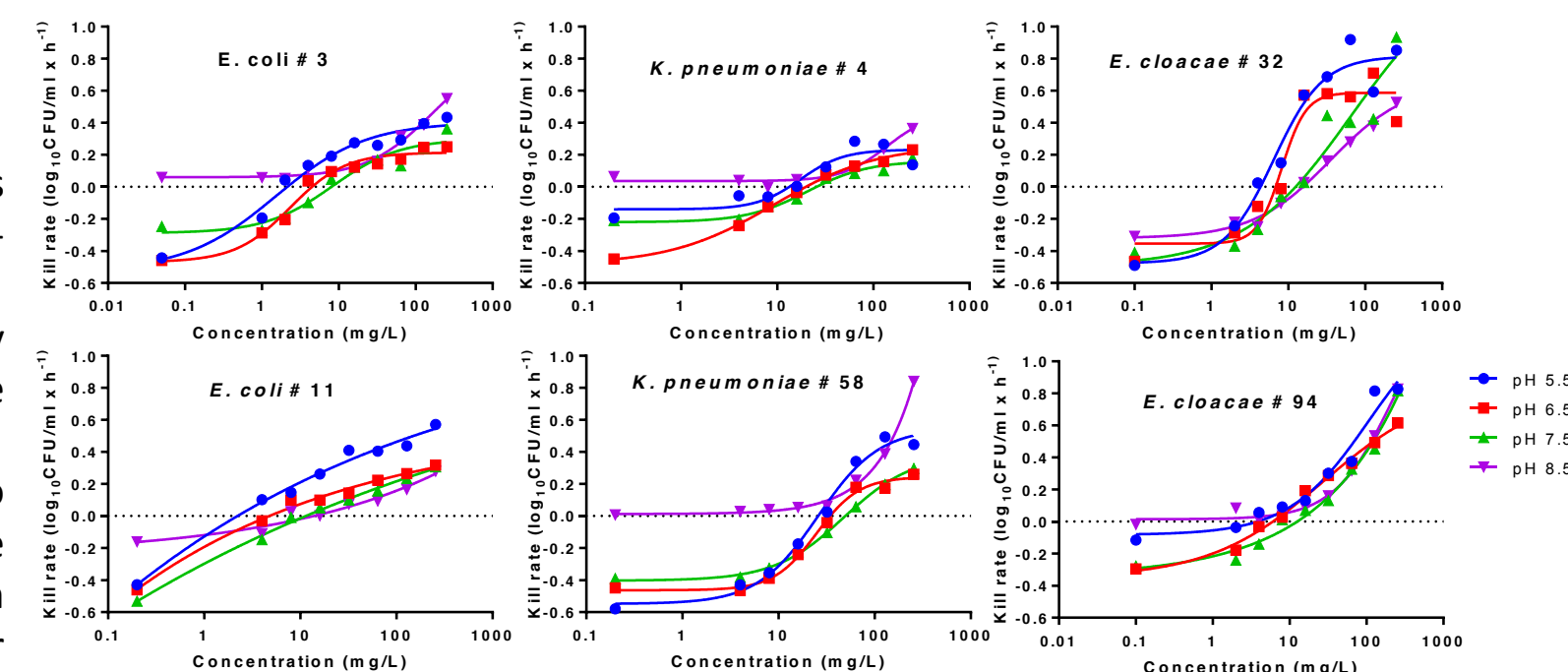


Fig 2. Best fitted sigmoid curves obtained from sigmoid maximum effect (Emax) model for several strains exposed to nitrofurantoin between 1-6 hours.

Results

The growth rates in the drug-free control as determined over the first 6h varied significantly between and within isolates for the different pH levels.

- Reduced growth rate at pH 8.5 (6 strains)

- Delay in killing observed for some *E. coli*/*E. cloacae* strains at higher pH levels compared to pH 5.5.

For *E. coli* and *E. cloacae* strains were the pH did not affect growth → bactericidal activity was observed at 24h for concentrations 0.5-2xMIC at pH 5.5 whereas at higher pH levels slightly higher concentrations (1-4xMIC) were needed.

- In the Emax model no apparent differences in mean maximum kill-rates were observed between the pH 5.5/6.5 or 7.5 (0.52 vs. 0.47 vs. 0.54)h⁻¹.

- Higher nitrofurantoin concentration was needed to reach a 50% effect in pH level 8.5 as compared to pH levels 5.5/6.5. EC50s (116.44 vs 13.98 mg/L) indicating an increased susceptibility to nitrofurantoin at lower pH levels.

Conclusion

Urine pH had an effect on the growth of bacteria with significant species- and isolate-dependent differences. Nitrofurantoin activity increased at lower pH levels. The efficacy of nitrofurantoin against urinary tract infections may be dependent on urine pH level and the pH susceptibility of the causative pathogen.

Acknowledgments

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