

Tigecycline: Rationale for EUCAST Clinical Breakpoints

Current version	3.0	April 2023
Previous versions	2.0 1.0	July 2022 March 2006

Introduction

Tigecycline is an injectable antibacterial derived from the tetracyclines and classified by the manufacturer as a glycylcycline. Its in vivo potency is similar to tetracyclines with the exception that it is active against many bacterial strains which are resistant to existing tetracyclines. It is available only in an intravenous formulation. Tigecycline is licenced for use in complicated skin and skin structure infections (CSSSI), complicated intra-abdominal infection (IAI).

This version is extracted from version 2.0, and will be format for future updates. Previous versions are available on request.

Dosages related to clinical breakpoints

Standard dosage: 50 mg x 2 iv, preceded by a 100 mg loading dose

High dosage: See Guidance document

(https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Tigecycline_Guidance_document_v2_20220720.pdf)

MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

Pharmacokinetics

PK parameter	Pharmacological studies		Efficacy studies	
	100mg	50mg	50mg	100mg x2*
Dosage				
C _{max} (mg/L)	1.45 ± 0.32	0.87 ± 0.23	0.80 ± 0.46	0.34 [0.15-1.03]
C _{min} (mg/L)	0.90 ± 0.27	0.63 ± 0.10	0.49 ± 0.28	0.09 [0.05-0.26]
Total body clearance (L/h)	NA	0.13 ± 0.08	0.16 ± 0.09	42.1
T _{1/2} (h), mean (range)	21.8 ± 8.9	23.8 ± 7.8	19.9 ± 8.1	7.2
AUC ₀₋₁₂ (mg.h/L)	27.1 ± 14.3	42.4 ± 35.3	NA	
AUC ₀₋₂₄ (mg.h/L)	NA	4.70 ± 1.70	5.85 ± 2.48	3.61 [2.55-10.39]
AUC _{0-∞} (mg.h/L)	5.19 ± 1.86	NA	NA	
Fraction unbound (%)	13-29	13-20	NA	
Volume of distribution _{ss} (L)	568 ± 244	639 ± 307	NA	438.6

* Values expressed as median and [interquartile range]

Pharmacodynamics

Index*	In vitro PD	Neutropenic mouse thigh		Neutropenic mouse thigh		Hospital-acquired pneumonia
	<i>K. pneumoniae</i>	<i>E. coli</i>		<i>K. pneumoniae</i>		
	Median (Range)	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	
fAUC/MIC for bacteriostasis	Inoculum: 10 ⁷ = 69 (54-133) 10 ⁶ = 40 (25-172) 10 ⁵ = 35 (21-63)	5.96 (3.88-7.50)	5.79 ± 1.48	5.27 (2.02-6.53)	4.61 ± 1.69	
fAUC/MIC for success						Clinical: 0.9 Microbiological: 0.35

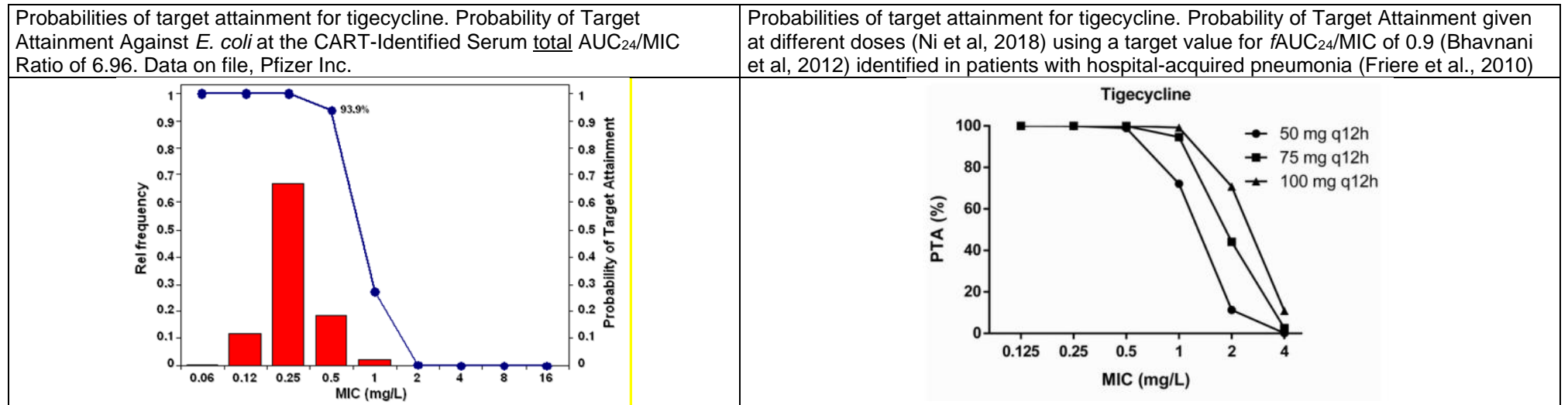
Tsala et al. demonstrated an exposure-response relationship using an in vitro model against *K. pneumoniae* strains with different MICs ranging from 0.125 to 2 mg/L. Exposures were simulated for 50 mg x 2 dosage. The $fAUC_{24}/MIC$ values were influenced by the size of the inoculum, Better responses were seen with simulated unbound lung concentrations ($fC_{max} = 0.125$ mg/L) than with serum concentrations ($fC_{max} = 1.25$ mg/L).

Bhavnani et al. examined the pharmacodynamic relationship between exposure ($fAUC_{24}/MIC$) and outcomes in hospital-acquired pneumonia. A $fAUC_{24}/MIC$ of >0.9 was associated with clinical success and >0.35 was associated with microbiological success, defined as response rates of 78%, compared to $\sim 30\%$ for patients below these $fAUC_{24}/MIC$ values

Monte Carlo simulations

The left-hand figure shows the probability of target attainment for *E. coli*. The target is taken from the clinical study on and complicated intra-abdominal infection. The use of this target in the Monte Carlo simulations suggests a PK/PD breakpoint of ≤ 0.25 - 0.5 mg/L. Similarly, for Gram-positives simulations suggest a PK/PD breakpoint of ≤ 0.25 mg/L using the target of 12.5 obtained from the clinical cSSSI study (data not shown).

The right-hand figure shows the probability of target attainment at different dosages (Ni et al., 2018), based on a target $fAUC/MIC$ value of 0.9 identified for the treatment of hospital acquired pneumonia by Bhavnani et al., 2012



Clinical studies

Tigecycline registration and post-registration studies have been performed in complicated skin and skin structure infections, complicated intra-abdominal infections and community-acquired pneumonia. Most of these trials were subjected to meta-analysis in 2011 (Cai et al.) and showed non-inferior efficacy to comparator agents. The most common isolates were *S. aureus* (MSSA and MRSA) in cSSSI, *E. coli*, *B. fragilis* group, *S. anginosus*, *K. pneumoniae* and *E. faecalis* in cIAI, and *S. pneumoniae* in CAP. A 2020 study of tigecycline monotherapy for infections caused by ESBL-producing *Enterobacterales* in critically-ill patients showed inferior outcomes for infections caused by *K. pneumoniae* compared those caused by *E. coli* (Yu et al., *Antibiotics* 9,231).

Studies have been conducted in hospital-acquired pneumonia, but outcomes were suboptimal and tigecycline was unable to be registered for the treatment of this condition. Tigecycline is licensed for the treatment of community-acquired pneumonia in North America, but its use for this indication is limited.

Clinical breakpoints

The clinical breakpoints for tigecycline can be found in the most recent version of the Breakpoint tables: https://www.eucast.org/clinical_breakpoints
Tigecycline has inadequate activity against *Klebsiella* spp., *Proteus* spp., *Morganella* spp., *Providencia* spp. and *Pseudomonas* spp.

Higher (non-licensed) doses have started to be used in certain clinical circumstances for infections caused by *Enterobacterales*, See guidance document (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Tigecycline_Guidance_document_v2_20220720.pdf)

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