

# Pharmacological comparison of the activity of antibiotics against intracellular *S. aureus*

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# S. aureus is an opportunistic intracellular pathogen

infection of the vacuolar apparatus in macrophages



Seral et al. (2003) AAC 47:2283-92

## **PK-PD to rationalize antibiotic choice**



Carryn et al. (2003) Infect Dis Clin North Am. 17:615-34

## Aim of the study

to compare the concentration-effect relationships
against extracellular AND intracellular *S. aureus*for antibiotics with markedly different

cellular pharmacokinetic properties



#### **Methods**

#### **Extracellular activity**

 exposure of bacteria to antibiotics (0.05-1000 X MIC) in RPMI medium

#### Intracellular activity

infection of THP-1 human macrophages (4 bacteria/cells)

- elimination of extracellular bacteria by washing with GEN
- incubation for 24 h with antibiotics (0.05-1000 X MIC) or to GEN 1 X MIC (control)

#### **Extracellular activity**

All AB are concentration-dependent



## **Intracellular activity**

#### Decrease of CFU is observed at clinically-achievable concentr.

![](_page_6_Figure_2.jpeg)

## Extracellular activity vs intracellular activity

#### But intracellular activity is always < than extracellular activity

![](_page_7_Figure_2.jpeg)

# Comparison of concentrations needed for a static effect

antibiotic	Static dose (X MIC)		
	extracellular	intracellular	
ΟΧΑ	0.52	2.09	
MXF	0.29	0.63	
GEN	0.30	2.09	
ORI	0.29	4.79	

# **Comparison of maximal effects**

antibiotic	maximal effect (log CFU decrease from 0h)			
	extracellular	intracellular		
ΟΧΑ	- 3.70	- 1.58		
MXF	- 4.29	- 2.77		
GEN	- 5.76	- 2.54		
ORI	- 5.55	- 3.15		
>>				

# **Correlation with accumulation and effect of pH**

antibiotio	effect	cellular	cellular	MIC at pH	
antibiotic	at Cmax	accumulation	(µg/ml)	7.4	5.0
ΟΧΑ	-2.12	< 4 X	< 256	0.125	0.06
MXF	-2.64	7.8 X	31	0.06	0.25
GEN	-0.66	4.4 X	79	0.5	16
ORI	-2.88	148 X	3700	0.25	0.25

# Conclusion

Intracellular activity is always << extracellular activity

- irrespective to the antibiotic accumulation level
- for all drug classes tested
   Acid pH is not the only culprit for this decrease of activity
  - higher <u>extracellular</u> concentrations are needed to kill <u>intracellular</u> bacteria
  - intracellular activity cannot been predicted from accumulation levels <u>only</u>, and should therefore be tested in appropriate models

among the drugs studied, a definite bactericidal intracellular effect at clinically achievable extracellular concentrations can be obtained for a few of them only (ORI, MXF) ...

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