LINEZOLID DOSE OPTIMISATION USING MONTE CARLO SIMULATION.

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BACKGROUND: The pharmacokinetic/ pharmacodynamic (PK / PD) index for the efficacy of linezolid is defined as the area under the plasma drug concentration-time curve (AUC_{24}) / minimum inhibitory concentration (MIC). .

Methods:

PK/PD index Linezolid→ $AUC_{24}/MIC=100$
$AUC_{24}=D_{24h}/Cl_{Lin}$

PK
- The pharmacokinetic parameters of linezolid were obtained from published studies.

PD
- MIC data were collected of our center for the years 2013 and 2014 for Staphylococcus aureus (S. aureus) and coagulase-negative Staphylococcus (CNS) isolates.
- The method of determining the MIC was using an automated microdilution (Phoenix®BD) and the MIC > 1 was confirmed by E-test (BioMerieux®).

- ✓ The pharmacokinetics parameters were defined as a log-normal distribution in the Monte Carlo simulation, and in the case of MIC, a discrete distribution. A Monte Carlo simulation with 10000 subject was performed using SimulAr® program.
- ✓ Acumulative fraction of response (CFR) was calculated (CFR values of > 90% represent an optimal regimen).

Results:

❖ ***S. aureus:***

- Cl_{Cr} < 25 mL/min dose 900 mg/day

-Cl_{Cr}=25-60 mL/min dose 1200 mg/day

-Cl_{Cr}=60-125 mL/min dose 1800 mg/day

- Cl_{Cr}>125 mL/min dose 2400 mg/day

One-compartment PK model was used with a first order elimination process
(Matsumoto et al. 2014)

Cl_{Lin}= 0,0258(ClCr*)+2,03 ± 30,5%.
*Cockcroft and Gault method.

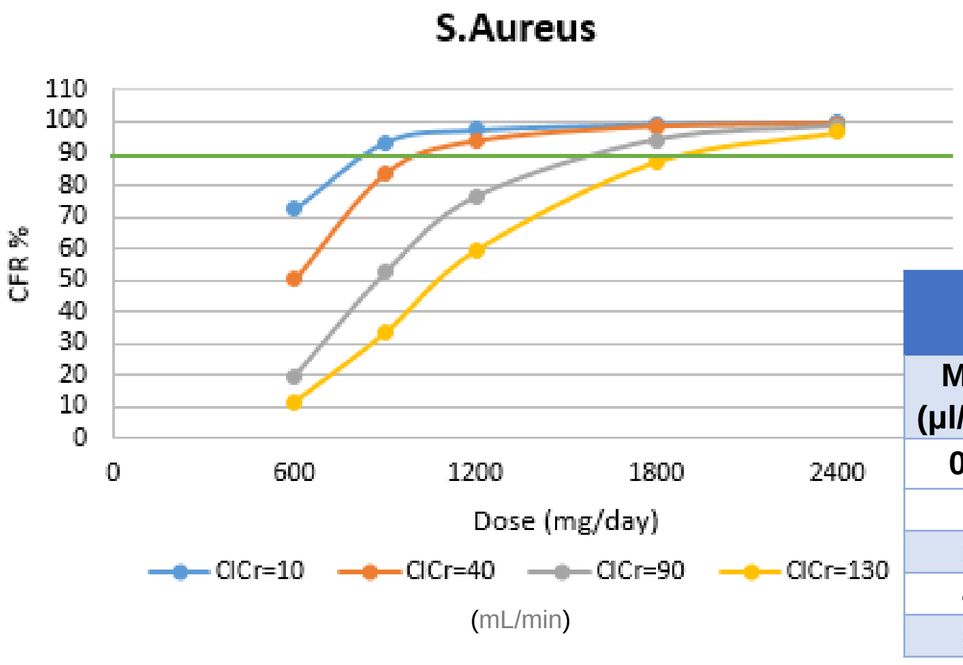
Suggested doses depending on PK / PD analysis

❖ **SCN:**

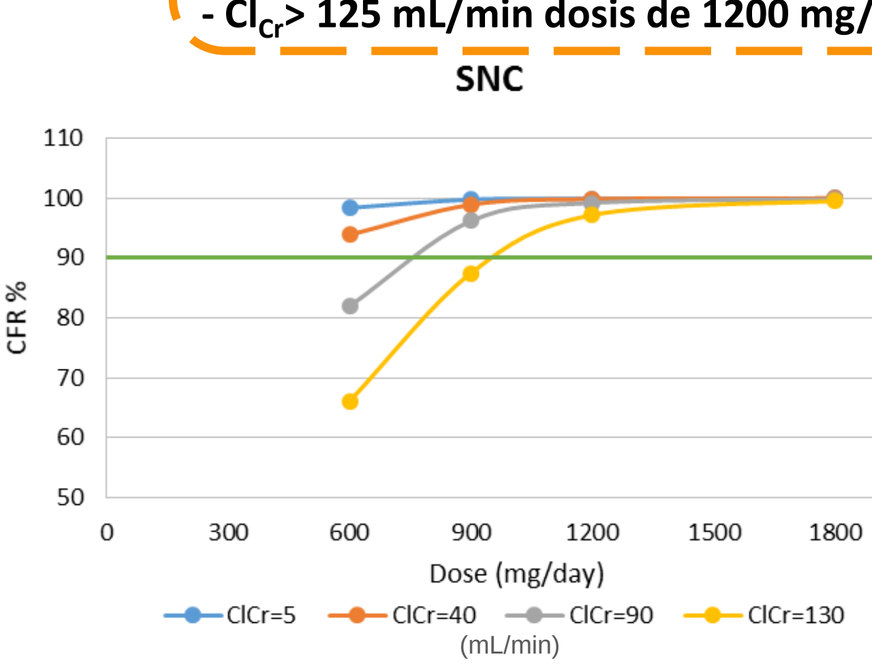
- CL_{Cr} <60 mL/min dose 600 mg/day

- Cl_{Cr}= 60-125 mL/min dosis de 900 mg/day

- Cl_{Cr}> 125 mL/min dosis de 1200 mg/day



S.aureus	
MIC (µl/mL)	**Relative distribution**
0,5	0,0075
1	0,3387
2	0,4807
4	0,1667
8	0,0064



SCN	
CMI (µl/mL)	**Relative distribution**
0,5	0, 3267
1	0, 6707
2	0, 0013
4	0, 0013

CONCLUSIONS: According to the population pharmacokinetic model and the CMI chosen, linezolid doses should be individualized based on patients Cl_{Cr} and strain Staphylococcus spp. isolated.

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