

# Pharmacokinetics-pharmacodynamics approach for Meropenem and Piperacillin/Tazobactam after extended infusion improves effectiveness in septic burn patients with renal function preserved.

**Authors:** Marc Y Chalom<sup>1</sup>; P Romano<sup>1</sup>; Persio AR Ebner<sup>1</sup>; Maria S Santos<sup>1</sup>; Marcio S. Garcia<sup>1</sup>; Nairo M Sumita<sup>1</sup>; Nilo JC Duarte<sup>1</sup>; Alberto JS Duarte<sup>1</sup>; Gabriela A Ferreira<sup>1</sup>; Leonard VK Kupa<sup>2</sup>; Ronaldo Morales Junior<sup>2</sup>; João M. Silva Jr<sup>1</sup>; David S Gomez<sup>1</sup>; Silvia RCJ Santos<sup>2</sup>

<sup>1</sup>Division of Plastic Surgery & Burns, Division of Central Laboratory, Hospital of Clinics of Medical School, <sup>2</sup>Clinical Pharmacokinetics Center, School of Pharmaceutical Sciences; University of Sao Paulo, Sao Paulo, SP, Brazil.

## Introduction:

Piperacillin/tazobactam and meropenem are largely prescribed to critically ill septic patients with nosocomial infections caused by Gram-negative strains.

Recommended dose cannot achieve the target, once serum levels result below those required for effectiveness MIC > 2mg/L strains.

## Objective:

Rational of study was to investigate drug effectiveness after the 3hrs-extended infusion of both agents by drug serum monitoring and pharmacokinetics-pharmacodynamics (PK/PD) approach in septic burn patients.

Develop and validate a bioanalytical LC-MS/MS assay

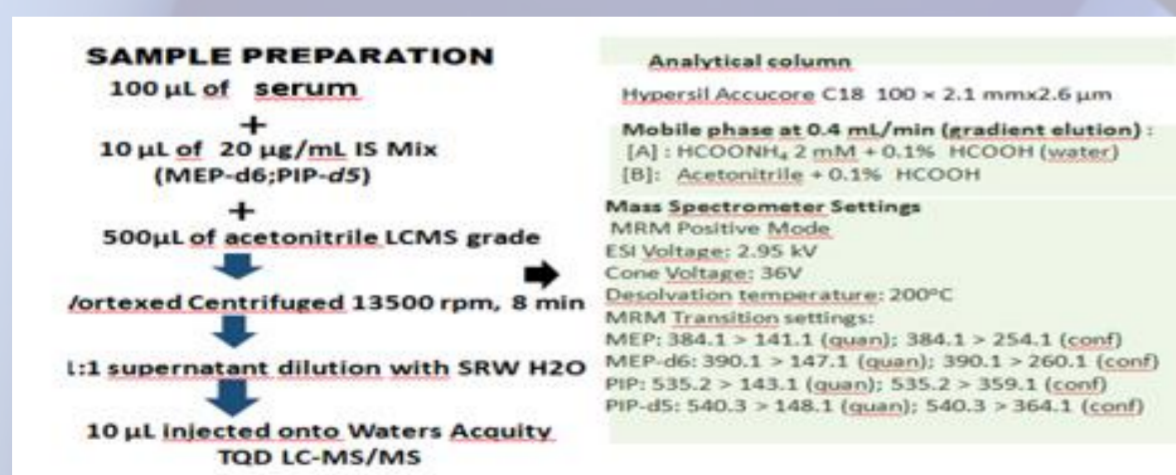
## Methods:

Ethical Comitee approval:CAAE nº 07525118.3.0000.0068

Characteristics of patients admission in ICU	
Medians (IQR)	Proportion n=28 patients
31 (24-41) yrs	18/10 Gender (M/F)
71 (61-75) kg	21/28 Inhalation injury
27 (16-42) %TBSA	28/28 Mechanical ventilation
SAPS3 59 (44-60)	28/28 Vasopressors requirements

### 3-hrs Extended Infusion Strategy - Critically ill Septic Burn Patients

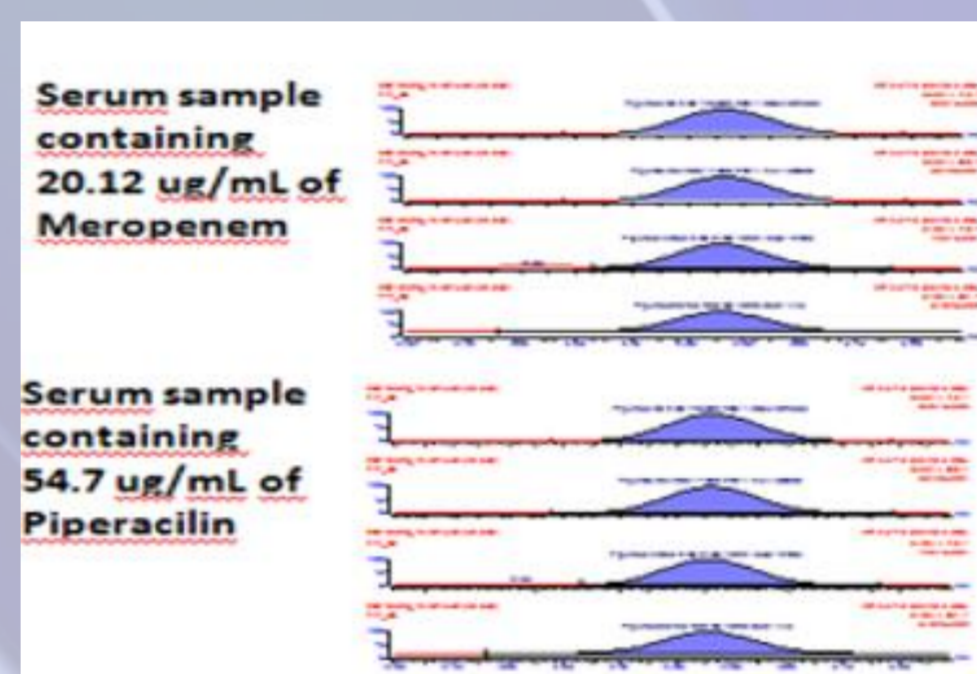
G1: Piperacillin-Tazobactam N =16	G2: Meropenem N=12
Regimen: 4.5g q8h or q6h	Regimen: 1g q8h
Blood was sampling at the steady state level: 3 <sup>rd</sup> 5 <sup>th</sup> hr of start infusion	
TDM: new bioanalytical method LC MS/MS for simultaneous serum monitoring in ICU patients of our hospital	
PK: Noncompartmental data analysis: t(1/2) $\beta$ : half-life, CL <sub>r</sub> : clearance, Vd <sup>ss</sup> : vol. distribution	
PK/PD approach: predictive index of effectiveness (%fDT > MIC). Target considered: 100%fDT > MIC	



## Results:

### Bioanalytical Method LC-MS/MS

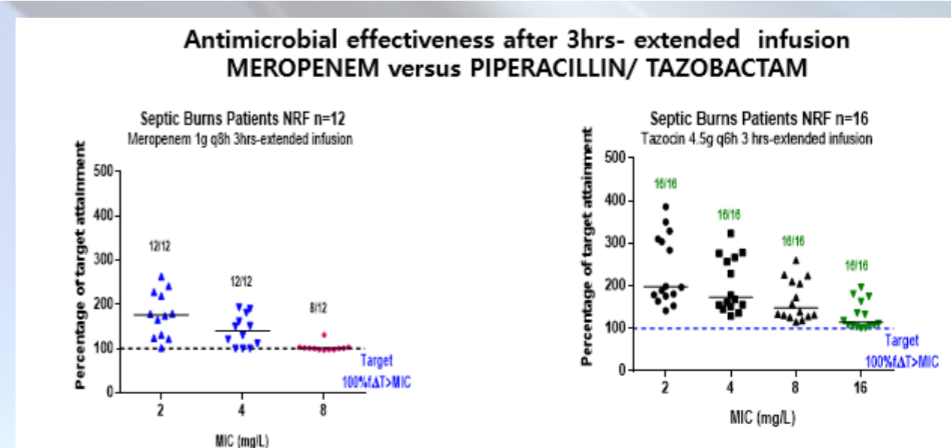
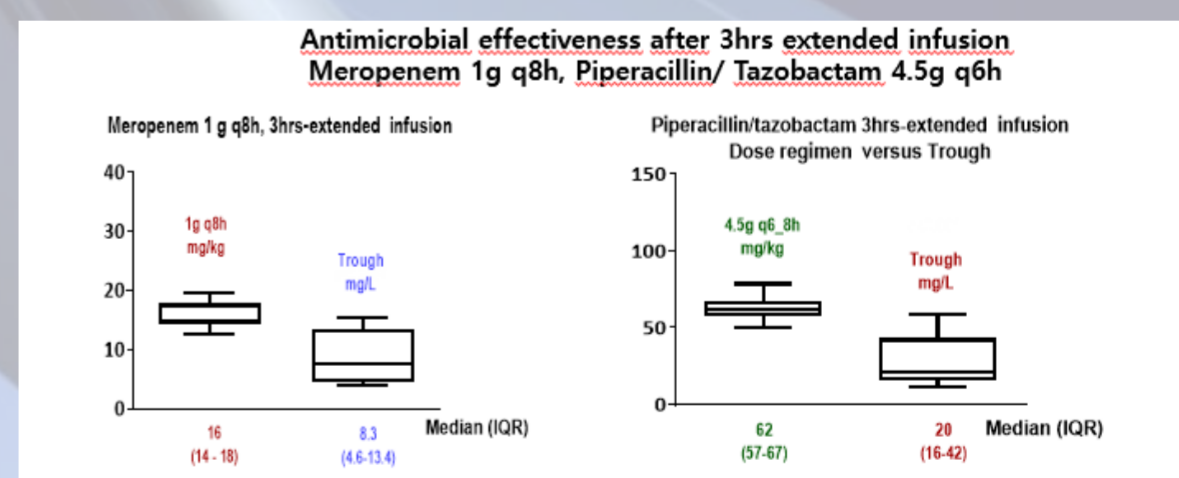
1. It was developed and validated a liquid chromatographic tandem mass spectrometry method to quantify Meropenem-Piperacillin in serum simultaneously
2. A high specific and selective bioanalytical method was developed and validated in the Central Laboratory of our hospital
3. Good linearity 1-250 mg/L (r<sup>2</sup>: 0.995), sensitivity 1mg/L precision and accuracy
4. LC-MS/MS is considered the gold standard for TDM\_antimicrobials.



Desired outcome reached  
Clinical and microbiological cure against Gram negative nosocomial pathogens

Meropenem: clinical cure occurred by eradication of pathogens up to MIC 2 mg/L and isolates of intermediate susceptibility *K. pneumoniae* and *P. aeruginosa* MIC 4 mg/L

Piperacillin: clinical cure by Tazocin 4.5g q6h for all patients up to MIC 16 mg/L strains.



## Conclusion:

- Recommended dose of Piperacillin or Meropenem by 3 hrs-extended infusion must be prescribed to ICU septic patients to reach soon the desired outcome based on PK/PD approach.
- We demonstrated that the developed LC-MS/MS bioanalytical method is an excellent tool to quantify simultaneously Meropenem and Piperacillin in Human Serum
- This strategy is considered an important tool to assess drug effectiveness, mainly at the earlier period of septic shock.