

# Development of an on-line application to support a program aimed to evaluate antimicrobial dosing optimization without therapeutic drug monitoring in critically ill patients in Brazil

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## ABSTRACT

**Background:** Enhancing the quality of prescribing and administration of antibiotics should be considered a key priority for improving therapeutic outcomes and suppressing the increasing rates of resistance that is presently observed worldwide. The availability of therapeutic drug monitoring (TDM) for many of the commonly used antibiotics is a rarity in a considerable number of centers around the world. Alternatively, the use of a widely available web based application utilizing population PK models and sophisticated simulation algorithms may have the potential to be a valuable tool in optimizing PKPD indices. The aim of this study was to describe the process of modifying an on-line dose optimization application to meet the needs of a program designed to evaluate the adaptation of published population PK models for dose optimization in the absence of TDM into the care of Brazilian critically ill patients.

**Materials/methods:** Piperacillin and tazobactam PK models are coded into Individually Designed Optimum Dosing Strategies (ID-ODSTM) on - line using the R language to provide the necessary background for the high - level computations to estimate concentration - time profiles for 5000 virtual patients per simulation. The user provides patient demographic and laboratory information (including MICs) via a user friendly html interface in international units. PTAs for up to 200 short and extended infusion regimens from 2000 to 8000 mg of piperacillin at 50 mg intervals given every 12, 8, 6 and 4 hours for the target  $fT>MIC$  of 50% for MICs up to 32  $\mu\text{g/ml}$  in serum are established assuming 70% protein binding and lognormal distribution for all pharmacokinetic parameters.

**Results:** PTAs for all simulated regimens are evaluated and a subset reaching 90% or more is separated for further analysis to provide the dosing regimen that achieves the optimal target at the pre-specified MIC with the least amount of drug in mgs to be administered in a 24 h time period. Once computation is accomplished, clinically relevant information including patient demographics, suggested dosing regimens, PTAs, and creatinine clearance will be displayed using uncomplicated and adequately descriptive plotting designs and in the Portuguese language (Figure 1. and 2.).

**Conclusion:** The development of this modified application provides the foundations for a multi-model based, point of care clinical decision support tool on the web and mobile devices for clinicians focusing on optimizing antimicrobial therapy. In the absence of available and affordable TDM, this system will be used to evaluate the adaptation of published population PK models for dose optimization into the care of the Brazilian critically ill patients. By setting the application to give the dosing regimen that uses the lowest amount of drug per day, the cost will also be kept to the minimum necessary to provide optimal exposure.

## INTRODUCTION

- In the past several years, adaptation of the use of on-line applications on mobile devices by health care professionals has become increasingly more common.<sup>1,2</sup>
- Tablets, iPad<sup>®</sup>s and smartphones are mobile technologies that combine telecommunications and data processing in a devices that can facilitate computing at the point of care.
- ID - ODS<sup>™</sup> is a TDM and simulation tool powered by the R<sup>®</sup> software with an extensive model library built from population pharmacokinetic models published in peer reviewed literature. Based on patient demographic information readily available at the bedside, ID - ODS<sup>™</sup> incorporates Monte Carlo simulation and inverse Bayesian modeling into the design of personalized dosing regimens via a graphical user interface.<sup>3</sup>
- In this report we describe the process of modifying the on-line dose optimization application ID - ODS<sup>™</sup> to meet the needs of a program designed to evaluate the implementation of published population PK models for dose optimization in the absence of TDM into the care of critically ill patients in Brazil.

## METHODS

- Piperacillin and tazobactam PK models are coded into Individually Designed Optimum Dosing Strategies (ID-ODSTM) on - line, where the user provides patient demographic and laboratory information (including MICs) via a user friendly html interface in Portuguese and in international units.
- Using any of the popular devices and browsers all parameters passed to Optimum Dosing Strategies (ODS) website are seamlessly transmitted to Rapporater servers over a secure channel for evaluation.<sup>4</sup>
- The cluster of webservers process the queries and read the required models and programs to memory from the distributed system of databases to be passed along to the R<sup>®</sup> workers.<sup>5</sup>
- PTAs for short and extended infusion regimens from 2000 to 8000 mg of piperacillin at 50 mg intervals given every 12, 8, 6 and 4 hours for the target  $fT>MIC$  of 50% for MICs up to 32  $\mu\text{g/ml}$  in serum are established assuming 30% protein binding.
- Subsequently, all simulated regimens are evaluated and a subset reaching 90% or more is identified for further analysis to provide the regimen that achieves the optimal target at the pre-specified MIC with the least amount of drug in mgs to be administered in a 24 h time period.
- The results are returned in Pandoc's markdown format that could be transformed to any popular document format - along with the generated plots in the analysis.

### Data Analysis and Graphics

- The R<sup>®</sup> software environment for statistical computing and graphics is used to generate the plots and calculate summary statistics of the data.
- Respective R<sup>®</sup> software packages are used to support computations related to Monte Carlo simulation



Figure 1. Graphical overview of the technology of ID - ODS<sup>™</sup>

## RESULTS

Figure 2. Graphical User Interface of ID-ODSTM for Monte Carlo simulation translated in Portuguese

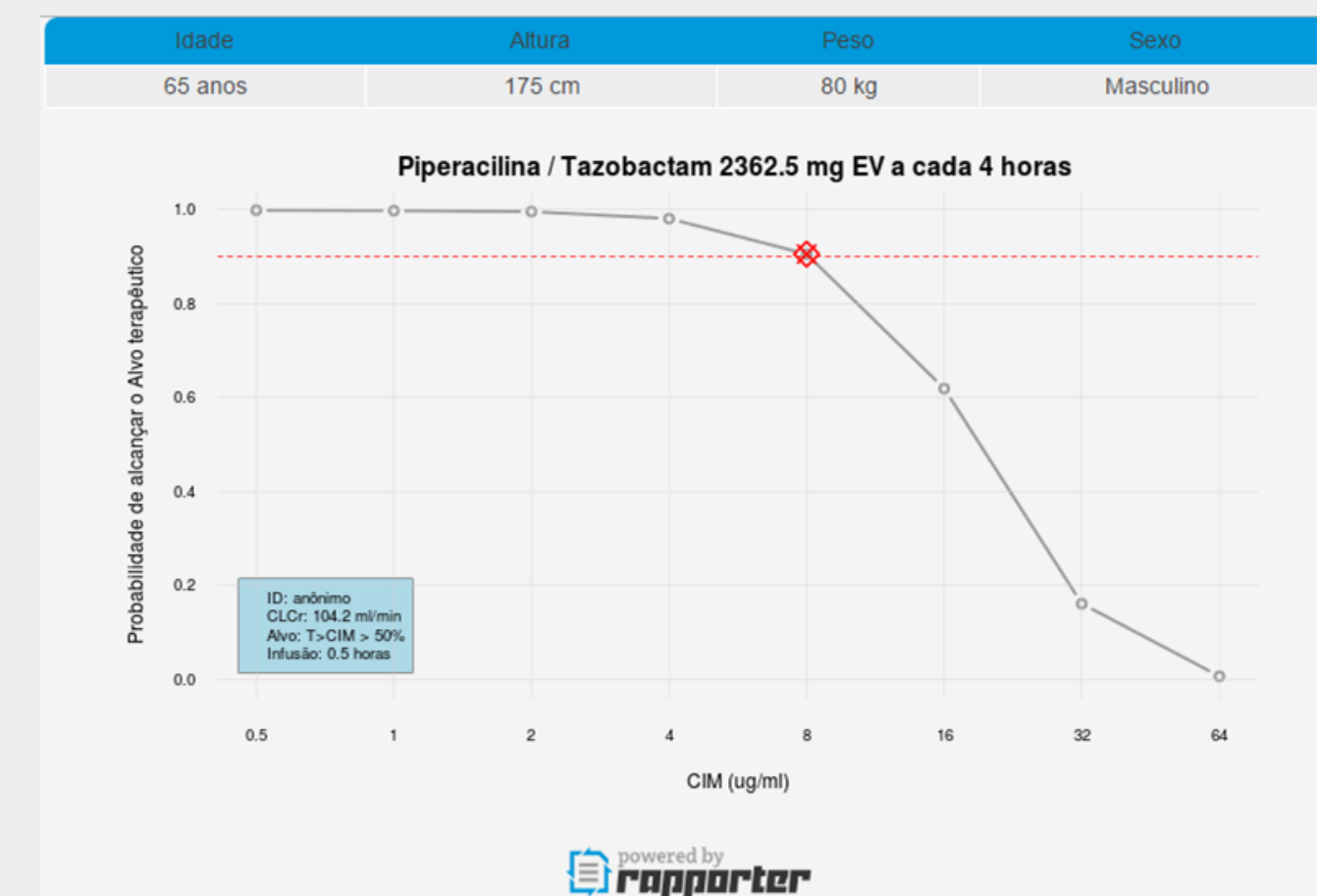


Figure 3. Output of the Monte Carlo simulation based optimization in Portuguese

## CONCLUSION

- The availability of this cross-platform application provides a multi-model based, point of care clinical decision support tool on desktops and mobile devices for clinicians interested in optimizing anti-infective therapy.
- This system has been used to facilitate the optimization of antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacokinetics and pharmacodynamics.
- Current updates in the development of this application enable Portuguese speaking practitioners to evaluate Monte Carlo simulation driven dose optimization at the bedside.
- In the near future, the clinical utility of the application in a resource limited setting will be evaluated by comparing predicted and observed PKPD index target attainment to establish the viability of model based dose optimization without therapeutic drug monitoring for antimicrobial agents.

## REFERENCES

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