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ABSTRACT/REVISED

Objectives: Smart phone technology can help facilitate mobile computing at the point of care. The objective of this study was to develop a mobile phone application to provide individual dosing recommendations based on Cumulative Fraction of Response (CFR), Probabilities of Target Attainment (PTA), Bayesian feedback and combination drug interaction modeling for several antibiotics. Here the example of Cefepime (CEF) is presented.

Methods: Population pharmacokinetic (popPK) model for CEF in critically ill patients is used as the Bayesian prior and to estimate concentration - time profiles for 5000 virtual patients per simulation. Additionally, the Greco interaction equation is employed and linked to simulated concentration - time profiles to generate the curve of killing effect for combination therapy. The models and conditions are coded into Individually Designed Optimum Dosing Strategies (ID-ODSTM) on - line to provide the necessary background for the high - level computations.

Results: The user provides patient demographic and laboratory information (including institution specific MIC distribution) via a user friendly interface in conventional units, which is then passed through the template of conditions in ID-ODSTM. PTAs for short, extended, or continuous infusion regimens for the target $fT > MIC$ of 60% for MICs up to 32 $\mu\text{g/ml}$ in serum are established assuming lognormal distribution for all pharmacokinetic parameters. These PTAs are also used to calculate CFRs, allowing to compare up to 4 different regimens side by side at a time. For Bayesian dose individualization, a total of 5000 iterations are completed using a sequential approach allowing for the change of PK parameters from time to time. After the computation, clinically useful information including individual PK parameter estimates and suggested dosing regimens, PTAs, CFRs, and the predicted killing effect of the candidate dosing strategies will be displayed using uncomplicated and adequately descriptive plotting designs.

Conclusions: This mobile-platform application provides the opportunity for clinicians interested in optimizing antimicrobial therapy at the point of care. This system can be used to improve antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacodynamics, popPK model based approach, Bayesian feedback and Monte Carlo simulation.

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.^{1,2}
- Tablets, iPad[®]s and smartphones are mobile technologies that combine telecommunications and data processing in a devices that can facilitate computing at the point of care.
- Drug reference resources generally provide information on the pharmacology, dosing, dosage form, drug interactions and the contraindications associated with the use of the agents.
- Popular and trusted resources like The John Hopkins Antibiotic Guide and the Sanford Guide both have been available for many years now, with sections focusing on the dosing of antibiotics^{3,4}. Neither of these two resources directly provide drug dosing information based on the results of high quality popPK models.
- They also do not provide the opportunity to evaluate different dosage regimens for probabilities of target attainment based on Monte Carlo simulation. As on-line computing and the use of mobile devices become more and more popular, transition of the free-standing software to a web - based application is likely inevitable. Virtually all available devices have the option to view websites, with some having significantly better aesthetic appearance compared to others⁵.
- In this experiment, we report on the enhancement of a multi-platform, web-based clinical application equipped to provide optimum antibiotic dosing information via the use of population pharmacokinetic models and Bayesian adaptive feedback or Monte Carlo simulation and drug interaction modeling for critically ill patients at the point of care.

METHODS

ID – ODS™ Technology Overview^{6,7,8}

- Using any of the popular devices and browsers [1] all parameters passed to Optimum Dosing Strategies (ODS) website [2] are seamlessly transmitted to Reporter servers over a secure channel for evaluation.
- The channel is backed up by a content delivery network [3] that is also speeding up connection as well as making it possible to provide high availability for ODS users.
- The cluster of webservers [4] process the queries and read the required models and programs to memory from the distributed system of databases [5] to be passed along to the R [6] workers.
- The computations are run in a secured and stateless R environment so that no sensitive information would be stored for future R sessions. The statistical tasks will use any of the numerous, user contributed packages found on CRAN like the FME package as a Bayesian interface.
- The results are returned in Pandoc's markdown format [8] that could be transformed to any popular document format – along with the generated plots in the analysis.

Data Analysis and Graphics

- The R[®] software environment for statistical computing and graphics was used to generate the plots and calculate summary statistics of the data.
- Respective R[®] software packages are used to support computations related to Monte Carlo simulation, Bayesian analysis and drug interaction modeling.



Figure 1. Graphical overview of the technology of ID - ODS™

RESULTS

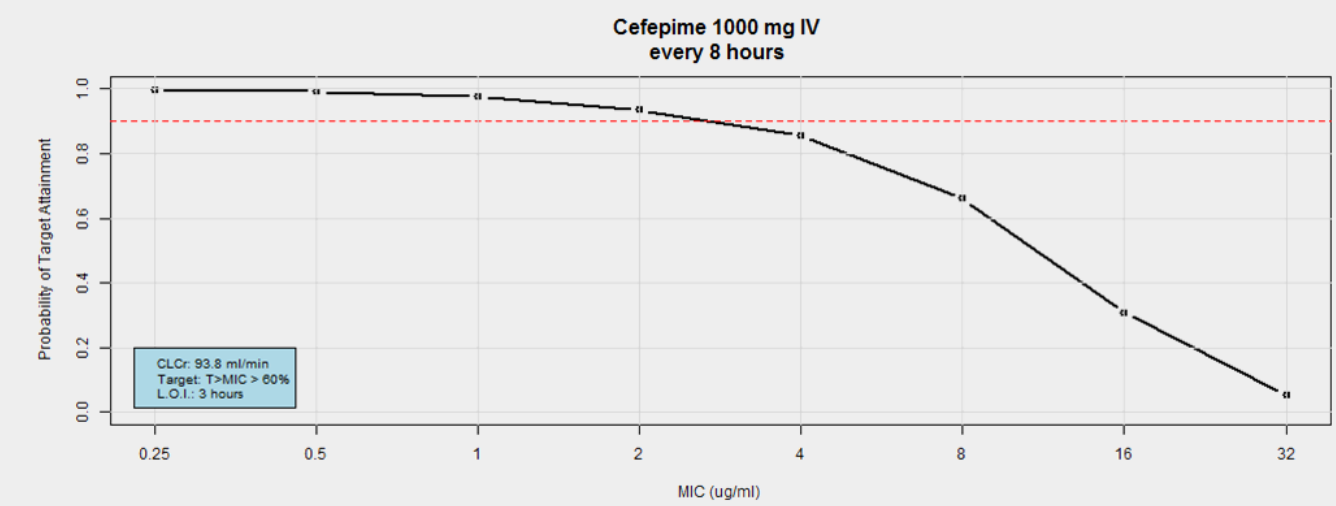


Figure 2. Output of the Monte Carlo simulation based optimization application

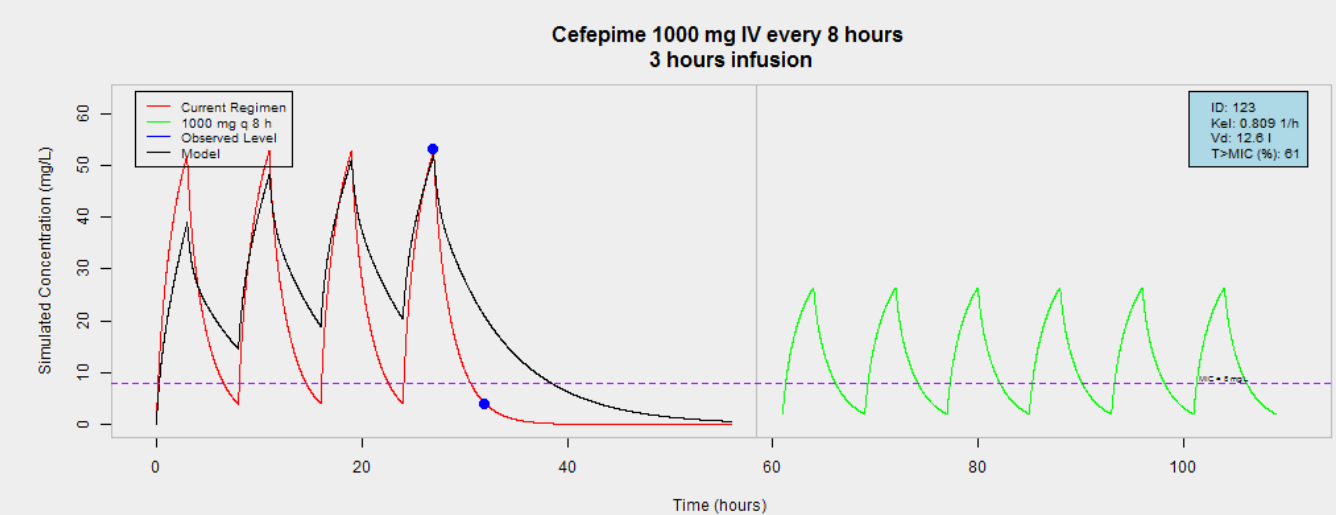


Figure 3. Output of the Bayesian feedback driven dose optimization application

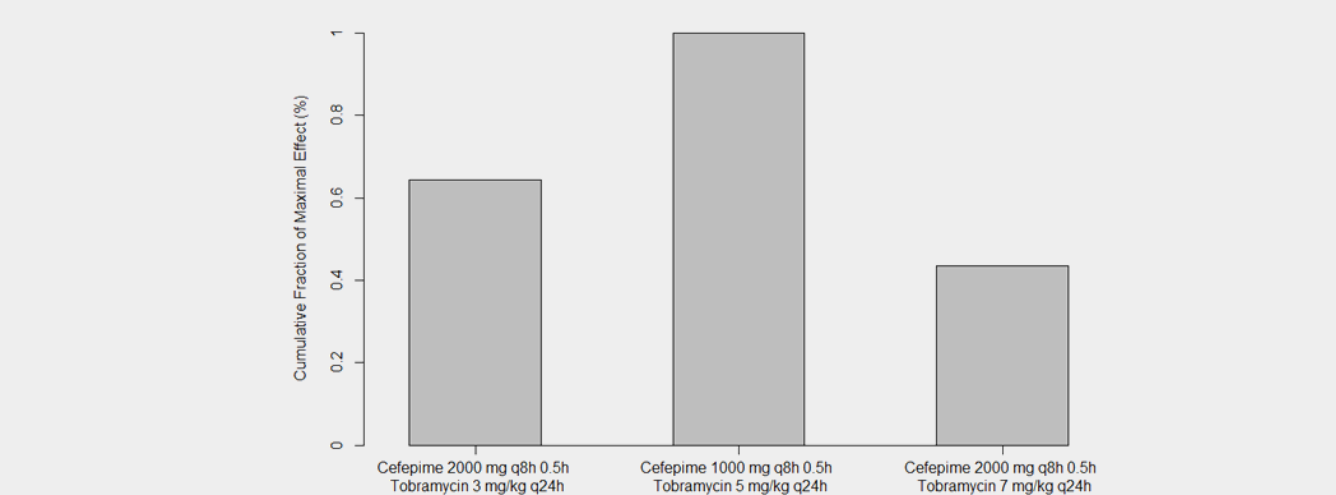


Figure 4. Output of the drug interaction simulation based application

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 improve antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacodynamics, popPK model based approach and Monte Carlo simulation over 5000 times since implementation.
- Current updates in the development of this application enable practitioners to utilize Bayesian feedback driven dose optimization at the bedside. In addition, the availability of drug interaction simulation option allows for the evaluation of the cumulative fraction of maximum effect for different combination therapy regimens aimed to maximize killing effect throughout the course of treatment.

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