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Pharmacokinetics-Pharmacodynamics, Computer Decision Support Technologies, and

Antimicrobial Stewardship: The Compass and Rudder

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Abstract

The first guidelines for conducting antimicrobial stewardship in the hospitalized setting were published in 2007. These guidelines recommend that stewardship programs employ the science of pharmacokinetics-pharmacodynamics (PK-PD) as well as adopting computerized decision support (CDS) technologies when possible. The United States Food and Drug Administration have adopted PK-PD as a cornerstone in the evaluation of antimicrobial agents during clinical development. The core principles of PK-PD center around describing the relationship between drug exposure indexed to the susceptibility of the infecting bacterial pathogen and patient response. Using such relationships with population pharmacokinetic models and simulation, rational drug and dosing regimens can be selected. But because PK-PD modeling and simulation programs are generally absent in clinical practice, systematic application of this science is missing. Herein we explain advances in technology that allow clinicians to apply PK-PD to optimize the agents and dosing regimens selected for the treatment of hospitalized patients with infection.
Introduction

*He who loves practice without theory is like the sailor who boards ship without a rudder and compass and never knows where he may cast.* - Leonardo da Vinci

Microbes account for 90% of the cells in the human body; therefore, the administration of antimicrobial agents has a significant impact on our microbiome. While the intended therapeutic effects of antimicrobial agents are undeniable, they must be used judiciously to mitigate the occurrence of undesired collateral consequences in patients (McDonald et al., 2005; Owens, 2005; Owens and Nolin, 2006; Owens et al., 2008). The imprudent use of antimicrobials has contributed to the emergence of resistant organisms such that the Centers for Disease Control and Prevention (CDC) report more than two million infections caused by antibiotic-resistant organisms each year, resulting in approximately 23,000 deaths annually (Owens and Rice, 2006; Huttner et al., 2013; CDC, 2014). Current strategies to counter antimicrobial-resistant organisms include new drug development, infection prevention measures, environmental cleaning strategies, and antimicrobial stewardship. (Owens, 2008 DMID)

Antimicrobial stewardship has been defined as coordinated efforts to ensure that patients receive the right antimicrobial agent, at the right dose, and for the right duration while minimizing adverse drug events and antimicrobial resistance (Dellit et al., 2007; Owens, 2008 DMID; Septimus and Owens, 2011; McDonald et al., 2005; Owens, 2005; Owens and Ambrose, 2005; Owens and Nolin, 2006). The need for shepherding antimicrobial agents was first raised in the 1950s from the noted microbiologist Ernest Jawetz when he wrote “(it is important)... to
call attention to the abuse of antibiotics, its causes and results...” (Jawetz, 1956). Over the next several decades, certain notable hospitals researched the best approaches to antimicrobial stewardship and the numbers of implemented antimicrobial stewardship programs (ASP) began to slowly multiply (Owens, 2008 DMID; Owens et al., 2009; Pope et al, 2009). Pharmacists and physicians have traditionally coordinated antimicrobial stewardship activities, yet this approach is not feasible at every hospital (Septimus and Owens, 2011; Drew et al., 2009; Owens, 2008 DMID; Owens, 2009; Owens et al., 2009). In 2007, the first guidelines for systematically conducting antimicrobial stewardship in hospitalized patients were put forth by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) (Owens, 2008; Dellit et al., 2007). A decade later, governmental regulatory bodies have issued hospital accreditation standards requiring institutions to participate in antimicrobial stewardship. Furthermore, the new Centers for Medicare and Medicaid Services draft guidelines for surveying healthcare facilities report specific goals for antimicrobial stewardship in healthcare settings (Evans et al., 2015). Therefore, it is ostensible that ASPs will be well anchored in healthcare for our foreseeable future.

IDSA/SHEA guidelines on antimicrobial stewardship recommend the use of PK-PD dose optimization, as well as the adoption of computer decision support (CDS) when possible (Dellit et al., 2007; Barlam et al., 2016). PK-PD is the science that describes the relationship between drug exposure indexed to the susceptibility of the infecting bacterial pathogen and patient response (Ambrose et al., 2007). The current paradigm for the development of antimicrobial
agents is to use PK-PD to systematically determine the dose and dosing interval for clinical studies (Boucher et al., 2017; Ambrose, 2011; Ambrose et al., 2012 Lancet Inf Dis, Ambrose et al., 2012 Antimicrob Agents Chemother). Simulations based on population pharmacokinetic models yield patient-specific drug exposures which can be indexed to the minimum inhibitory concentration (MIC) distribution of a suspected or documented pathogen to provide probabilistic outputs. These outputs, when available, can be used to educate the clinician, thereby allowing them to make the most informed decision regarding antimicrobial selection and dose for a given infection. Performing PK-PD analyses in routine patient care settings is not usually done, due in part, to insufficient access to simulation programs that would allow for the determination of the dosing regimen’s ability to achieve PK-PD targets for efficacy (Ambrose et al., 2012 Lancet Inf Dis). Recent advances in technology have made it possible to integrate PK-PD into clinical decision making at the point of care (Bulik et al., 2017). This is important for many reasons including optimizing the treatment of infections and patient outcomes (Ambrose, 2008), minimizing the development of antimicrobial resistance (Ambrose, 2008; Patel et al., 2010; Drusano et al., 2012), and improving patient safety. For example, dosing mistakes are the most common type of medication error resulting in preventable adverse drug events (Oppenheim, et al., 2002; Gleason et al., 2004; Koppel et al., 2005; Fischer et al., 2003; Owens, 2008). In one study, over 60% of prescribing errors involved incorrect medication doses or improper regimen frequencies (Fischer et al., 2003). The incorporation of PK-PD into clinical decision making at the point of care for antimicrobials will result in a decrease in dosing errors and subsequent adverse drug events.
In concert with the growth of ASPs in the U.S. is a parallel growth of CDS technologies supportive of stewardship activities. CDS technologies range from single center custom-built or homegrown platforms to large commercial multifunctional CDS programs (Evans et al, 1995; Baysari et al., 2016). A common theme with large commercial multifunctional CDS technologies is that they all seem to have originated with a central focus (e.g., billing, pharmacy, infection control, microbiology laboratory) with antimicrobial stewardship applications developed as afterthoughts. Over time these large commercial platforms have adapted to the needs of the ASP through the supplementation of more specialized CDS applications. The use of CDS technologies is variable throughout the U.S. as cost, simplicity of use, and functionality relative to the needs of the institution determine the success of a technology. Studies have shown that the most multifunctional, broadly-scoped, and knowledge-based systems are the most expensive (upwards of $500,000 annually) (Evans et al., 2015; Baysari et al., 2016; Kullar et al., 2013). Moreover, once a CDS technology is purchased, it is not a guarantee of uptake. For example, a technology may not see widespread usage due to the clinicians being cautious of taking recommendations from a computer-based decision support technology or because the technology is inconvenient relative to the clinician’s workflow. Usage of CDS technologies that require clinicians to log into multiple computer systems to obtain information has been shown to be as low as 50% (King et al., 2007; Rohrig et al., 2008).

In an attempt to increase the exposure of CDS technologies, this review will primarily focus on the commercially available programs intended to enhance antimicrobial stewardship by
providing PK and PK-PD based dosing and regimen guidance. We will also discuss the emerging developments in the healthcare information technology (IT) field that are making integration of CDS programs possible and convenient.

Antimicrobial Stewardship and CDS: A Solution to Information Overload?
In the 20th century, the chief question in healthcare was how much of our clinical practice was based on scientific evidence (Pestotnik and Olson, 2008). The question in this new millennium is how much of the available evidence is applied at the patient’s bedside. As an example of the breadth of knowledge available to a clinician, the U.S. National Library of Medicine reports more than 800,000 new citations each year (Fact Sheet Medline 2017). However, much of this knowledge is unfiltered or not easily applicable to daily practice (Pestotnik and Olson, 2008). It is estimated that if clinicians had access to a filtered version of this knowledge and were able to combine it with patient-specific data at the time clinical decisions are made, 30-60% of decisions would be different (Pestotnik and Olson, 2008; Djulbegovic et al., 2004).

How can CDS technologies help the clinician handle this large amount of information? In the broadest sense, these technologies are a means to focus consideration, handle information, and offer a patient-specific consultation. CDS is software that employs individual patient data, population statistics, and computerized clinical knowledge to offer a real time means to perform daily undertakings and espouses technology that meets this objective. To realize this goal, CDS must integrate into the clinical workflow and utilize instinctual configurable user interfaces. The features of a CDS that would likely influence the uptake of said program within
an institution include, but are not limited to, attributes such as speed, degree of integration within the clinician’s workflow, the provision of alternate recommendations, simplicity of interventions, and the volume of data entry required. In general, an ideal CDS would focus attention and enhance patient context to content (evidence-based), allowing the clinician to focus on who they need to see, what data/information needs to be reviewed, and the path that can be followed. CDS advocates the intervention and provides the rationale for why it is necessary (literature), and importantly, allows for documentation to complete the intervention (Pestotnik and Olson, 2008). Notably, the spirit of CDS outputs must be considered as solely recommendations rather than mandates. These recommendations should be pithy and nourished with properly filtered referential material and patient information (Pestotnik and Olson, 2008). Finally, the antibiotic library should be robust and include most, if not all, formulary agents.

There is great diversity amongst the commercial CDS technologies in use today. Commercial technologies can be grossly categorized as EHR vendor-supported CDS, large multifunctional add-on CDS, and specialized add-on CDS. The leading EHR providers with the most US market share, EPIC and Cerner, offer entry level tools to assist antimicrobial stewardship functions. These tools are limited to medication safety and report generation to capture the “low hanging fruit”, leaving most of the decision support to add-on CDS technologies. Multifunctional add-on CDS technologies include the following programs: TheraDoc (Premier, Inc., Charlotte, North Carolina), Medmined (CareFusion Corporation, San Diego, California), Sentri 7 (Pharmacy OneSource Bellevue, Washington, now Wolter Kluwer Health), Allscripts (Chicago, Illinois), and
Vecna (QC Pathfinder, Cambridge, Massachusetts). Specialized add-on CDS technologies, such as the PK-PD Compass (Institute for Clinical Pharmacodynamics, Schenectady, New York), provide expert-level functionality including infection-specific antimicrobial treatment and dosing regimen guidance based on PK-PD principles (Bulik et al., 2017) or Bayesian-based PK solutions (e.g., DoseMeRx).

Antimicrobial stewardship guidelines by IDSA/SHEA have recommended the use of CDS technologies in ASPs as many studies have demonstrated the value of these technologies (Dellit et al., 2007; Barlam et al., 2015; McGregor et al., 2006; Hermsen et al., 2012). Generally speaking, ASP activities can be supported by CDS technologies with features such as custom report generation, infection-specific empirical/directed treatment and dosing guidance, antibiotic “time outs”, de-escalation opportunities, flagging/alerting to inappropriate therapy, changes in laboratory function tests, new microbiologic culture results, and parenteral to oral switch opportunities (Owens, 2008; Pestotnik and Olson, 2008; Pogue et al., 2014). In addition, the means to record interventions and assign clinical outcomes and the ability to identify of use and approval of restricted or non-formulary drugs are vital to ASPs (Pogue et al., 2014). These features aid the ASP clinician in the complex process of prescribing antimicrobials, which in the context of other drug classes, has been equated to prescribing cancer chemotherapy due to the associated patient, disease, and treatment complexities. The initial prescribing of antimicrobials is often carried out in the setting of incomplete information with regard to both the infection and the patient. The use of CDS technologies in ASP activities fills the void of incomplete information and provides immense resources to the ASP clinician.
A multitude of studies since the late 1980s have reported outcomes associated with various single-centered homegrown and commercial CDS technologies (Evans et al., 1998, 2015; Pestotnik et al., 1996; Beaudoin et al., 2016; Baysari et al., 2016). Baysari and colleagues published a meta-analysis of CDS technologies and associated outcome measurements. The intent of this was to determine if consistent outcomes from these studies could be identified despite the variability in CDS technologies. (Baysari et al., 2016) Outcomes evaluated included appropriate antimicrobial use, hospital length of stay (LOS), and patient mortality. The authors noted there were reliable improvements in the appropriateness of antimicrobial therapy when human decisions were augmented by CDS technology (pooled RR: 1.49, 95%CI: 0.96-2.44) (Baysari et al., 2016). However, more variable results were noted for LOS and patient mortality.

**PK-PD and Antimicrobial Stewardship**

The IDSA/SHEA antimicrobial stewardship guidelines have recommended using PK-PD dose optimization since 2007 (Dellit et al., 2007). However, just how much of this is actually happening in clinical practice is an important issue, considering dosing regimen adjustments are often the most commonly reported interventions performed by an ASP (Pope et al., 2009; Owens, 2009; Septimus and Owens, 2011; Cao et al., 2016; Davey et al, 2013). Even if basic PK-PD concepts are used, the collective variables that affect drug exposure such as age, weight, and organ function, are not always considered. Even when these variables are accounted for, the dosing adjustment often comes from standard dosing guides rather than being individually customized to the infection site and indexed to the MIC of the expected or isolated
pathogen(s). As described above, the field of PK-PD seeks to improve the ability to predict the probability of treatment success by applying relationships between antimicrobial exposures indexed to a measure of potency (MIC) and non-clinical or clinical outcomes to select dose. Data from decades of clinical, animal, and in vitro studies provide support for a strategy that uses such data to optimize both the magnitude of dose and the frequency of administration. The administration strategy is determined based upon experiments that show the impact of drug concentration and dosing frequency on the reduction in bacterial burden and the presence of post-exposure effects. These studies have for example, demonstrated the importance of achieving concentrations above the MIC for a prolonged period of time, defined as the percent of the dosing interval that concentrations exceed the MIC or %T>MIC, for certain classes of antimicrobial agents, including beta-lactams (Craig, 2007). This observation has led to the development of dosing regimens that prolong the infusion of short half-life beta-lactams to optimize drug exposure. The second output of importance is the PK-PD index magnitude for a given antimicrobial agent that is needed for treatment success. Pre-clinical in vitro and animal infection model studies have defined the magnitude of the PK-PD index associated with endpoints ranging from no growth (i.e., net bacterial stasis) to net killing (e.g., a 1-log10 CFU reduction relative to the start of therapy). A laudable goal of optimizing the PK-PD of a treatment regimen is to prevent the emergence of resistance.

A growing list of clinical databases has allowed assessment of dosing regimens derived using PK-PD data from preclinical models. In many instances, predictions from pre-clinical drug development models about the effectiveness of dosing regimens for a given agent have
paralleled those observed in clinical trials (Ambrose et al., 2007). The utility of these data to predict regulatory outcomes has been demonstrated in post-approval analyses of pre-clinical and clinical data (Ambrose, 2008; Bulik et al., 2013). While PK-PD is used to support dose selection in both early and late stage clinical drug development, these principles are not systematically applied in clinical settings, primarily due to the aforementioned lack of proper technologies or tools available at the bedside. Despite these challenges, the clinical impact of these efforts in the daily management of patients is just now beginning to be realized.

**Advances in Information Technology**

ASPs are recommended to have a representative of the IT department on the stewardship team (Dellit, et al., 2007). Consultation with local IT experts arise when adopting CDS technologies, and once they are in use, the IT representative is often called upon for a variety of functional requests. However, the integration of CDS technologies within the IT infrastructure at each institution can be challenging. This requires communication between often disparate healthcare computer systems (e.g., radiology, pharmacy, physician order entry systems, clinical laboratory, microbiology, financial, EHR). Interoperability is the ability of different IT systems and software (CDS) applications to communicate, exchange data, and use that information once it is exchanged. Two main levels of interoperability exist and have been defined as functional and semantic (Pestotnik and Olson, 2008). Both functional and semantic interoperability occur as a result of messaging standards that permit multiple healthcare computer systems to exchange information resulting in a human readable output (Pestotnik and Olson, 2008). Functional interoperability is the capability to reliably exchange information without error.
Semantic interoperability provides a relationship between data and the meaning of that data, akin to a dictionary (Pestotnik and Olson, 2008). Different communication standards exist for functional and semantic interoperability; historically, this has been inefficient and has posed great challenges to both clinicians and IT specialists. One communication standard that exists, Consolidated Clinical Document Architecture (C-CDA), is designed to transfer entire documents, rather than a single piece of requested information. (Dolin et al., 2001) For CDS applications, the use of C-CDA for all data results in logarithmic inefficiencies. Later versions of the Health Level 7, or HL 7 (Health Level Seven® International, 2017) communication standard resulted in changes where discrete data were transferred, but its large bandwidth has been equated to a “firehose” that can become “bottlenecked” and can put limits as to what data can be sent. A new interoperability messaging standard known as Fast Health Interoperability Resources (FHIR) from Health Level 7 has emerged. FHIR is a truly advanced technology because it is based on a modern web services approach (used by companies such as Yahoo, Facebook and Google). A primary advantage is that it “fetches” discrete data from a variety of often disparate computer systems and has very few limits to providing real-time information exchange. Aside from their efficiency and integration differences, both communication standards (HL 7 and FHIR) provide a flow of information from the EHR to the CDS software. For example, patient-specific information (e.g., demographics, clinical laboratory results, microbiology data, etc.) can be automatically populated from different computer systems into respective fields within the CDS technology, thereby allowing for calculations to occur and is presented in a single user interface. Another term is used in conjunction with FHIR is Substitutable Medical Applications Reusable Technologies, or SMART. SMART is a collaboration between Harvard Medical School
and the Office of the National Coordinator to create an application program interface for substitutable health apps that run across multiple EHRs (SMART, 2017; Mandl and Kohane, 2012). Simply put, SMART has partnered with FHIR to create healthcare applications or apps. The CDS technologies that have been built upon this new FHIR interoperability standard and are able to use SMART technology exist in a fast, friendly, and easy to use app-like ecosystem. SMART technology was designed to remove the proprietary nature of commercially available EHRs, allowing simple plug-and-play applications to be used more easily. These applications were developed for use across all EHRs, regardless of vendor. Hospitals using either HL 7 or FHIR communication standards can allow CDS technologies to access real-time patient-specific data, therefore simplifying the clinician’s workflow. The value of SMART on FHIR is that it benefits both end-users, including clinicians and ASPs, IT developers, and local IT specialists as it allows for more software applications that are simple to use and are available for use from all EHR vendors. Conversely, integration of enhanced CDS functionality is more complicated and labor intensive for healthcare systems using the HL 7 interoperability standard. Ultimately, software developers that provide their applications for use in HL 7 and FHIR will be best equipped to assimilate their technology into healthcare systems.

Specialized “Add On” CDS Technologies

Large commercial multifunctional add-on CDS software (e.g., TheraDoc, Medmined) have been available for over a decade and are well explained elsewhere (Forrest et al., 2014); thus, it is not our intention to review these systems. Instead, we will review novel specialized add-on CDS technologies that are specifically used to assist antimicrobial treatment selection and/or dosing
regimen design using PK-PD principles and/or Bayesian modeling (Table 1). Because the right antibiotic, at the right dose, and for the right duration defines antimicrobial stewardship, these specialized add-on technologies are essential considerations for the ASP.

**PK-PD Compass**

Because it is robust in terms of both patient-specific covariate inputs and antibiotic library, exists in a mobile platform, and has published outcomes data available, the PK-PD Compass is the principle specialized add-on CDS technology for infection-specific dosing regimen selection. The PK-PD Compass serves as an educational tool that enables clinicians to use the science of PK-PD to inform their antimicrobial stewardship practice habits (Bulik et al., 2017). Specifically, the proprietary engine performs thousands of calculations and/or simulations using population pharmacokinetic models, an MIC value to a specific pathogen or regional MIC distributions from the SENTRY Antimicrobial Surveillance Program (a worldwide susceptibility surveillance database), and Monte Carlo simulation. The intended patient population are those 18 years and older and who are receiving intravenous antimicrobial therapy. Thousands of patient simulations are rapidly processed in the background, yielding a comprehensive list of results. These results are displayed as a list of antibiotic regimens with their associated percent probabilities of PK-PD target attainment (Bulik et al., 2017). Presented with this information, the clinician can chose one of the dosing regimens formulated for a given pathogen that is output by the program. What’s more, the program reminds the clinician to record clinical outcomes at both an early time point and at the end of therapy. The workflow of the PK-PD Compass mobile platform is presented below.
(1) **Infection type.** The program requires the clinician to choose from a list of bacterial infections that encompass the majority of those that would result in an adult patient requiring inpatient intravenous antimicrobial therapy, and for which reliable PK-PD targets for efficacy are available. ([FIGURE 1](#))

(2) **Pathogen selection.** The user is then prompted to select the pathogen of concern from an alphabetically ordered list of those most commonly associated with a given infection ([FIGURE 2](#)).

(3) **Antibiotics.** The clinician then chooses which antibiotic(s) they would like evaluated from a list of antibiotics that are appropriate, based on guidelines and product labels, for the infection-pathogen combination ([FIGURE 3](#)). In order to be eligible for inclusion in the program, each antibiotic must have reliable PK-PD targets for efficacy and a population PK model that describes the drug’s disposition. The ability to evaluate prolonged infusions of beta-lactams is also offered for clinicians.

(4) **Pathogen susceptibility data.** In this sequence, the clinician is prompted for pathogen-susceptibility data ([FIGURE 4](#)), chosen from among three different options: 1) An individual MIC value; 2) The pathogen-antibiotic specific MIC value representing the susceptibility breakpoint; and 3) SENTRY MIC distribution data which encompasses regionally-specific and national antimicrobial-pathogen specific MIC distribution data. If the user selects the susceptibility
breakpoint, the portion of the SENTRY reported MIC distribution up to and including the MIC value representing the breakpoint is used. This truncated distribution is used to weight all subsequent calculations (Bulik et al., 2017).

(5) **Patient-specific data.** The clinician is prompted to enter patient-specific demographic, medical history, and comorbidity data (FIGURE 5) which the program then uses to identify the antibiotic dosing regimens that are appropriate for the patient based on body weight, renal and/or hepatic function.

(6) **Results.** The clinician is then presented with a list of dosing regimens ranked ordered by the percent probability of PK-PD target attainment, for every antibiotic-pathogen pair selected. (FIGURE 6). In order to present these results, the program uses the population PK model for each antibiotic-infection category combination to calculate the patient-specific final parameter estimates plus inter-individual variability and integrate these values into Monte Carlo simulations to generate steady-state plasma concentration–time profiles for 3000 simulated subjects. Using these steady state plasma concentration–time profiles, percent probabilities of PK–PD target attainment by MIC values ranging from 0.008 to 256 mg/L for the antibiotic agent are determined and weighted over geographically-specific SENTRY MIC distribution data, when applicable (Bulik et al., 2017).

(6) **Following the patient in your service.** In addition to providing dosing guidance that is unique to each patient, the PK-PD Compass delivers the opportunity to conduct assessments of
the patient’s clinical progress and record antimicrobial stewardship interventions during the patient’s course of therapy. One current limitation is the PK-PD Compass does not offer Bayesian pharmacokinetic dosing based on drug concentrations for longitudinal monitoring of vancomycin and the aminoglycosides; however, this functionality will appear in a future update. Another potential limitation is that the PK-PD Compass is not meant for ages <18 years.

**TDMx**

TDMx (http://www.tdmx.eu) is a web-based program designed by an interdisciplinary team of scientists from the University of Hamburg. This web-based program allows users to employ pharmacometric principles to inform therapeutic drug monitoring for meropenem, piperacillin, gentamicin, amikacin, and tobramycin. The program consists of multiple modules including the following: the “patient module” which allows the user to enter patient-specific covariates; the “probabilistic dosing module” which predicts the probability of PK-PD target attainment for dosing regimen \textit{a priori} to drug concentrations; the “Bayesian dosing module” which utilizes drug concentration measurements to individualize the PK of the patient; and the “optimize sampling module” which uses a D-optimal design theory to inform the user what the best sampling strategy is for their patient. This program affords users many benefits including the multiple available features and modules, the ability to customize the inputs for a specific patient, and the ability to perform therapeutic drug monitoring. However, the user must be well-versed in the field of pharmacometrics in order to benefit from the full advantages of the program. The user interface is complex and, while allowing users to customize patient-specific data, the program also allows the users to adjust inputs such as protein binding and the PK-PD
target for the drug. This added customization may be beneficial to PK-PD- and pharmacometric-savvy users. However, this option may be too advanced for those clinicians who do not have the background knowledge to fully utilize this option.

**DoseMeRx**

DoseMeRx (http://doseme-rx.com) is a cloud-based, mobile and EMR integrated program that employs Bayesian dosing methods to provide patient-specific dosing for amikacin, gentamicin, meropenem, tobramycin, vancomycin and oral voriconazole, in addition to anti-coagulation, oncology, transplant and pediatric medications. The program allows users to input patient-specific information including demographic data, dosing history, drug concentrations, as well as optionally, genomic profiles. The program will then combine this patient data with published PK-PD models to output patient-specific results to provide individualized dose calculations which are then compared to the FDA label dose or local hospital dosing guidelines. Currently, the program is only available through purchase of one of many different licensing packages. This program offers the benefit of multiple drugs and the incorporation of pharmacogenomics in dosing regimen determination. While DoseMeRx can provide label, guideline, and population-model based dosing decision support, in order to use full Bayesian dosing individualization, a minimum of one drug level is required.

**InsightRx**

InsightRx (http://insight-rx.com) is a cloud-based and EMR-integrated program that integrates pharmacokinetics, patient-specific covariates, pharmacogenomics, and drug-concentrations to
perform model-based simulations and Bayesian analyses, enabling dosing optimization and response simulations for antibiotics (vancomycin, gentamicin, amikacin and tobramycin), transplantation/oncology medications (Tacrolimus, Busulfan and ATG), in addition to other medications (Voriconazole, Methotrexate and anticoagulants). Currently, the platform is available as a stand-alone or as an EMR-integrated product. The platform is agnostic to the PK model, algorithm, therapeutic monitoring target, such that the institution can select between any published or internally built and validated PK-PD model, fitting an algorithm and then optimizing therapy based on a user defined target. The company also provides the opportunity for an institution to customize the user interface (e.g., institution preferred PK-PD metrics, PK-PD target attainment probabilities etc.). The individual institution can also input their own drug nomograms into this program for all initial dosing recommendations. Another benefit of InsightRx is the ability to offer treatment decision guidance at the individual level with drug concentrations and biomarker data, in addition to the population level, at which learning algorithms may be applied to identify new predictors of drug response. Finally, the program also offers the ability to simulate the probability of toxicity of some of the agents in the program. Although PK-PD simulations can be performed without drug concentration levels in the program, the Bayesian capabilities provide a more accurate representation of a patient's pharmacokinetic profile, enabling the user to learn about the patient over time and adjust therapy as appropriate.

Clinical Outcomes
Among the programs described above, the only clinical outcomes that have been reported are those based on the use of the PK-PD Compass. (Bulik et al, 2016). An analysis of the first set of patients in whom the PK-PD Compass was used identified a significant relationship between the percent probability of PK-PD target attainment and the probability of clinical improvement 48 hours after selection of antimicrobial therapy where the probability of clinical improvement increased with increasing probability of target attainment (Bulik et al., 2016). Using additional data, these analyses were repeated and the same positive relationship was observed for clinical improvement after 48 hours, as well as after Days 7-10 (Bulik et al., abstr. 2017). The results of the repeat analyses demonstrated that, for every 10% increase in the PTA of the initially chosen dosing regimen, a patient was 1.74 times more likely to demonstrate clinical improvement after 48 hours (OR [95% CI] 1.74 [1.28-2.37], p<0.001) and, 1.82 times more likely to have a successful clinical response after Days 7-10 (OR [95% CI] 1.82 [1.29-2.58], p<0.001). These data demonstrated that the use of the PK-PD Compass yielded positive clinical outcomes in patients with a variety of infections.

Summary

It is important that we view CDS technologies not as a panacea for mankind, but that their availability has become a necessity in modern medicine in order to sift through a morass of published clinical information as well as a means to navigate through hospital computer systems in search of patient data. CDS technologies now support a number of ASP functions as well as offer the capability of precision medicine. ASPs that operate without CDS technologies can be overwhelmed by the sheer number of patients receiving antibiotics that require
interventions. The manual identification and prioritization of patients in need of intervention is
time and resource consuming and results in reductions in the overall effectiveness of the ASP.
CDS technologies today streamline this process leaving more time for clinicians to strengthen
their recommendations with supporting data. PK-PD principles are used by the FDA to evaluate
antimicrobial dose and regimen decisions in early through late phase antimicrobial
development, yet they are not consistently used in clinical practice. Previously considered
luxuries in clinical practice, the ability to perform complex calculations accounting for infection
type, drug exposure, and pathogen-specific MIC, or the provision of drug exposure information
based on measured concentrations from the patient for select antimicrobials with narrow
therapeutic indices, are now commercially available as specialized add-on CDS technologies. It
is important to remember, all CDS technologies are analogous to a compass, guiding the
clinician through complex uncertainties, variables, and byzantine calculations. However, one
must always keep in mind that the human element in all of this is akin to the steadfast rudder,
remaining fully autonomous to navigate through all final therapeutic decisions intended to
optimize clinical outcomes for hospitalized patients.

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<table>
<thead>
<tr>
<th>Name</th>
<th>Program description</th>
<th>Available platforms</th>
<th>Based on PK-PD Targets for Efficacy?</th>
<th>Program inputs</th>
<th>Reference</th>
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<td>TDMx</td>
<td>Uses population PK models and Monte Carlo simulation to inform dosing regimens for meropenem, piperacillin, gentamicin, amikacin, and tobramycin. Allows for conventional and extended infusion durations to be evaluated for beta-lactams. Allows for OSS and TDM for the above-described drugs.</td>
<td>Web-based</td>
<td>Yes</td>
<td>Age; weight; height; sex; dose; dosing time; duration of infusion; dosing interval; serum creatinine; date and time of creatinine measurement; MIC value; drug concentration; date and time of concentration measurement; PK-PD target magnitude; protein binding value.</td>
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<tr>
<td>InsightRx</td>
<td>Uses population PK models, Monte Carlo simulation, and Bayesian dosing to predict the optimal dose of drugs through therapeutic drug monitoring. Includes vancomycin (neonates, children, adults), amikacin (neonates), gentamicin (neonates), and tobramycin (children, adults).</td>
<td>Cloud-based and EMR-integrated</td>
<td>Yes</td>
<td>Program inputs depend on selected drug and underlying PK-PD model. Examples include: age; weight; serum creatinine; dose; dosing time; duration of infusion; drug concentration; date and time of drug.</td>
<td><a href="http://insight-rx.com">http://insight-rx.com</a></td>
</tr>
</tbody>
</table>
| PK-PD Compass | Uses population PK models and Monte Carlo simulation to perform PK-PD target attainment analyses for 35 intravenous antimicrobials across 29 infection categories  
- Dosing regimens for 35 different intravenous are based on clinical guidelines and FDA-approved package inserts  
- Allows for PK-PD target attainment calculation based on fixed MIC or MIC distributions based on a specific region for selected pathogen  
- Allows for clinical follow-up at 48 hours and at Days 5-14 | Mobile platform and EMR integration | Yes | Infection category; pathogen; antimicrobials; MIC data; Sex; age; weight; height; serum creatinine; immunocompromised status; diabetes status; liver disease; Prior antimicrobial use; Infection scoring system | http://www.pkdcompass.com/ |
|---|---|---|---|---|
Figure 1. PK-PD Compass – Infection type selection options
Figure 2. PK-PD Compass - Pathogen selection options

- **Acinetobacter baumannii**
- **Acinetobacter baumannii, MDR**
- **Enterobacter spp.**
- **Escherichia coli**
- **Escherichia coli, MDR**
- **Klebsiella pneumoniae**
- **Klebsiella pneumoniae, MDR**
- **MRSA**
- **MSSA**
- **Proteus spp.**
- **Pseudomonas aeruginosa**
- **Pseudomonas aeruginosa, MDR**
- **Serratia marcescens**

[Infection: Healthcare-associated pneumonia]
[Pathogen: --]
[Antibiotics: --]
[Patient: --]
Figure 3. PK-PD Compass - Antibiotic selection options

<table>
<thead>
<tr>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
</tr>
<tr>
<td>Aztreonam</td>
</tr>
<tr>
<td>Cefepime</td>
</tr>
<tr>
<td>Ceftaroline</td>
</tr>
<tr>
<td>Ceftazidime</td>
</tr>
<tr>
<td>Ceftriaxone</td>
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<tr>
<td>Ciprofloxacin</td>
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<tr>
<td>Gentamicin</td>
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<tr>
<td>Imipenem</td>
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<tr>
<td>Levofloxacin</td>
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<tr>
<td>Meropenem</td>
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<tr>
<td>Piperacillin-tazobactam</td>
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<tr>
<td>Tigecycline</td>
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<tr>
<td>Tobramycin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTION</td>
</tr>
<tr>
<td>Healthcare-associated pneumonia</td>
</tr>
<tr>
<td>PATHOGEN</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>ANTIBIOTICS</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>PATIENT</td>
</tr>
<tr>
<td>---</td>
</tr>
</tbody>
</table>
Figure 4. PK-PD Compass – Pathogen susceptibility data options
Figure 5. PK-PD Compass – Required patient-specific data
Figure 6. PK-PD Compass - Results

**Results**

**ANTIBIOTICS YOU CHOSE**

- **100% Cefepime**
  - 2 g IV q12h over 0.5h
  - 100% over 0.5h
  - 100% over 1h
  - 100% over 2h

- **97% Ciprofloxacin**
  - 400 mg IV q12h over 1h

- **93% Piperacillin-tazobactam**
  - 3.25 g IV q8h over 0.5h
  - 92% over 0.5h
  - 94% over 1h
  - 97% over 2h

- **90% Meropenem**
  - 1 g IV q12h over 0.5h
  - 82% over 0.5h
  - 90% over 1h
  - 91% over 2h

- **82% Cefepime**
  - 2 g IV q24h over 0.5h
  - 82% over 0.5h
  - 83% over 1h
  - 86% over 2h

- **67% Tobramycin**
  - 93 mg IV q12h over 0.5h

- **63% Tobramycin**
  - 4,000 IU IV q6h over 0.5h

Percentages represent probabilities of PK-PD target attainment.

**PATHOGEN**

*Klebsiella pneumoniae*

**INFECTION**

Healthcare-associated pneumonia

**ANTIBIOTICS**

- Cefepime
  - 4 mg/L
- Ciprofloxacin
- Piperacillin-tazobactam

**Resistance Breakpoints**

- Meropenem
  - SENTRY 2015
- Tobramycin
  - SENTRY 2015
- Ideal Body Weight

**PATIENT**

- Female
- 78 yrs
- 148 lbs
- 64 in
- 1.3 mg/dL serum creatinine
- 37.8 mL/min creatinine clearance
- Not immunocompromised
- Diabetes without end organ damage
- No severe liver disease
- No prior antibiotic therapy
- CPIS Score: 7
References

Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore.
Clin Infect Dis. 44:79-86.


