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Right dose, right now: using big data to optimize antibiotic dosing in the critically ill

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Abstract

Antibiotics save lives and are essential for the practice of intensive care medicine. Adequate antibiotic treatment is closely related to outcome. However this is challenging in the critically ill, as their pharmacokinetic profile is markedly altered. Therefore, it is surprising that critical care physicians continue to rely on standard dosing regimens for every patient, regardless of the actual clinical situation. This review outlines the pharmacokinetic and pharmacodynamic principles that underlie the need for individualized and personalized drug dosing. At present, although therapeutic drug monitoring may be of help, it has major disadvantages, remains unavailable for most antibiotics and has produced mixed results. We therefore propose the AutoKinetics concept, taking decision support for antibiotic dosing back to the bedside. By direct interaction with electronic patient records, this opens the way for the use of big data for providing the right dose at the right time in each patient.

Key words: autokinetics, pharmacokinetics, antibiotics, electronic patient record, decision support, intensive care, critical care

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THE CONTINUING BURDEN OF SEPSIS

Antibiotics are essential for treating sepsis [1]. Their early and appropriate use has repeatedly been shown to reduce ICU and hospital mortality rates [2, 3]. However, these mortality rates still remain high, i.e. around 30% for severe sepsis and up to 82% for septic shock [4]. This is despite major scientific efforts, including many clinical sepsis trials, mainly focusing on inflammatory mediators [5] and the introduction of care bundles [6, 7]. This is an alarming fact especially since the incidence of sepsis continues to increase and now exceeds that of colon cancer, breast cancer and AIDS combined [8].

AN OVERLOOKED CAUSE: INADEQUATE ANTIBIOTIC DOSING IN THE CRITICALLY ILL

There is a strong rationale for optimization of antibiotic treatment and exposure in patients with severe sepsis. As recently reviewed, this is primarily on the robust relationship between adequate antibiotic exposure, bacterial killing and clinical cure; and in addition, on the major challenge to achieve adequate antibiotic exposure in critically ill patients [9]. The latter can be understood by considering the markedly different pharmacokinetic (PK) profiles in the critically ill (table 1; for a brief update on the PK and pharmacodynamic (PD) concepts, please refer to the boxed text). Of note, these changes may vary greatly between patients but also in the same patient over the time course of disease and treatment, implicating inter- and intra-individual variations.

UNDERSTANDING PK/PD FOR ANTIBIOTICS

Pharmacokinetics (PK) describes how the body handles a certain drug, in this case the antibiotic, resulting in a particular plasma and effect site concentration. Pharma-

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Table 1. Pharmacokinetics are markedly altered in critically ill patients

Phenomenon	Effect on Vd	Effect on CL
Hyperdynamic circulation		Increased
Positive fluid balance	Increased	
Reduced protein concentration	Increased	Increased
Renal dysfunction or decreased renal blood flow		Decreased
Hepatic dysfunction or decreased hepatic blood flow or CYP inhibition by other drugs		Decreased
CYP induction by other drugs		Increased
Renal Replacement Therapy	Increased	Increased
ECMO	Increased	Varies

Vd — volume of distribution; CL — clearance; CYP — cytochrome P; ECMO — extracorporeal membrane oxygenation

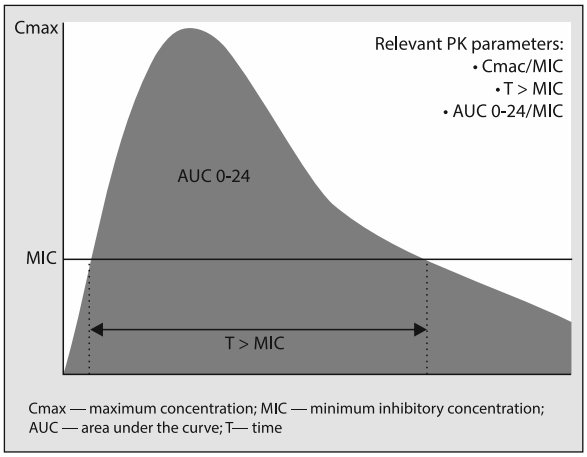

Figure 1. A time versus concentrations curve to illustrate relevant PK/PD parameters

codynamics (PD) relates these concentrations to a specific effect, i.e. how the antibiotic affects the body.

Antibiotic plasma concentrations are determined by dosing strategy, volume of distribution (Vd) and clearance (CL). Antibiotic efficacy is commonly expressed as its minimum inhibitory concentration (MIC) of the targeted microorganism. It is the lowest concentration at which there is no growth *in vitro*. This should be determined locally for cultured microorganisms. For empiric therapy, local historical prevalence and resistance data should be used. If these are unavailable, clinical breakpoints provided by bodies such as EUCAST (European Committee for Antimicrobial Susceptibility Testing) or CLSI (Clinical Laboratory Standards Institute) could be consulted.

Concentration measures can be combined with MIC values to provide meaningful PK/PD parameters as illustrated in Figure 1. These include Cmax/MIC, i.e. the maximum plasma concentration divided by MIC; T > MIC, i.e. the time during which the antibiotic plasma concentration is above the MIC; and AUC 0–24/MIC, i.e. the area under the 24 hour time versus antibiotic plasma concentration curve divided by MIC. As illustrated in Table 2, the most important PK/PD target varies per antibiotic class. Antibiotics can be concentration dependent, time dependent or both. These concepts have important implications for dosing schemes. For example, it follows that the glycopeptides should be dosed intermittently, as Cmax is the PK parameter of importance and toxicity is determined by their trough concentration. Conversely, a strong case for continuous or extended infusion can be made for the beta lactams, fluoroquinolones and glycopeptides. Of course, this will sometimes require surplus venous access with its associated complications. In this context, it should be remembered that the true additional value of continuous dosing for these drugs is yet to be firmly established. Similar considerations should be kept in mind when dose adaptations are required because of fear for toxicity if clearance is reduced, e.g. because of acute kidney or liver injury. This would imply lengthening the dosing interval for aminoglycosides, whereas dose reduction would be the strategy of choice for beta lactams, fluoroquinolones and glycopeptides.

Table 2. Antibiotics have specific relevant pharmacokinetic (PK)/pharmacodynamic (PD) parameters

PK/PD class	Antibiotic Classes	Relevant PK/PD parameter
Concentration Dependent	Aminoglycosides	Cmax/MIC
Time Dependent	Beta lactams	T > MIC
Time and concentration dependent	Fluoroquinolones	AUC 0–24 > MIC
	Glycopeptides	

MIC — minimum inhibitory concentration; T — time; AUC — area under the curve

Table 3. For reference, targets for the relevant PK/PD targets for different antibiotic classes are given. Values were taken from a recent review [9]. Please note that these targets remain a subject of debate

Antibiotic Class	Setting	Clinical Cure
Aminoglycosides	Pneumonia, sepsis	Cmax/MIC > 8–10
Carbapenems	Febrile neutropenic patients with bacteremia	75% T > MIC
Cephalosporins	Serious bacterial infections	100% T > MIC
Fluoroquinolones	Gram negative sepsis	AUC 0–24/MIC >125–250
Vancomycin	MRSA sepsis and SA pneumonia	AUC 0–24/MIC > 400–450

Another important point to remember is that the initial concentration after starting an antibiotic is only dependent on the volume of distribution. This implies that for continuous dosing, a loading dose should be administered. In addition, this loading dose should only be reduced if the volume of distribution is thought to be reduced (which is only seldom the case in ICU patients) and not if clearance is thought to be reduced.

Finally, it should be pointed out that PK/PD targets remain the subject of heated debate. These targets were initially obtained from *in vitro* experiments and most clinical studies confirm the adequacy of these studies. However, the majority were conducted in small groups of either healthy subjects or patients who were not critically ill. In addition, there are concerns whether plasma antibiotic concentrations can truly be related to effect site concentrations, e.g. pleural epithelial lining, peritoneal fluid or abscesses. However, for guidance, we have stated the currently accepted PK/PD targets for several important antibiotics in Table 3.

Given these considerations, it is surprising that intensive care physicians continue to rely on standard dosing regimens when prescribing antibiotics that were developed using data from healthy volunteers and non-critically ill patients. This one-dose-fits-all strategy is inappropriate and unsafe for serious infections in complicated patients. Depending on patient characteristics, clinical course and therapy, this strategy may result in underdosing and/or drug-related toxicity during the course of intensive care treatment. Toxicity may lead to additional patient morbidity [10]. Underdosing may result in treatment failure, delayed response and increased antimicrobial resistance through selection pressure [11]. While clinical antibiotic dosing is often reduced for renal function to avoid toxicity, doses are rarely increased for well-known risk factors related to underdosing such as young age, large body weight, renal hyperfiltration, massive fluid therapy, and septic shock [9].

The recent "Defining Antibiotic Levels in Intensive care" (DALI) study [12–14] in 68 hospitals in 10 countries confirms the severity of the problem, showing up to a 500-fold variation in antibiotic concentrations in critically ill patients. Less than 50% of the 248 patients treated for infection, achieved the optimal PK/PD target. Moreover, one fifth of patients did not even achieve the most conservative target. In these patients, clinical cure was 32% less likely.

THE PROBLEM OF THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) has been advocated as a solution to antibiotic dosing [15]. TDM uses PK models and drug plasma level determinations to guide dosing. While helpful, TDM leaves important issues unresolved. First, TDM usually deploys relatively simple PK models using limited patient data often derived from small groups of non-critically ill patients. Simple models require fewer parameters, which facilitates manual data entry. However, this approach fails to acknowledge the complexity of critically ill patients. In addition, the availability of TDM remains limited for the most widely prescribed antibiotics, the beta-lactams [16]. This may explain why TDM studies on relevant outcomes including mortality and cost effectiveness are scarce and have produced mixed results [17–19]. A further explanation for this mixed effect is the fact that pharmacokinetic targets for plasma and effect site remain the subject of debate (see also the boxed text). This further complicates the problem of adequate drug dosing. However, the biggest problem with TDM is that it is not directly available at the bedside and relies heavily on measuring plasma drug levels. Thus, dosing guidance only becomes available after several antibiotic doses have already been administered. This is alarming as patients require adequate dosing right from the start of treatment. Of course this could be circumvented by dosing based on a worst case scenario, which would lead to higher than needed plasma drug levels in most patients. However, this would be problematic for drugs with a narrow therapeutic window because of toxicity, e.g. vancomycin and the aminoglycosides. In addition, it would incur tremendous extra costs.

AN INNOVATIVE SOLUTION: COMBINING INDIVIDUALIZED, PERSONALIZED MEDICINE WITH BIG DATA

We now propose a solution based on two developments in medicine, i.e. personalized healthcare and the use of big data. Personalised healthcare recognizes the complexity of large inter- and intra-individual patient variations. Big data refers to data sets so large and complex that information technology is needed to unveil important signals and patterns.

Indeed, with the advent of electronic patient records (EPR), although vast amounts of patient data are collected routinely, most of them are currently wasted. In the context of pharmacokinetics, EPRs are essentially data warehouses, especially in intensive care units where a large amount of precise patient information that determines their pharmacokinetic profile is constantly and instantly available. Thus, the key is to use these readily available data more effectively.

Therefore, we have gathered a team uniting experts in EPR programming, PK modeling and intensive care medicine. Together, and without commercial support, we have developed AutoKinetics (AutoK, see www.autokinetics.eu), a pilot version of a software solution. Based on VB.net (Microsoft, Redmond, USA), the software interacts directly and automatically with every modern EPR either through direct database queries or web services. AutoK is able to use published population pharmacokinetic models of any drug. Using the micro constants of these models, the software performs iterative calculations to predict future drug plasma levels based on the co-variates in the model. These typically represent individual patient characteristics such as demographics and a mix of physiological and laboratory parameters such as cardiac output, sequential organ failure assessment (SOFA) score, liver tests; and albumin and creatinine levels. As AutoK is able to directly import these parameters, the data density for predictions and therefore their potential accuracy is greatly improved, and theoretically bound by computational constraints only. Today, this is of limited practical concern, given the rapid progression of computer science. In addition, the AutoK concept envisions Bayesian maximum a posteriori adaptation of predictions based on plasma drug samples. It also enables one to directly import microbiology data, including MIC data, in order to directly adapt dosing advice to PK/PD indices and microbial susceptibility (e.g. %*f*T > 4MIC).

Thus, AutoK provides dosing advice reminiscent of TDM, but with vital additional advantages (see also Fig. 2). AutoK is available directly at the bedside, as it runs on the same computer as the EPR and no manual data entry is needed. Thus, dosing guidance is immediately available whenever physicians need it. Similarly, AutoK is able to immediately react to changes in individual PK profiles. Patient data continues to be generated throughout the clinical course resulting in automatic updated dosing guidance. The software provides real-time graphical feedback on proposed dosing regimes. This is expected to enhance physician understanding of pharmacokinetics and improve antibiotic dosing.

The importance of closely monitoring the critically ill patient has long been recognized. Bedside monitors, e.g. for hemodynamic parameters, enable rapid adaptation of therapeutic strategies. The AutoK concept extends this philosophy to the domain of antibiotic therapy. This can radically change the way antibiotics are dosed and improve exposure and outcome. Thus, it addresses the urgent need to optimize antibiotic use not only to improve immediate patient outcomes but also to preserve antibiotics for the future by limiting drug resistance [11].

Currently, we have implemented a working pilot version for vancomycin at OLVG hospital, in Amsterdam, The Netherlands. There, it has been fully implemented in the intensive care workflow and is directly available at the bedside. Preliminary analysis (personal communication) reveals that this has caused a vast improvement in the number of times the first determination of drug plasma levels was in the desired range, which went from 40% (n = 192) of cases to 65% (n = 172).

CHALLENGES FOR THE FUTURE

The challenge now is to further develop AutoKinetics and assess its clinical performance and its effect on relevant clinical outcome parameters. We are currently performing these studies. As a first step, we will evaluate existing models for commonly used antibiotics including meropenem, ceftriaxone and vancomycin. For all models, we will use the Monte Carlo simulation to compare standard dosing regimens versus AutoK based dosing. We will also implement Bayesian maximum a posteriori correction algorithms for drug plasma levels and test user satisfaction with various graphical displays of predicted concentrations, MIC values and PD indices associated with clinical cure. Based on these results, AutoK will be further refined.

Next, we will use the selected models and the optimized version of AutoK for a clinical feasibility and safety study. We will assess the influence of implementing our software on achieving PK targets and clinical end points. We will also include patients with severe sepsis. Patients will be randomized between physician exposure, to AutoK or standard therapy. Standard therapy will include TDM for vancomycin, but not for the beta-lactams as this is currently not routinely performed. The primary end-point is achievement of 100%-*f*T > 4MIC in the first 24 hours for the beta-lactams and *f*AUC/MIC > 400 for vancomycin. A power analysis (alpha 0.05, 1-beta 0.80) shows a required sample size of 42 patients per group, per antibiotic, for a reduction from a 60% to a 30% failure rate to attain PK/PD targets.

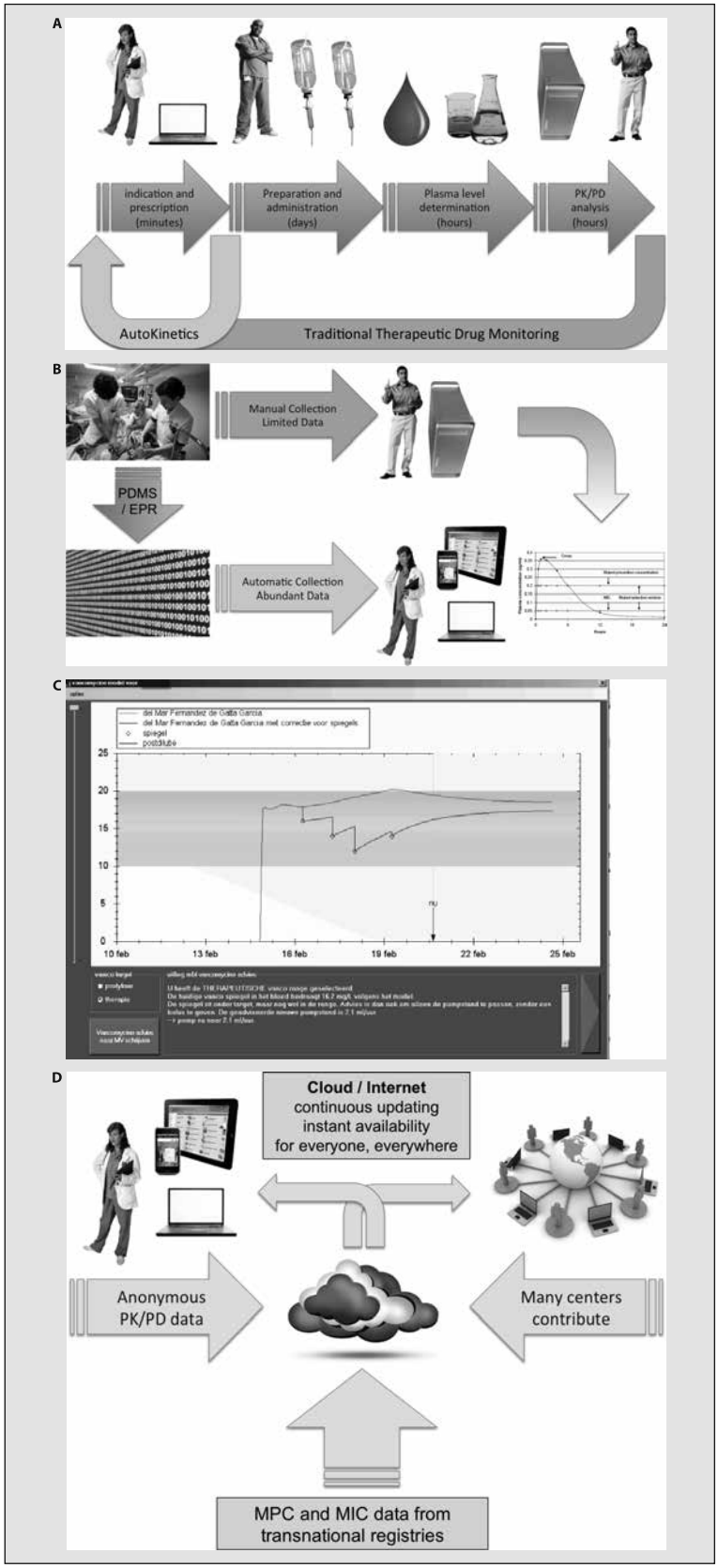

Figure 2. Panel A — AutoKinetics provides a shortcut by providing direct bedside dosing guidance to the intensivist; **Panel B** — By connecting directly to the electronic patient record, the need for manual data entry is circumvented, opening the way for complex model use; **Panel C** — Users are presented with real time graphical feedback and advice at the bedside; **Panel D** — By using the power of the internet, models and outcome may be continuously improved

THE NEXT FRONTIER: BIG DATA

The true value of the AutoKinetics concept is its scalability. As no manual data entry is necessary, the number of model parameters considered and the number of data points taken into account will only be limited by computational power and memory. Given the current state and continuing evolution of information technology, this should only be of limited concern. This opens the way for developing true big data models. Current PK/PD models for intensive care patients are usually only based on a limited number of patients (usually between 10 and 80), and parameters are frequently omitted because of a perceived limited contribution to the model. However, by reducing the cut-off level of significance for the model and by including many more patients for model development, the number of parameters in the model could be vastly increased. This could lead to true big data models and could be the beginning of an era in which we could truly start using the vast amounts of data that we now routinely collect from our patients on a daily basis. In addition, although AutoKinetics has been developed for two specific EPRs, i.e. MetaVision and EPIC, it could easily be ported to connect with other EPRs. Thus, the platform could be implemented on a large scale. As a corollary, this would allow us to gather patient and plasma drug concentrations anonymously from these hospitals, which in turn would again lead to better models.

A step further could bring us the birth of true artificial intelligence with closed loop systems. Within the EPR, data is available with regard to antibiotic dosing and administration in combination with laboratory results. So ideally the computer should be able to fine-tune the model in a closed loop based on the available data and interventions. Connected to its peers via the internet, the model could then become more and more robust over time. This model could also help to identify risk factors for altered pharmacokinetic parameters to better predict those patients at risk for under- and overdosing.

CONCLUSION

Given the marked pharmacokinetic variability in the critically ill, both between and within patients and over the time course of disease and therapy, it is remarkable that clinicians continue to rely on standard dosing for antibiotics in every patient regardless of the underlying disease and co-morbidities. While therapeutic drug monitoring may be helpful, it has produced mixed result and has major downsides. First, decision support is only available after plasma levels have been measured and analyzed. Second, it takes decision support away from the physicians that take care of the critically ill patient at the bedside. The development of AutoKinetics, a real time closed loop decision support system at the bedside may be a major step forward with readily available advice before the first dose is prescribed. As AutoKinetics directly connects to the electronic patient record, it also opens the way for the use of big data and further refinement of the model. This may help the next generation of critical care physicians to prescribe the right dose to the right patient at the right time regardless of the situation.

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