THERAPEUTIC DRUG MONITORING

KARVALY, GELLÉRT BALÁZS, PHARM.D., PH.D.

LABORATORY OF MASS SPECTROMETRY AND SEPARATION TECHNOLOGY

DEPARTMENT OF LABORATORY MEDICINE

SEMMELWEIS UNIVERSITY

Introduction to our laboratory

- HPLC- and LC-MS/MS- based diagnostic tests
- Approximately 100 test parameters, 80 of which are prescription drugs
- Continuous research and development in therapeutic drug monitoring and in assaying endogenous substances

TASKS AND RESPONSIBILITIES OF THE CLINICAL LABORATORY IN THE FIELD OF THERAPEUTIC DRUG MONITORING

- DELIVERY OF TECHNICAL INFORMATION CONCERNING PATIENT SPECIMENS AND ASSAYS
  - TYPE OF SAMPLE, TYPE OF COLLECTION TUBE, REQUIRED SAMPLE VOLUME, LIPEMIA/ICTERUS/HEMOLYSIS, STABILITY
  - COMPARABILITY OF ASSAY METHODS, METHOD-SPECIFIC PREANALYTICAL PROCEDURES
- MEASUREMENT OF DRUG CONCENTRATIONS
- PROCESSING OF MEASUREMENT RESULTS USING APPLICABLE SOFTWARE
- CONSULTATIONS WITH CLINICAL PHARMACISTS AND CLINICIANS

↓

EXPERTISE ON ALL ASPECTS OF THE PREANALYTICAL, ANALYTICAL AND POSTANALYTICAL PROCEDURES!

Definition of therapeutic drug monitoring (International Association of Therapeutic Drug Monitoring and Clinical Toxicology)

- ***a priori* TDM:**
  - consists of determining the initial dose regimen to be given to a patient, based on clinical endpoint and on established population pharmacokinetic-pharmocodynamic (PK/PD) relationships. These relationships help to identify sub-populations of patients with different dosage requirements, by utilizing demographic data, clinical findings, clinical chemistry results, and/or, when appropriate, pharmacogenetic characteristics.

- ***a posteriori* TDM:**
  - includes pre-analytical, analytical and post-analytical phases, each with the same importance;
  - is most often based on the specific, accurate, precise and timely determinations of the active and/or toxic forms of drugs in biological samples collected at the appropriate times in the correct containers (PK monitoring), OR can employ the measurement of biomarkers as a surrogate or end-point markers of effect (PD monitoring) e.g. concentration of an endrogenous compound, enzymatic activity, gene expression, etc. either as a complement to PK monitoring or as the main TDM tool;
  - requires interpretation of the results, taking into account pre-analytical conditions, clinical information and the clinical efficiency of the current dosage regimen; this can involve PK-PD modeling;
  - can potentially benefit from population PK/PD approaches possibly combined with individual pharmacokinetic forecasting techniques, or pharmacogenetic data.

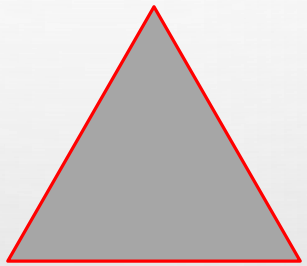
TO TOP

https://www.iatdmct.org/about-us/about-association/about-definitions-tdm-ct.html

„TDM IS A MULTIDISCIPLINARY TOOL”

https://www.iatdmct.org/about-us/about-association/about-definitions-tdm-ct.html

Clinician (specialist)



Clinical pharmacist

TDM laboratory

WHAT ONE CAN MEAN BY THERAPEUTIC DRUG MONITORING…

- APPLICATION OF THE TECHNIQUES AND PROTOCOLS FOR THE CLINICAL ASSESSMENT OF DRUG CONCENTRATIONS IN BODILY FLUIDS
- MEASUREMENT OF DRUG CONCENTRATIONS IN BLOOD WITH THE AIM OF CLINICAL INTERPRETATION BASED ON THERAPEUTIC RANGES
- A SERIES OF DRUG LEVEL MEASUREMENTS IN BLOOD AS PART OF A COMPLEX THERAPEUTIC STRATEGY
- A PILLAR OF CLINICAL DECISION MAKING AS PART OF PRECISION PHARMACOTHERAPY

WHY DO WE MONITOR DRUG CONCENTRATIONS IN BLOOD?

INDICATIONS OF TDM

- TO ASSESS OF THERAPY ADHERENCE
- TO TEST THE EFFICACY OF DRUG THERAPY
- TO CONFIRM OR RULE OUT ADVERSE EFFECTS
- TO ASSESS THE CONSEQUENCES OF ALTERED DRUG ELIMINATION
- TO EVALUATE THE DISTRIBUTION OF A DRUG TO PERIPHERAL FLUID SPACES
- TO IDENTIFY NON-TYPICAL METABOLIC CAPACITY
- TO IDENTIFY DRUG INTERACTIONS

CLINICAL DRUG ASSAYS CAN BELONG TO ONE OF THE FOLLOWING CATEGORIES

Checking the drug concentration in blood

- Clinical toxicology tests
- Major correction of dosage regimen
- Testing therapy adherence

THERAPEUTIC DRUG MONITORING

- Clinical pharmacokinetic interpretation

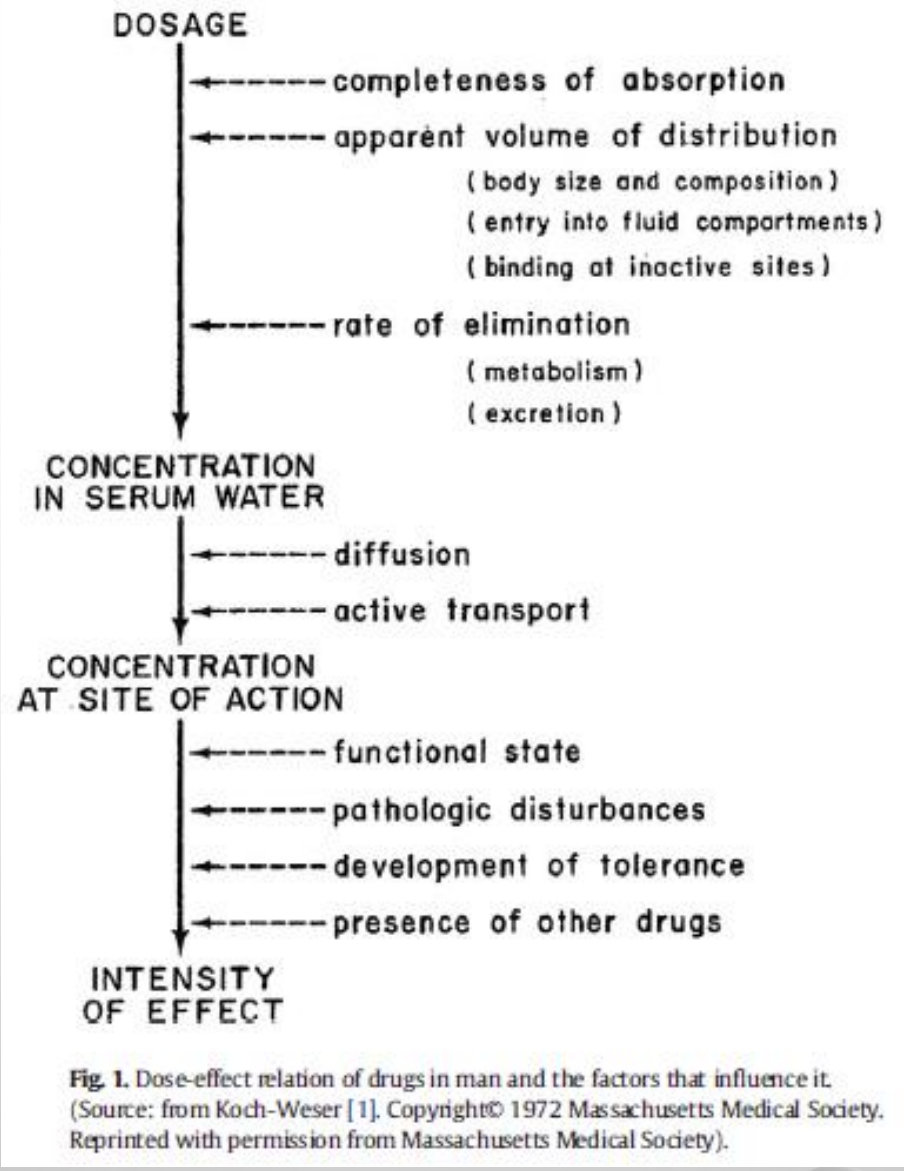
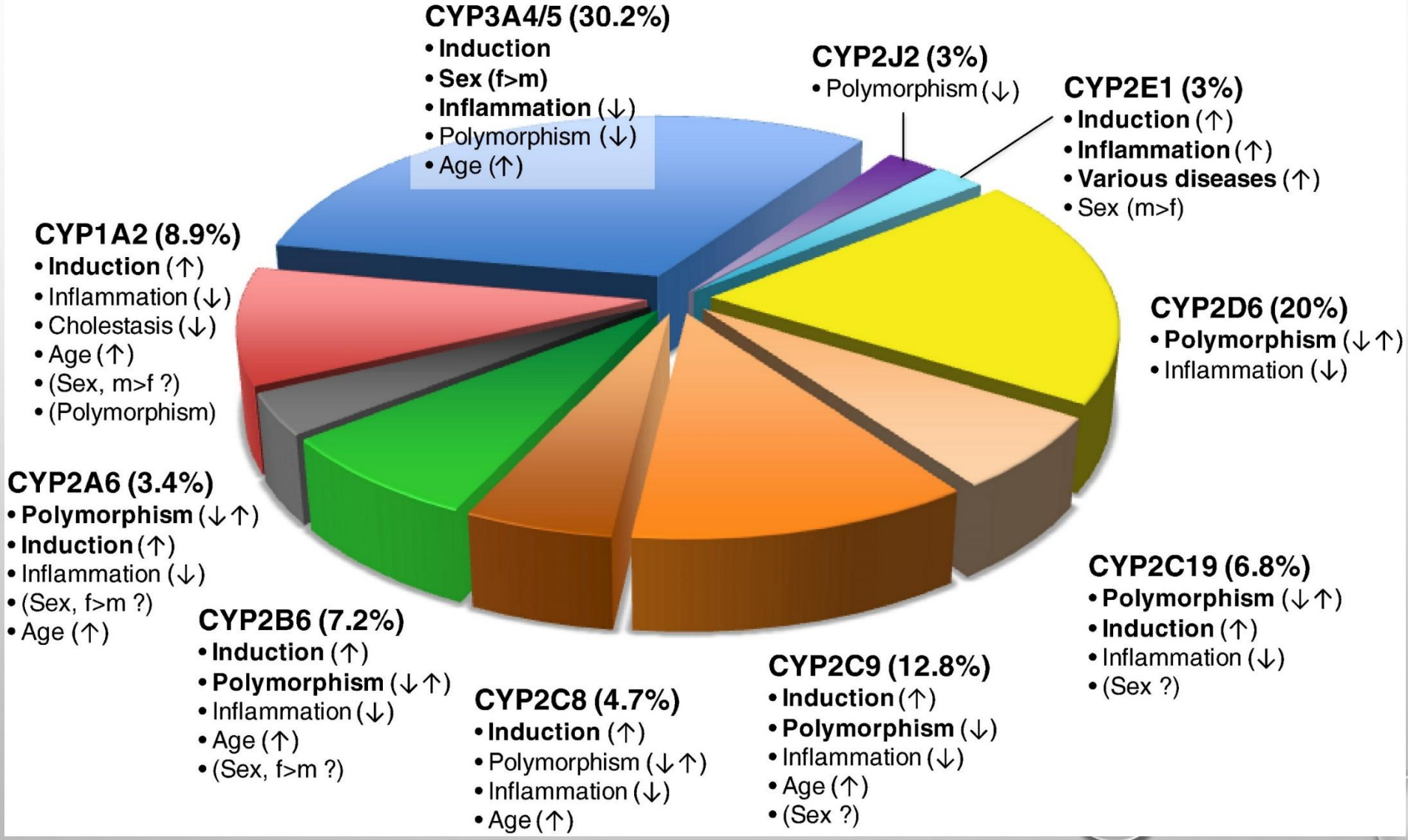


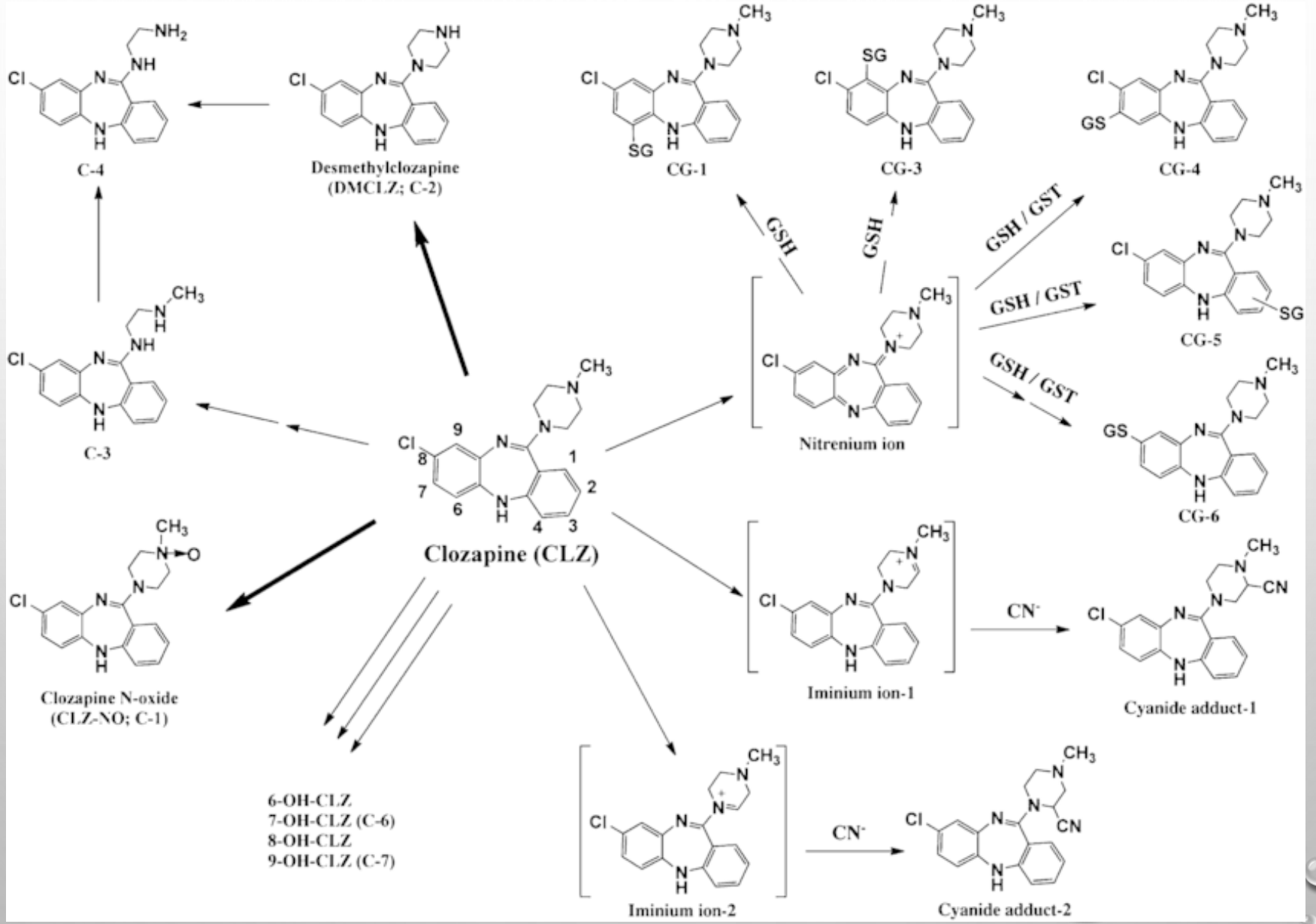
Fig. 1. Dose-effect relation of drugs in man and the factors that influence it. (Source: from Koch-Weser [1]. Copyright© 1972 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society).

Oellerich M et al. Clin Biochem 2017;50:375.

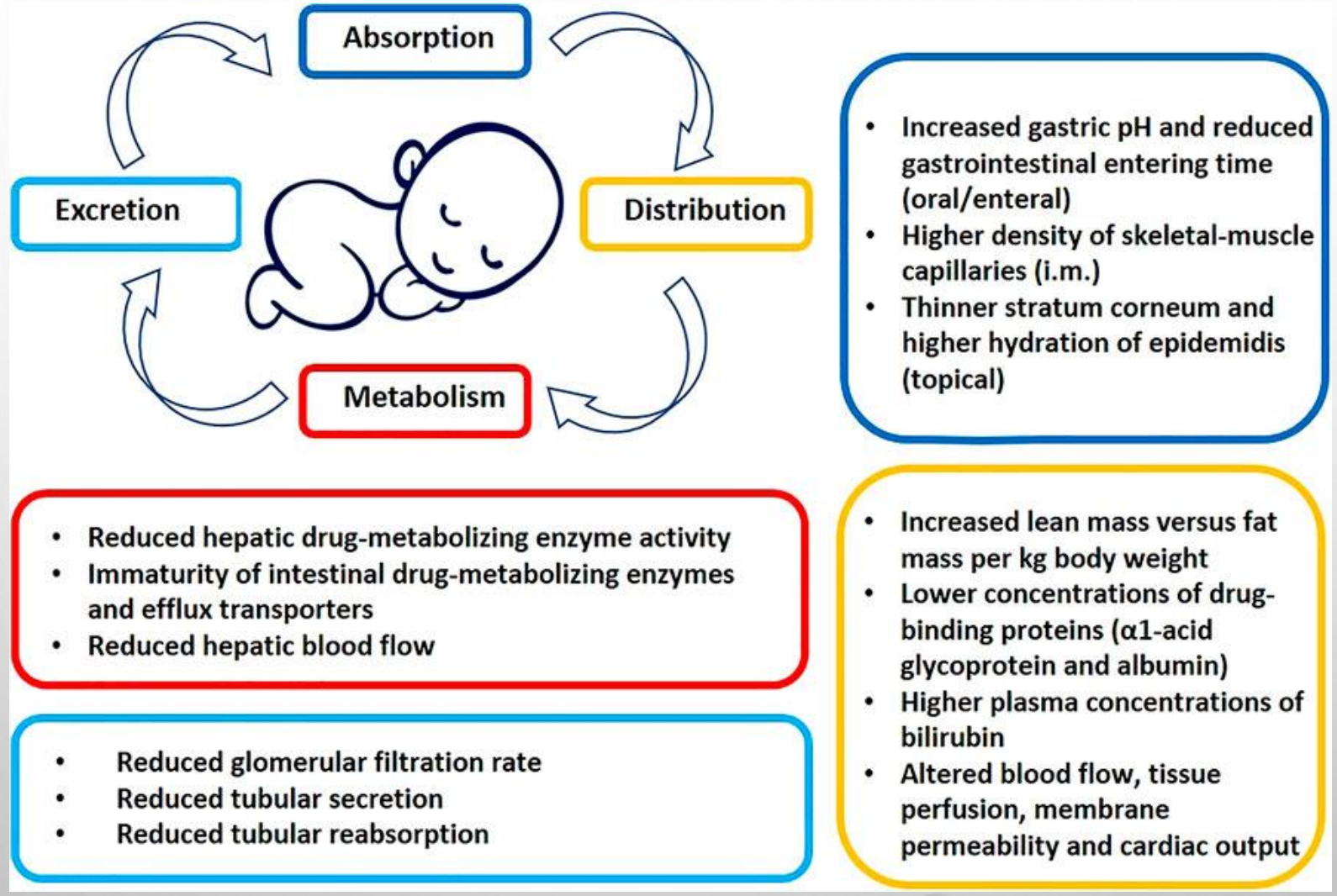
„P450 pie”: abundance of Cytochrome P450 isozymes in liver



Metabolism of clozapine



Altered pharmacokinetics in neonates



Mork ML et al. Frontiers Pharmacol 2022;13:Article 828010.

Altered pharmacokinetics in the elderly

Table 1. The most relevant age-related physiological changes influencing pharmacokinetics of drugs [26–29]

Body system	Physiological effect	Consequences for pharmacokinetics
Body composition	Decreased body water content by 20% Increased body fat content approx. 30% Decreased muscle mass 30%	Altered volumes of distribution for highly lipophilic/hydrophilic drugs
Renal function	Decline of glomerular filtration rate	Prolonged elimination half-life for all renally cleared drugs
Hepatic function	Decreased liver blood flow by approx. 10–25% Decreased enzymatic function with contradictory results	Prolonged elimination half-life, particular for drugs with high extraction ratios; reduced first-pass elimination

Thürmann P. Curr Opin Anesthesiol 2020;33:109.

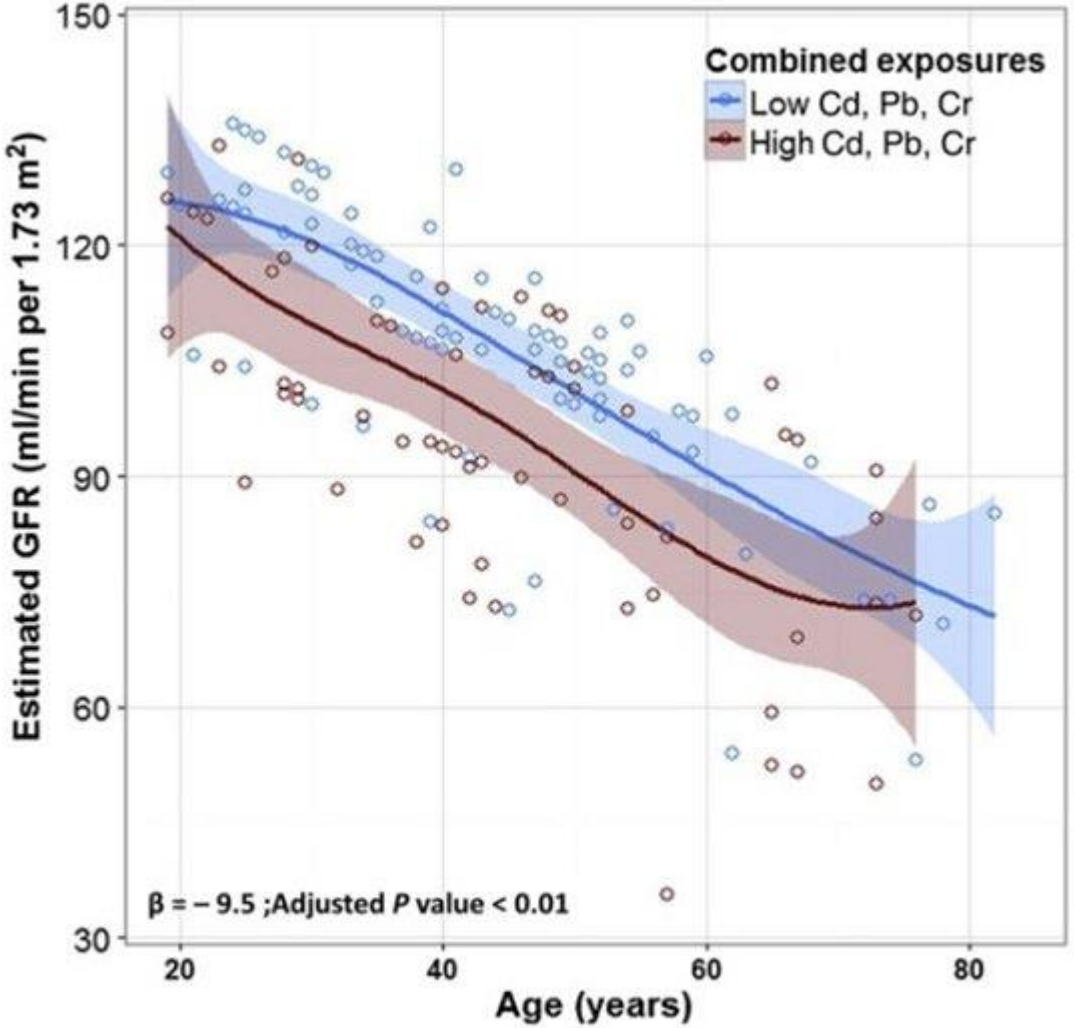


Figure. Decreased estimated glomerular filtration rate (eGFR) with age in participants with multiple metal exposure over the median of the general population

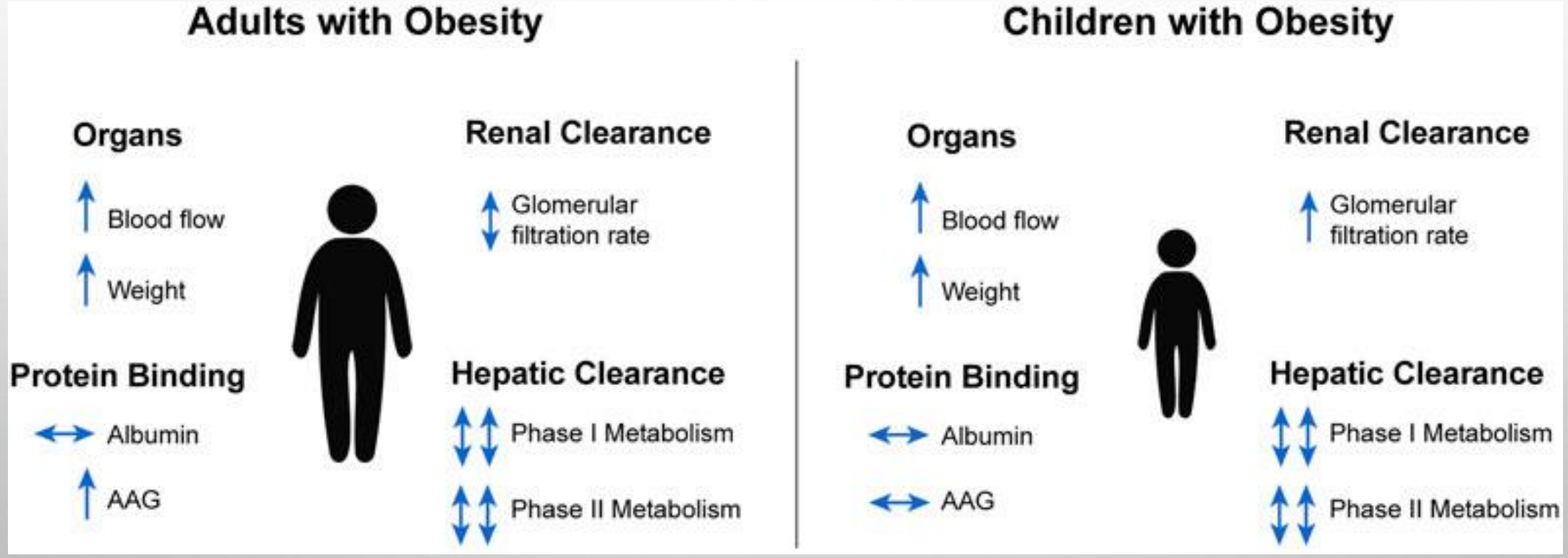
Table 2 Most common drugs causing ADR-related hospital admission in the elderly

Antibacterials[5,18,20]
Anticonvulsants[58]
Antineoplastic agents[5,35]
Antipsychotics[5,35]
Antithrombotics (anticoagulants and antiplatelets)[18,20,23,24,35,58]
Cardiovascular drugs (diuretics,[5,20,22–24,35] cardiac glycosides,[5,18,58] angiotensin-converting enzyme inhibitors,[18,23,24,29,58] beta-blockers,[29,58] antiarrhythmics,[18,24] calcium channel blockers[5])
Corticosteroids[5]
Hypoglycemics[35,58]
Nonsteroidal anti-inflammatory drugs[5,18,22–24,58]

Abbreviation: ADR, adverse drug reaction.

Parameswaran NN et al. Clin Interv Aging 2016;11:497.

Altered pharmacokinetics in obesity



Gerhart JG et al. Frontiers Pharmacol 2022;13:Article 818726.

Altered pharmacokinetics in patients receiving intensive care

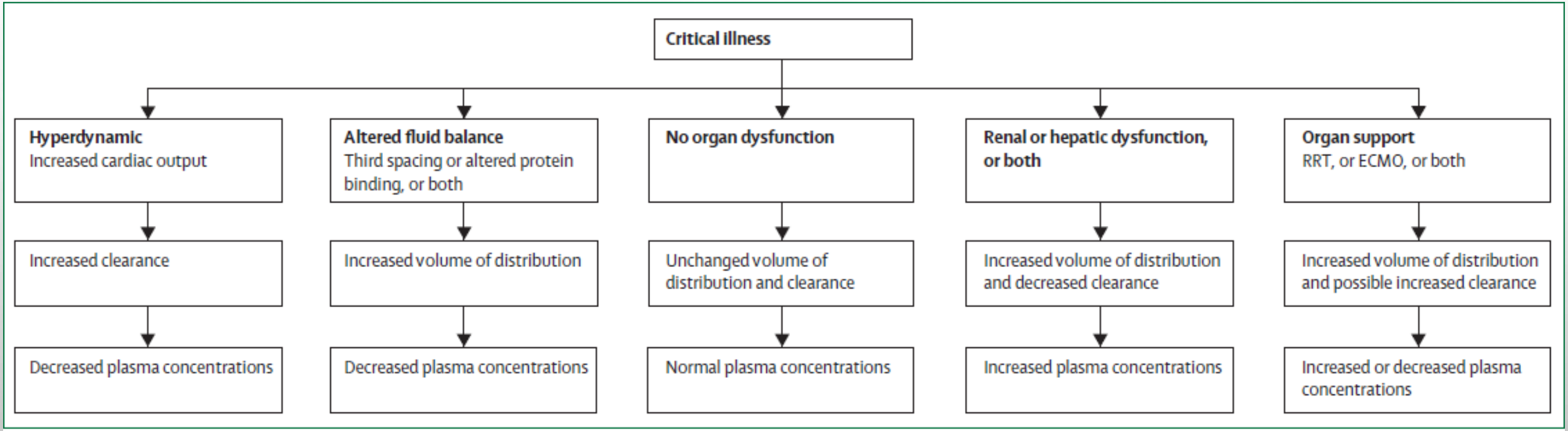


Figure: **The range of altered pathophysiology in patients with critical illness, and its effects on drug concentrations**
RRT=renal replacement therapy. ECMO=extracorporeal membrane oxygenation.

Roberts JA et al. Lancet Infect Dis 2014;14:498.

Prevalence, severity, and nature of preventable patient harm across medical care settings: systematic review and meta-analysis

Maria Panagioti,[1] Kanza Khan,[1] Richard N Keers,[2] Aseel Abuzour,[2] Denham Phipps,[2] Evangelos Kontopantelis,[1] Peter Bower,[1] Stephen Campbell,[1] Razaan Haneef,[3] Anthony J Avery,[4] Darren M Ashcroft[1]

the bmj | *BMJ* 2019;366:l4185 | doi: 10.1136/bmj.l4185

„preventable patient harm"

ABSTRACT

OBJECTIVE

To systematically quantify the prevalence, severity, and nature of preventable patient harm across a range of medical settings globally.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Medline, PubMed, PsycINFO, Cinahl and Embase, WHOLIS, Google Scholar, and SIGLE from January 2000 to January 2019. The reference lists of eligible studies and other relevant systematic reviews were also searched.

REVIEW METHODS

Observational studies reporting preventable patient harm in medical care. The core outcomes were the prevalence, severity, and types of preventable patient harm reported as percentages and their 95% confidence intervals. Data extraction and critical appraisal were undertaken by two reviewers working independently. Random effects meta-analysis was employed followed by univariable and multivariable meta regression. Heterogeneity was quantified by using the I^2 statistic, and publication bias was evaluated.

RESULTS

Of the 7313 records identified, 70 studies involving 337 025 patients were included in the meta-analysis. The pooled prevalence for preventable patient harm was 6% (95% confidence interval 5% to 7%). A pooled proportion of 12% (9% to 15%) of preventable patient harm was severe or led to death. Incidents related to drugs (25%, 95% confidence interval 16% to 34%) and other treatments (24%, 21% to 30%) accounted for the largest proportion of preventable patient harm. Compared with general hospitals (where most evidence originated), preventable patient harm was more prevalent in advanced specialties (intensive care or surgery; regression coefficient b=0.07, 95% confidence interval 0.04 to 0.10).

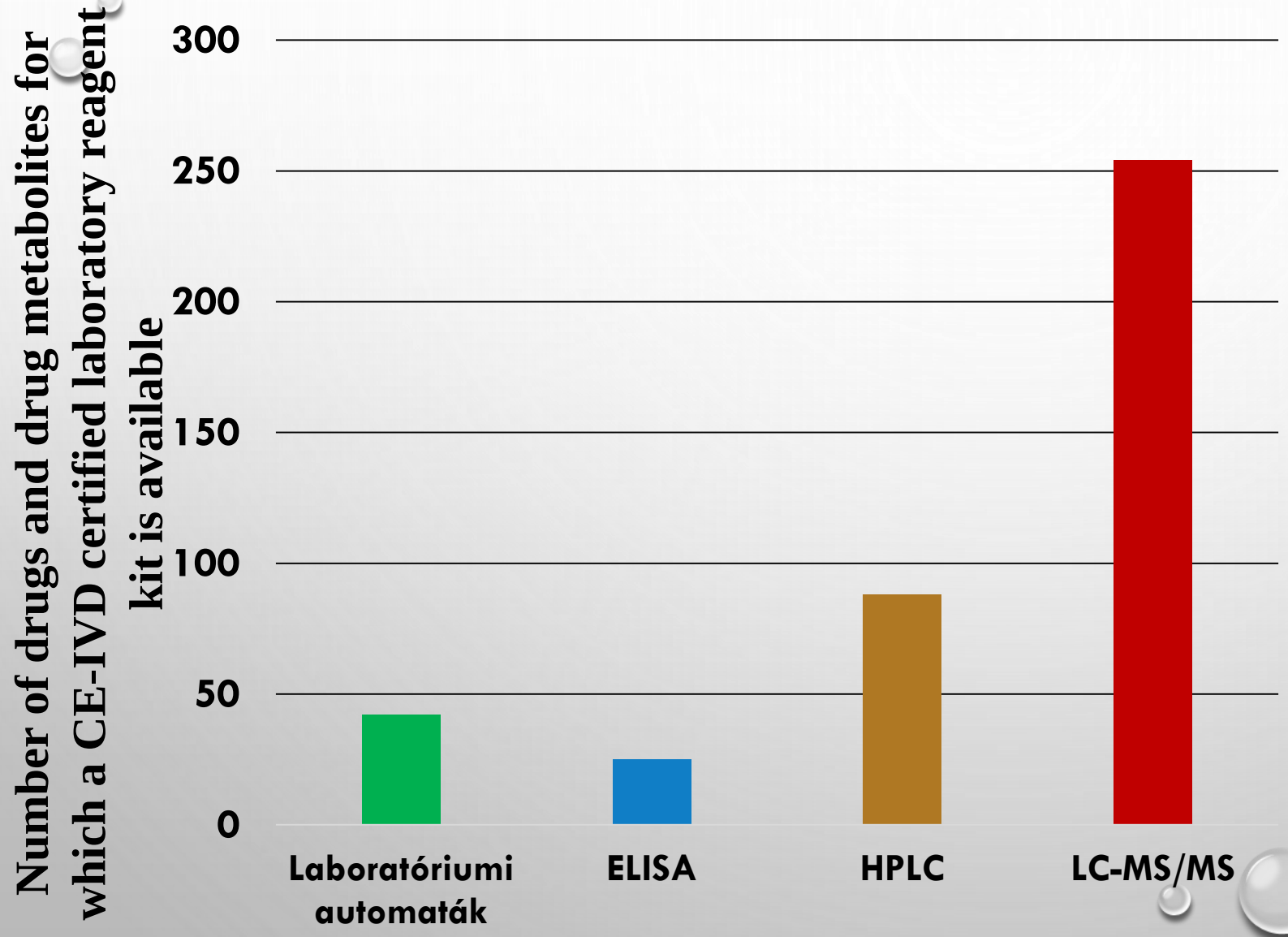
CONCLUSIONS

Around one in 20 patients are exposed to preventable harm in medical care. Although a focus on preventable patient harm has been encouraged by the international patient safety policy agenda, there are limited quality improvement practices specifically targeting incidents of preventable patient harm rather than overall patient harm (preventable and non-preventable). Developing and implementing evidence-based mitigation strategies specifically targeting preventable patient harm could lead to major service quality improvements in medical care which could also be more cost effective.

Introduction

Patient harm during healthcare is a leading cause of morbidity and mortality internationally.[1 2] The World Health Organization defines patient harm as "an incident that results in harm to a patient such as impairment of structure or function of the body and/or any deleterious effect arising there from or associated with plans or actions taken during the provision of healthcare, rather than an underlying disease or injury, and may be physical, social or psychological (eg, disease, injury, suffering, disability and death)."[3]

CLINICAL ASSAY TECHNOLOGIES OF THERAPEUTIC DRUG MONITORING

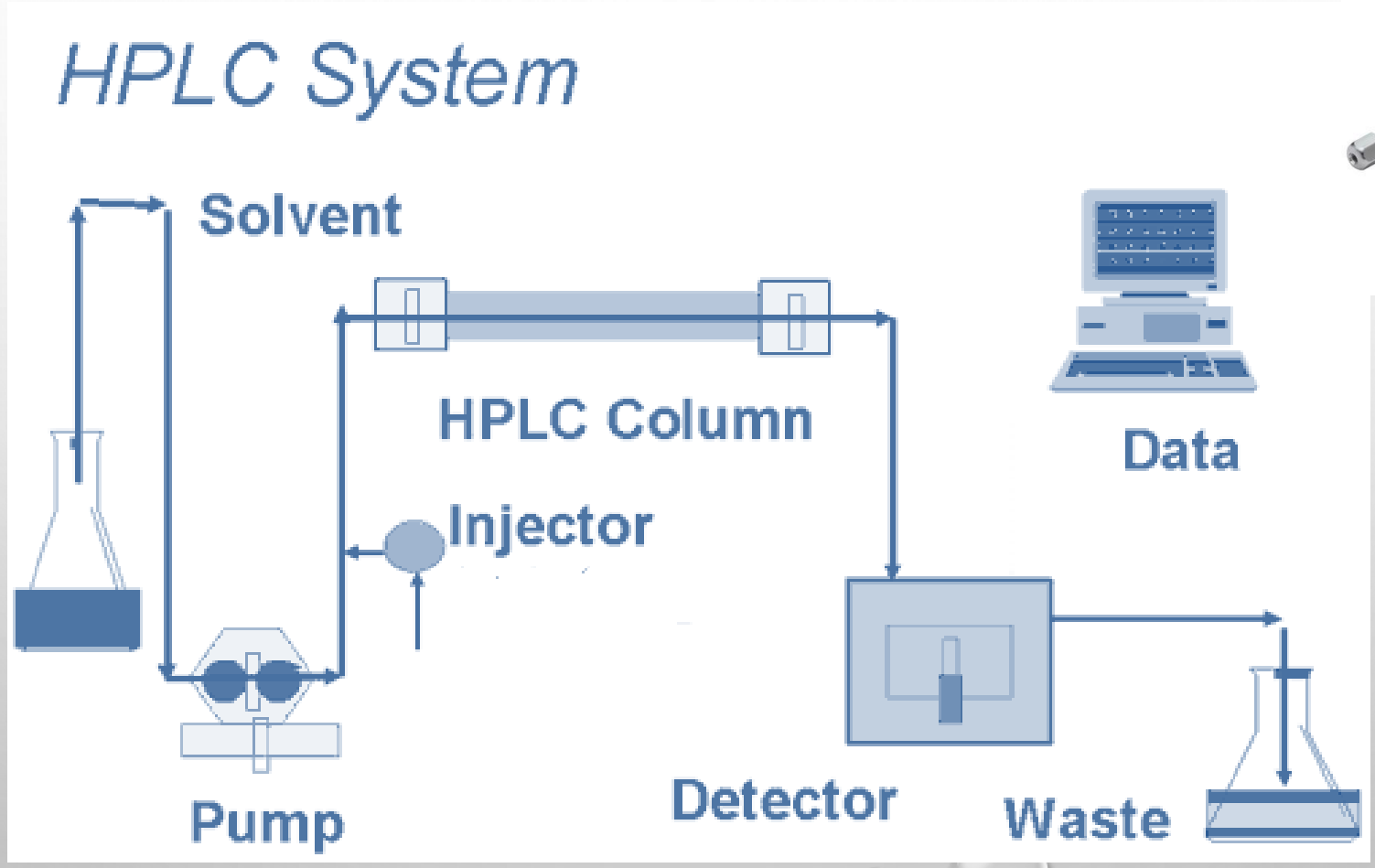


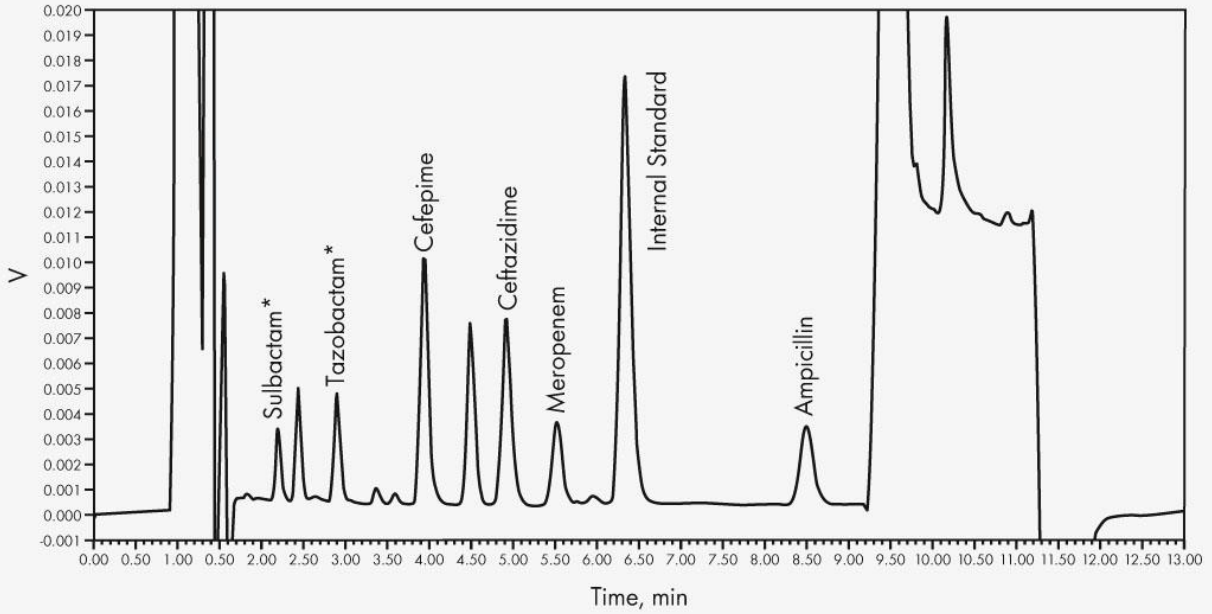
ELISA: enzyme-linked immunosorbent assay

HPLC: high performance liquid chromatography

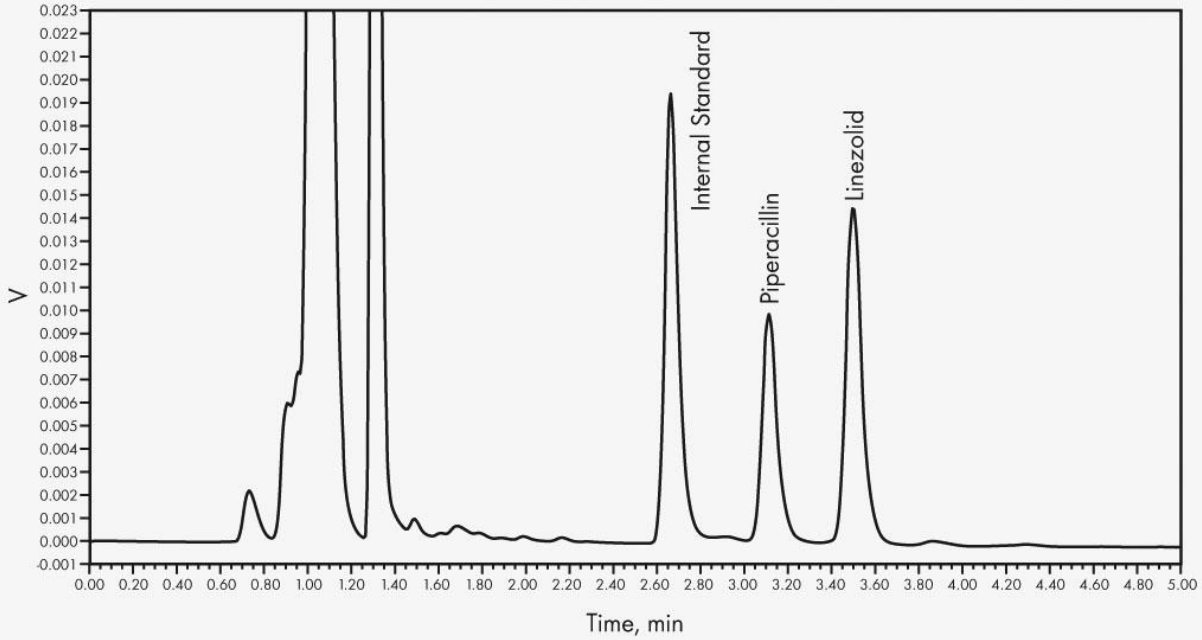
LC-MS/MS: liquid chromatography couples to tandem mass spectrometry

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY



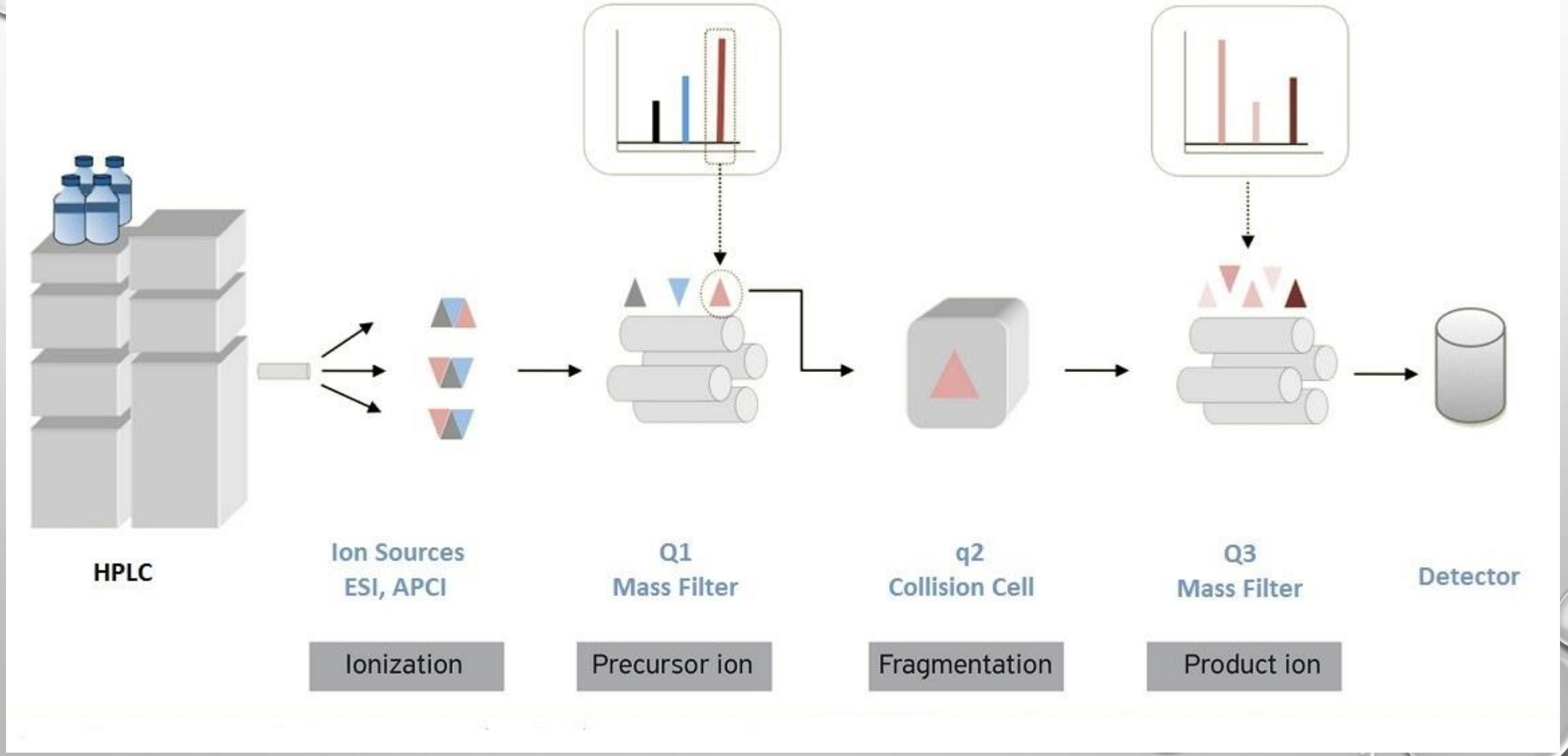


Group 1
Gradient run
210/290 nm

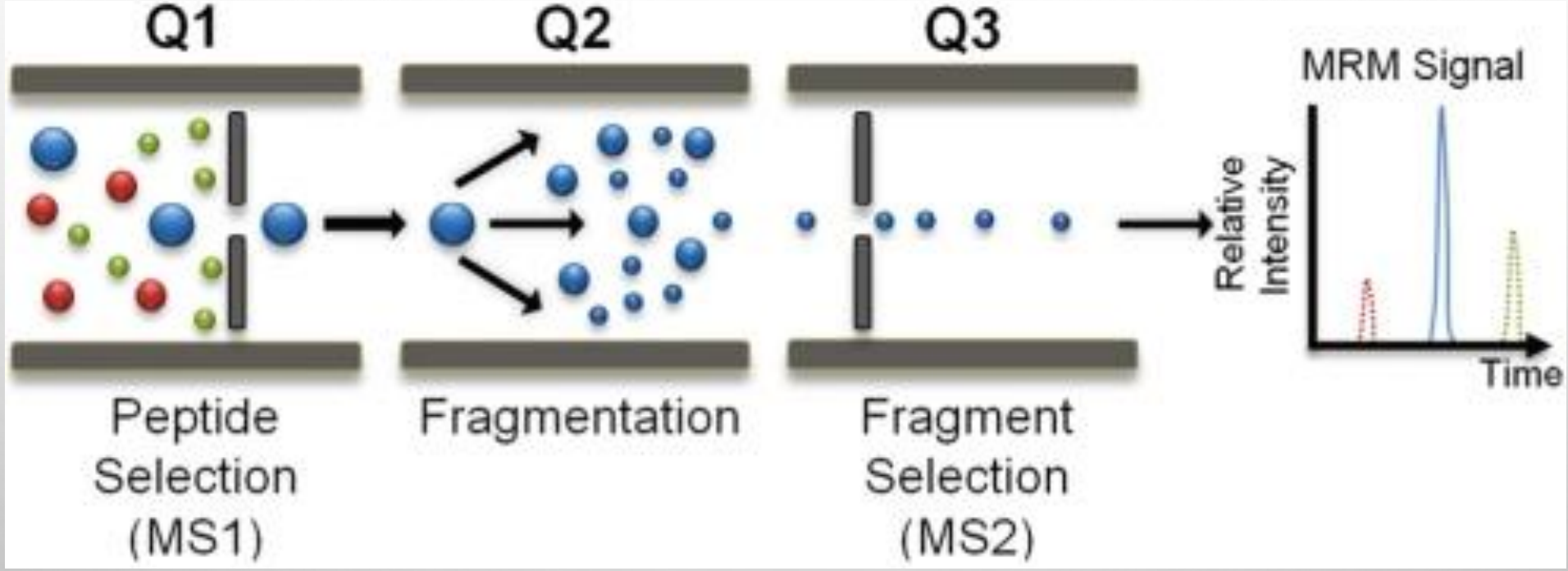


Group 2
Isocratic run
255 nm

LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY



MULTIPLE REACTION MONITORING



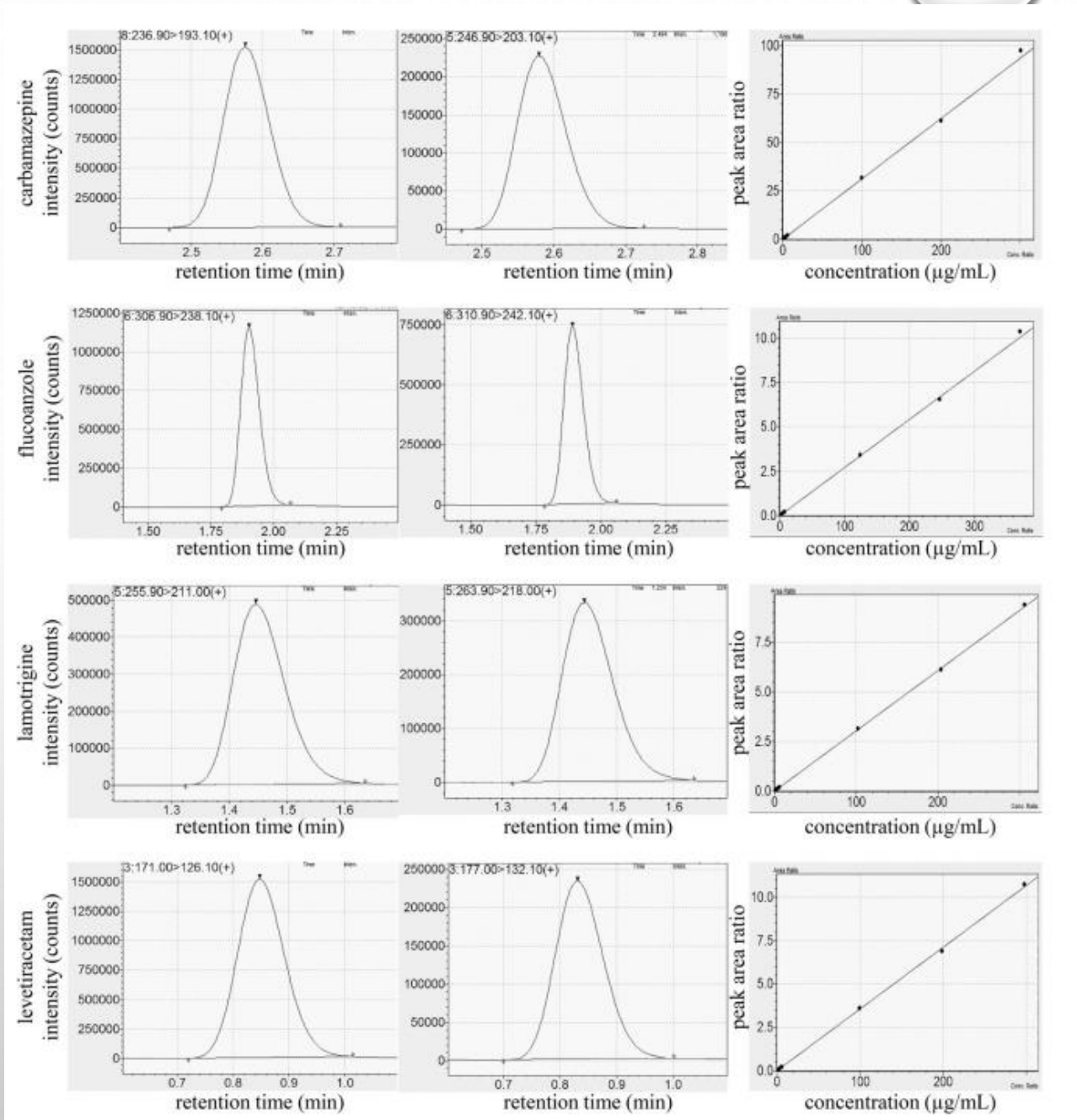


Fig 3. Representative analytical data. Ion chromatograms of the analytes (left) and the internal standards (middle), and representative calibration curves (right) obtained in the experiments.

Karvaly GB et al. Plos One 2020, https://doi.org/10.1371/journal.pone.0229873

QUALITY CONTROL OF TDM MEASUREMENTS

- CALIBRATION OF THE ANALYTICAL PROCEDURE
  - PERFORMED AT THE BEGINNING OF THE MEASUREMENT OF EACH SAMPLE BATCH
  - MATRIX-MATCHED CALIBRATORS
  - CALIBRATORS AND PATIENT SAMPLES ARE PROCESSED IN AN IDENTICAL MANNER
  - CALIBRATION MODEL CONSISTS OF 3-7 DATA POINTS
- INTERNAL CONTROLS
  - RUN ONE OR MORE TIMES, DEPENDING ON THE NUMBER OF SAMPLES
  - MATRIX-MATCHED PREPARATIONS PURCHASED FROM DEDICATED MANUFACTURERS
  - INTERNAL CONTROLS AND PATIENT SAMPLES ARE PROCESSED IN AN IDENTICAL MANNER
  - 2-4 CONCENTRATION LEVELS COVERING THE ANALYTICAL RANGE
- EXTERNAL QUALITY ASSESSMENT SCHEMES
  - TYPICALLY 2 MATRIX-MATCHED SAMPLES ARE SENT BY THE ORGANIZER TO PARTICIPATING LABORATORIES
  - TEST RESULTS TO BE SUBMITTED WITHIN 2 WEEKS OF SAMPLE DELIVERY
  - RESULTS ARE COMPARED TO A TARGET VALUE OR TO A MEASURE OF CENTRAL TENDENCY (MEAN OR MEDIAN) OF ALL RESULTS SENT BY PARTICIPANTS + STATISTICAL EVALUATION OF PERFORMANCE TREND

SAMPLE COLLECTION, SAMPLE

GYÓGYSZERSZINT VIZSGÁLATOKHOZ GYŰJTÖTT MINTÁK

- SZÉRUM (PROKOAGULÁNSSAL BEVONT FALÚ VÉRVÉTELI CSŐBE VETT MINTA FELÜLÚSZÓJA)
- PLAZMA (ANTIKOAGULÁNSSAL BEVONT FALÚ VÉRVÉTELI CSŐBE VETT MINTA FELÜLÚSZÓJA)
- TELJES VÉR: IMMUNSZUPRESSZÁNS SZEREK, B1 ÉS B6 VITAMIN
- MA MÁR MEGVAN A TECHNIKAI LEHETŐSÉG ARRA, HOGY EXTRAVASZKULÁRIS FOLYADÉKTEREKBEN ÉS EXKRÉTUMOKBAN IS MEGBÍZHATÓ VIZSGÁLATOKAT VÉGEZZÜNK
  - PL. CEREBROSPINÁLIS FOLYADÉK, PLEURÁLIS FOLYADÉKGYÜLEM, ASCITES FOLYADÉK, NYÁL, ONDÓ

MINTASTABILITÁS

Fekvőbeteg osztály, mintavételi labor stb.	Gyűjtött minta preklinikai stabilitása (teljes vér, plazma/szérum)
Vizsgáló laboratórium	Vizsgálati minta tárolási stabilitása Méréshez előkészített minták mintaadagoló- stabilitása Méréshez előkészített minta tárolási stabilitása

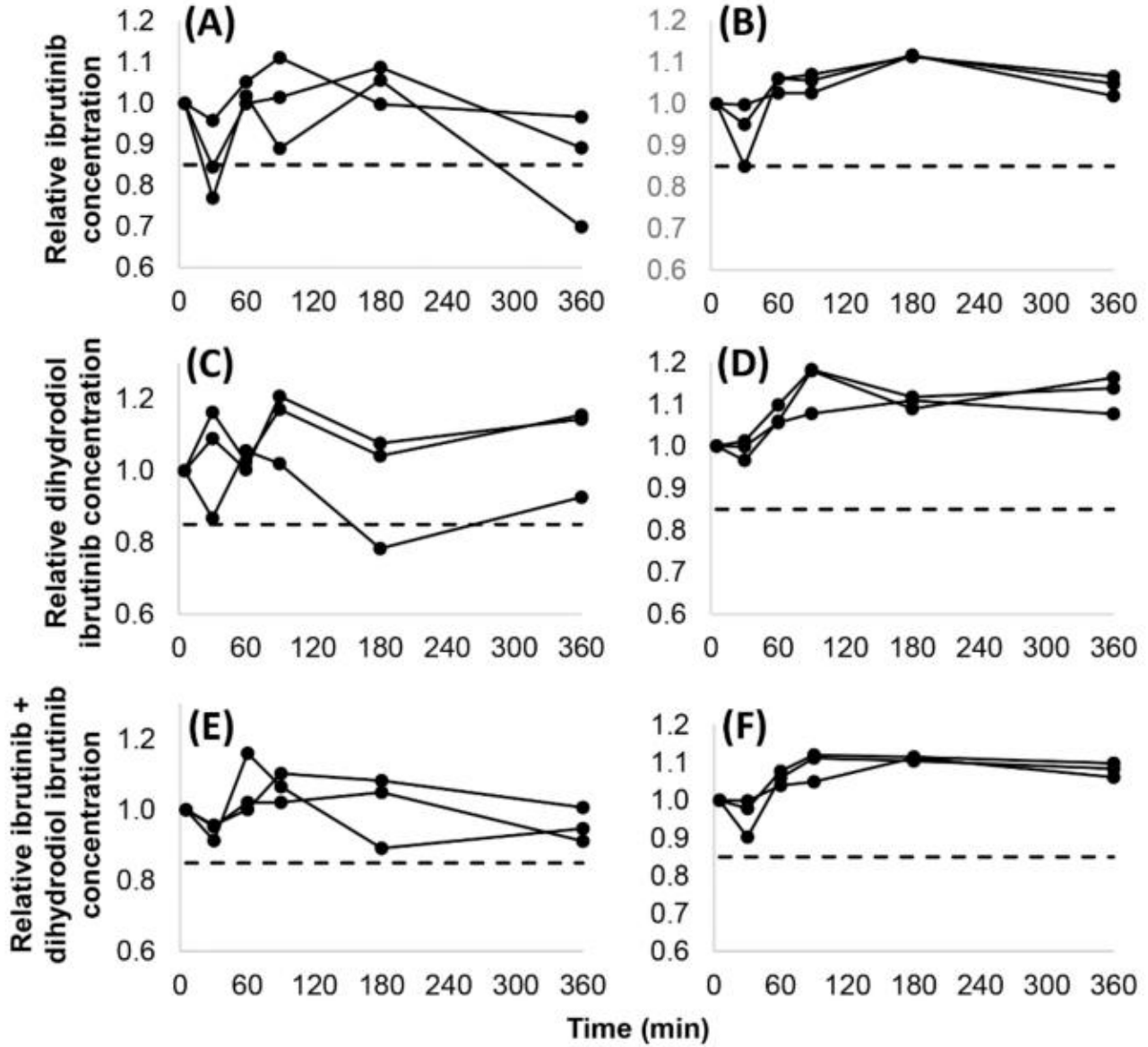


Figure 2. Stability of ibrutinib (**A**,**B**), dihydrodiol ibrutinib (**C**,**D**) and the active moiety (sum of ibrutinib and dihydrodiol ibrutinib concentrations) (**E**,**F**) in whole blood (**A**,**C**,**E**) and in plasma (**B**,**D**,**F**) at 25 °C over 6 h in 3 independent samples. The dashed line (- - -) displays the limit for judging analyte stability as acceptable (0.85).

Karvaly GB et al. Molecules 2022, https://doi.org/10.3390/molecules27154766

MINTA STABILITÁS A VIZSGÁLÓ LABORATÓRIUMBAN

- TÁROLÁSI STABILITÁS A VIZSGÁLATI MINTÁBAN:
  - KÖRNYEZETI HŐMÉRSÉKLET, 2-8 °C, -18 °C ALATT, -70 °C ALATT
- STABILITÁS FAGYASZTÁS-FELOLVASZTÁS SORÁN
- MÉRÉSHEZ ELŐKÉSZÍTETT MINTA TÁROLÁSI STABILITÁSA
- STABILITÁS A MINTAADAGOLÓ TÁLCÁN

ANTIBIOTIKUMOK STABILITÁSA SZÉRUMBAN, PLAZMÁBAN

Gyógyszer	Tartósítás nélkül			Tartósítva		
	RT	2-8 °C	< -18 °C	RT	2-8 °C	< -18 °C
Cefepime	4 h	8 h	2 hónap	24 h	4 nap	Nem vizsgálták
Ceftazidime	12 h	12 h	1 hét	12 h	4 nap	
Linezolid	24 h	4 nap	12 hét	48 h	4 nap	
Meropenem	1 h	3 h	45 nap	6 h	4 nap	
Piperacillin	4 h	24 h	2 hónap	24 h	4 nap	

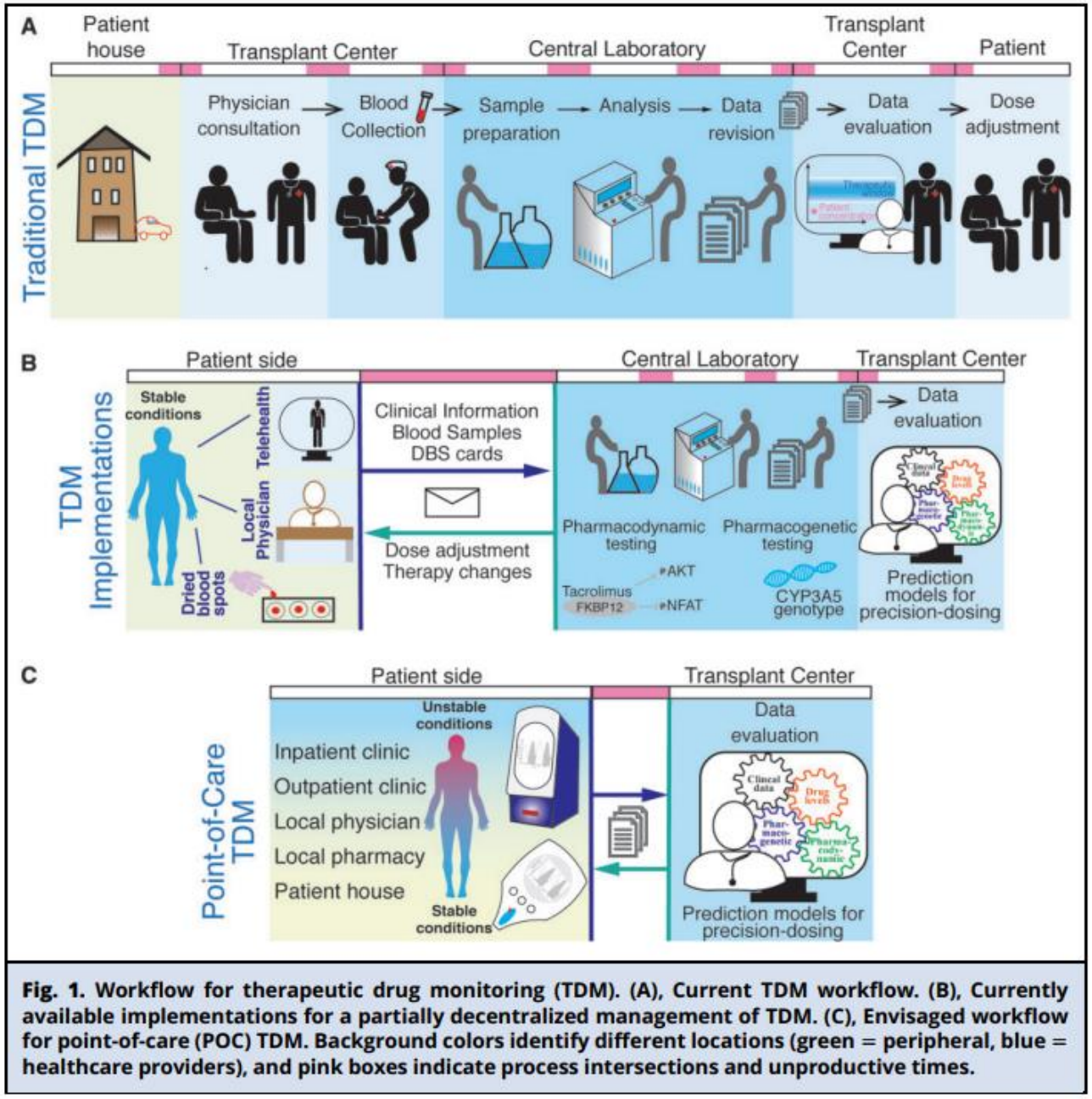


Fig. 1. Workflow for therapeutic drug monitoring (TDM). (A), Current TDM workflow. (B), Currently available implementations for a partially decentralized management of TDM. (C), Envisaged workflow for point-of-care (POC) TDM. Background colors identify different locations (green = peripheral, blue = healthcare providers), and pink boxes indicate process intersections and unproductive times.

Taddeo A. et al. J Appl Lab Med 2020;5:738.

A review of microsampling techniques and their social impact

Benson U. W. Lei [1,2] · Tarl W. Prow [1,2]

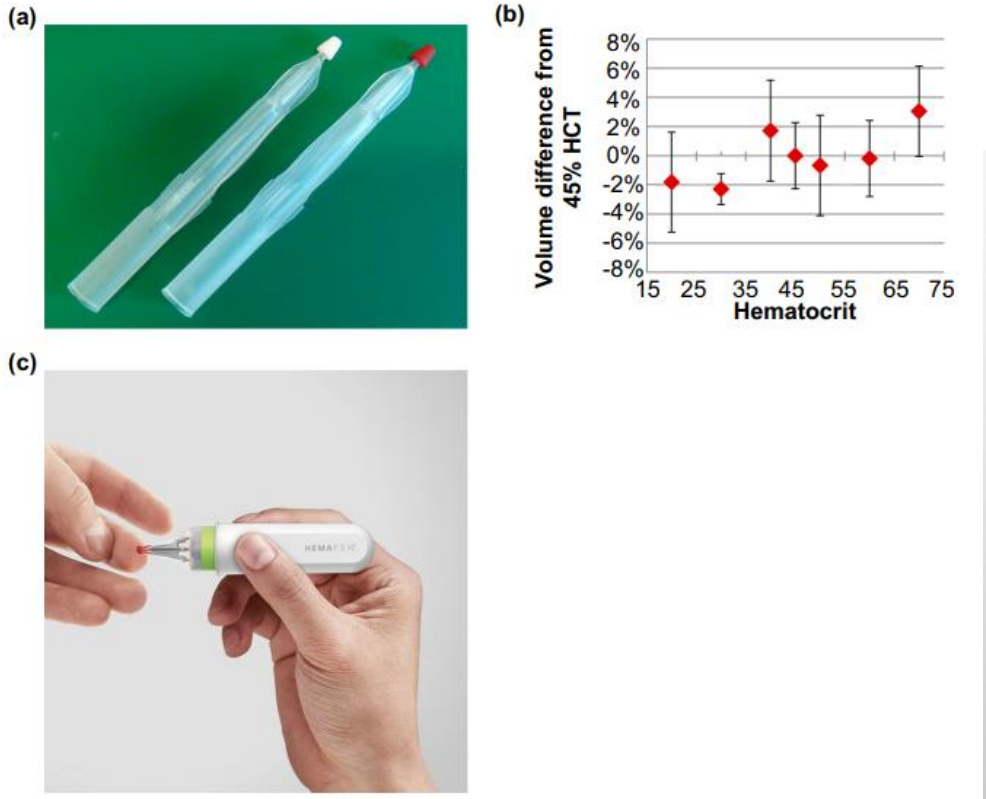


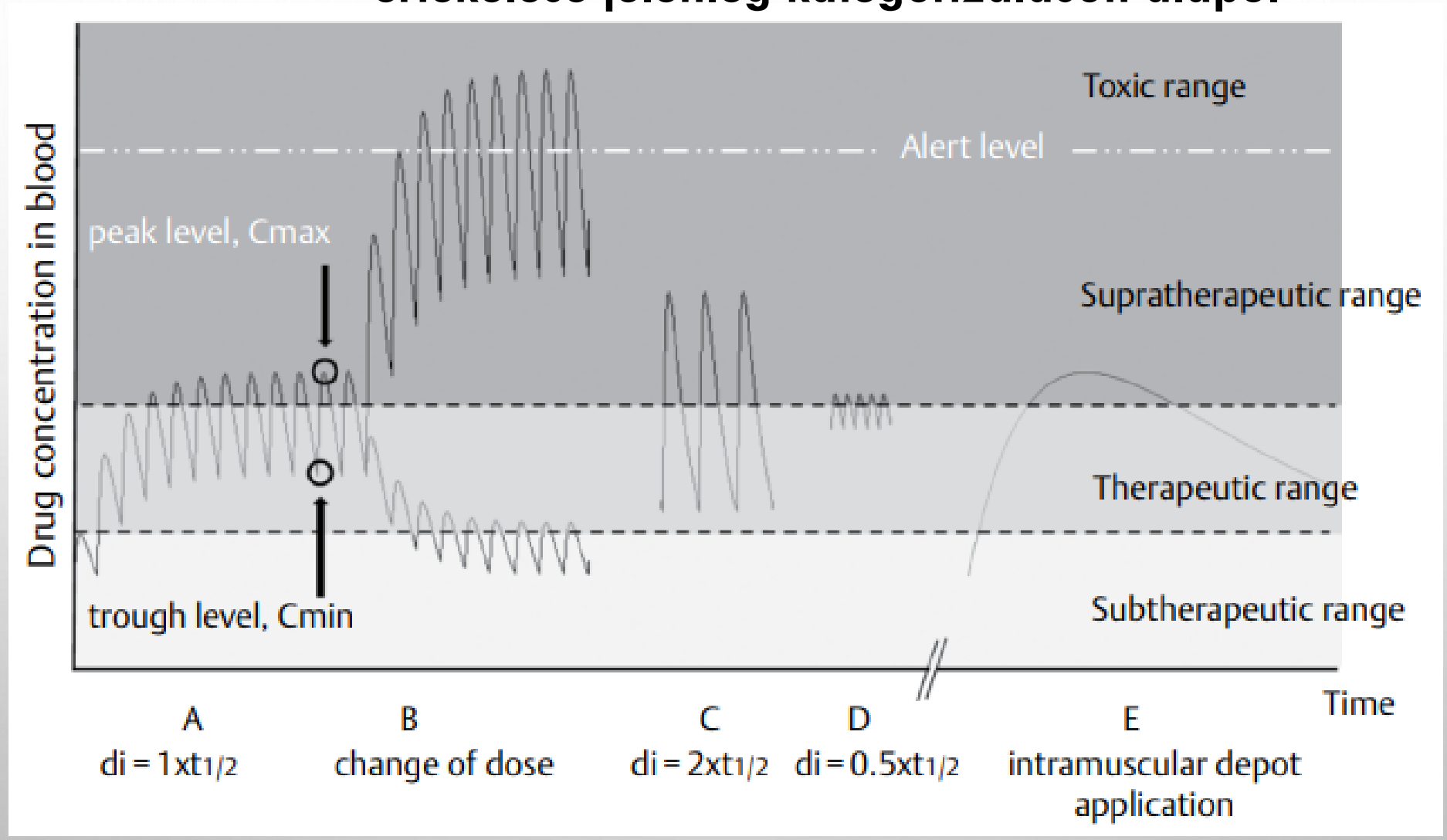
Fig. 4 Blood microsampling with volumetric absorptive microsampling (VAMS) and hemaPEN are emerging techniques for facilitating convenient and accurate sampling. a) VAMS sticks before (left) and after (right) sampling. b) Blood sample recovered from VAMS tip displayed less than 5% volumetric variation when compared to pipetting across the HCT range of 20 to 70%. c) The application of hemaPEN following finger-prick. Pictures retrieved from Denniff and Spooner 2014 and https://www.trajanscimed.com/pages/hemapen

Lei BUW, Prow TW. Biomed Microdev 2019;21:81.

A TDM JELENLEGI SZEMLÉLETE

… és az ezzel kapcsolatos problémák

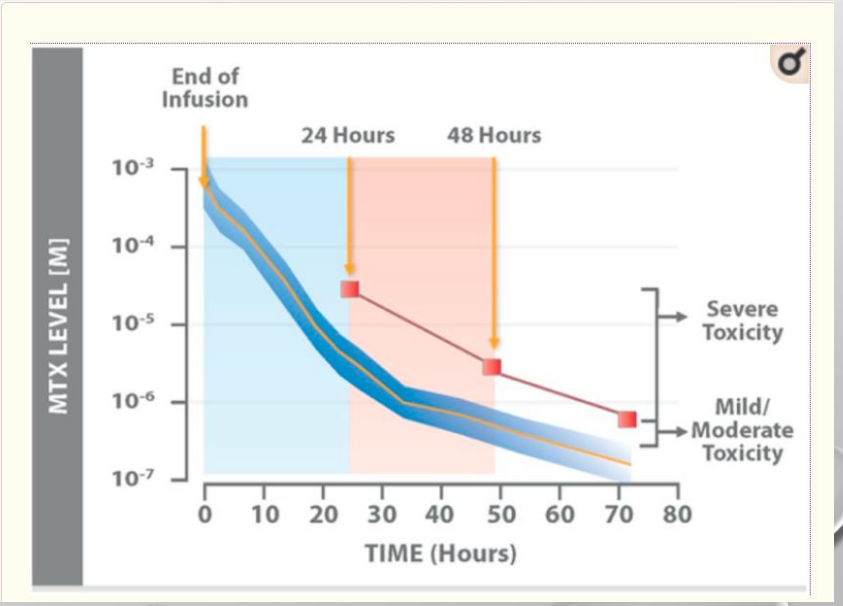
A TDM keretében végzett vizsgálatok eredményeinek klinikai értékelése jelenleg kategorizáláson alapul



Hiemke C et al. Pharmacopsychiatry 2018;51:9.

A GYÓGYSZERSZINT MÉRÉSHEZ LEGTÖBB ESETBEN A KÖVETKEZŐ DÓZIS BEADÁSA ELŐTT VESZIK A MINTÁT (ÚN. MÉLYPONTI, VÖLGY-MINTAVÉTEL)

- KIVÉTELEK:
  - CYCLOSPORINE: KÉT ÓRÁVAL BEADÁS UTÁN (C2)
  - AMINOGLIKOZID ANTIBIOTIKUMOK ÉS VANCOMYCIN: CSÚCS- ÉS MÉLYPONT
  - BUSULFAN: TÖBB MINTAVÉTEL ALAPJÁN AUC-T SZÁMÍTANAK
  - METHOTREXATE: 24 H, 48 H, 72 H BEADÁS UTÁN ⟶



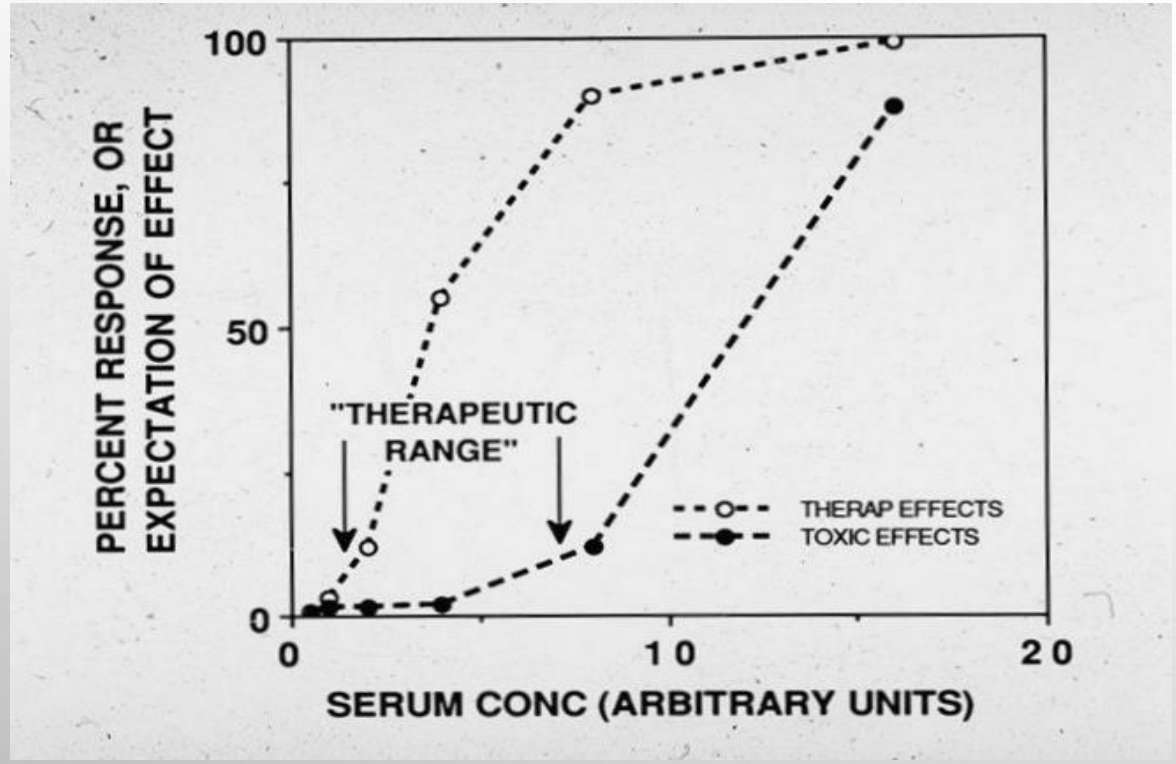
Howard SC et al. Oncologist 2016;21:1471-82.

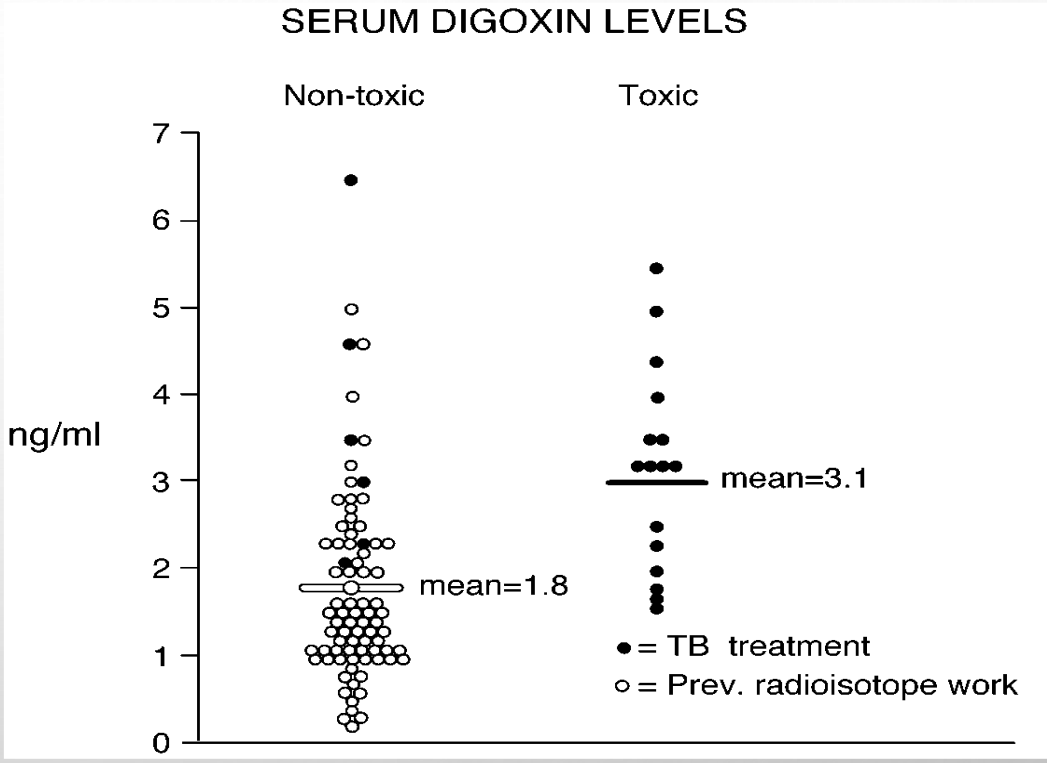
Az eredmények értékelése ún. *terápiás tartomány* alapján történik

- **PÉLDÁK:**
  - LAMOTRIGINE: 3-15 MG/L
  - VANCOMYCIN:
    - CSÚCS – 20-40 MG/L
    - MÉLYPONTI – 5-15 MG/L

- **A TERÁPIÁS TARTOMÁNY NEM FÜGGETLEN A KÖRÜLMÉNYEKTŐL!**
  - VIZSGÁLATI MÓDSZER
  - BETEGPOPULÁCIÓ
  - KLINIKAI ÉS INTÉZMÉNYI SZOKÁSOK → EZEK SZISZTEMATIKUS PREANALITIKAI HIBAFORRÁST JELENTHETNEK

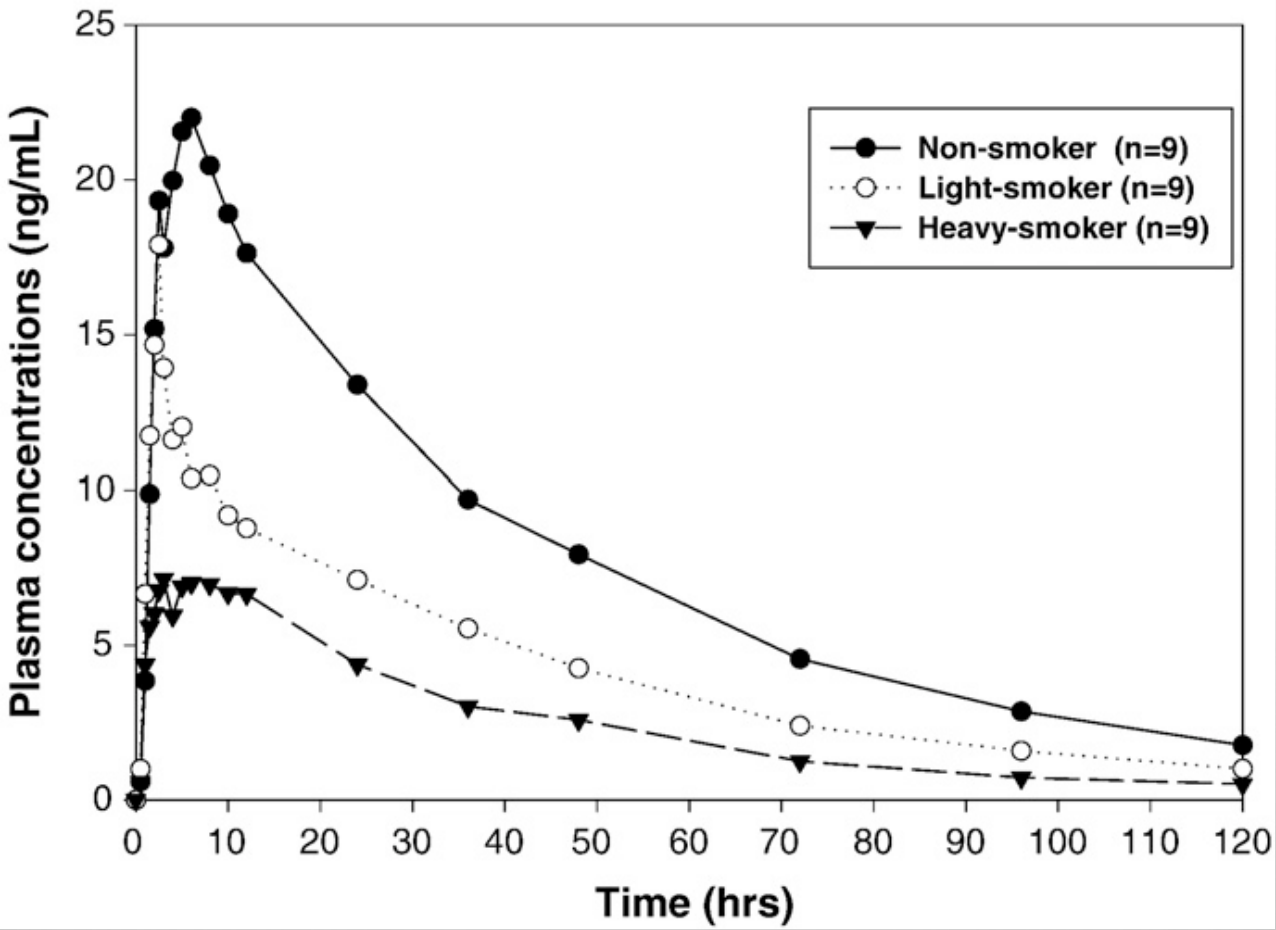
A terápiás tartomány átfedhet a toxikus koncentráció-tartománnyal!





Jelliffe RW, Neely MN (eds): Individualized drug therapy of patients 1st ed. Elsevier, 2017.

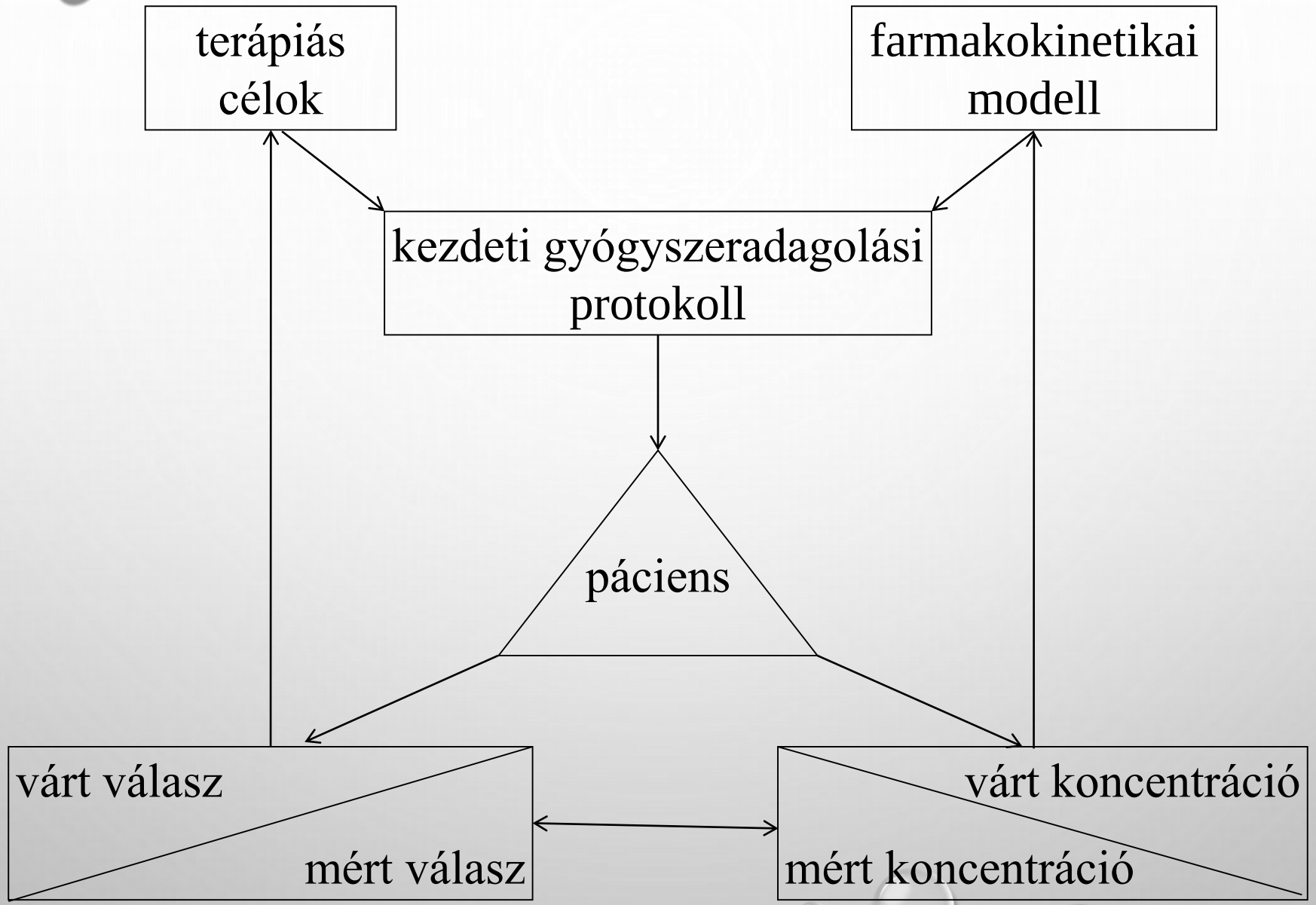
A mélyponti referencia tartományok tartalmazzák a biostatisztikai értelemben legkevésbé releváns információt



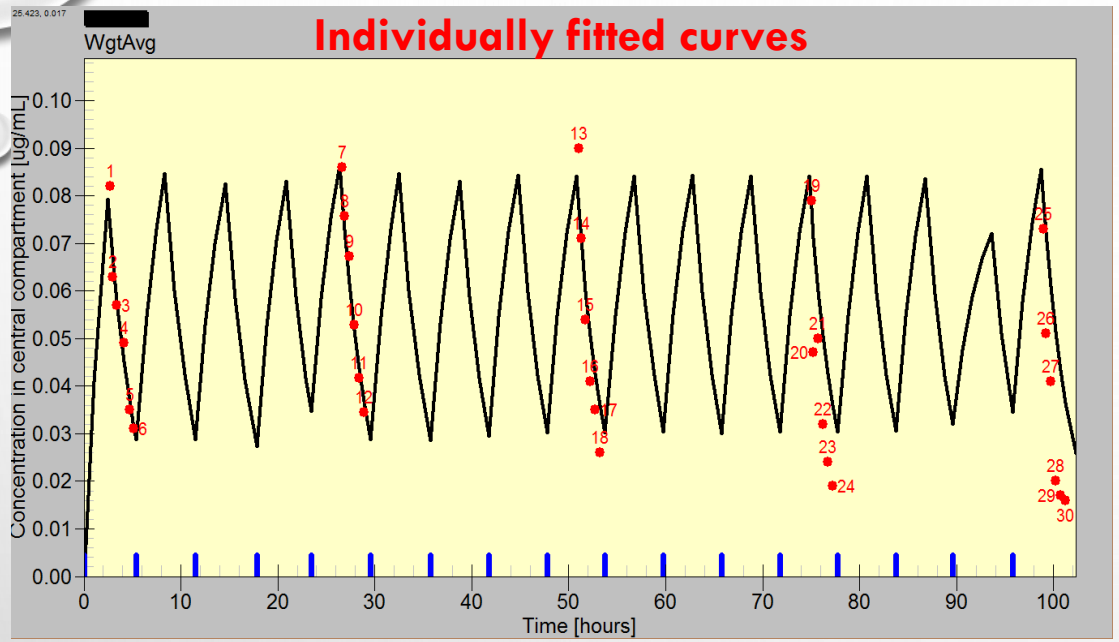
„ … **THERE IS A GAP BETWEEN THE AVAILABLE PHARMACOLOGIC KNOWLEDGE AND ITS UTILIZATION IN HEALTH CARE.** THE NEWEST INITIATIVE TO BRIDGE THIS GAP IS „PRECISION MEDICINE". IT CONSIDERS THE INDIVIDUAL VARIABILITY TO BUILD THE EVIDENCE BASE NEEDED TO GUIDE CLINICAL PRACTICE. **THERAPEUTIC DRUG MONITORING (TDM) IS A PATIENT MANAGEMENT TOOL FOR PRECISION MEDICINE.** IT ENABLES TAILORING THE DOSAGE OF THE MEDICATION(S) TO THE INDIVIDUAL PATIENT BY COMBINING THE QUANTIFICATION OF DRUG CONCENTRATIONS IN BLOOD, INFORMATION ON DRUG PROPERTIES AND PATIENT CHARACTERISTICS."

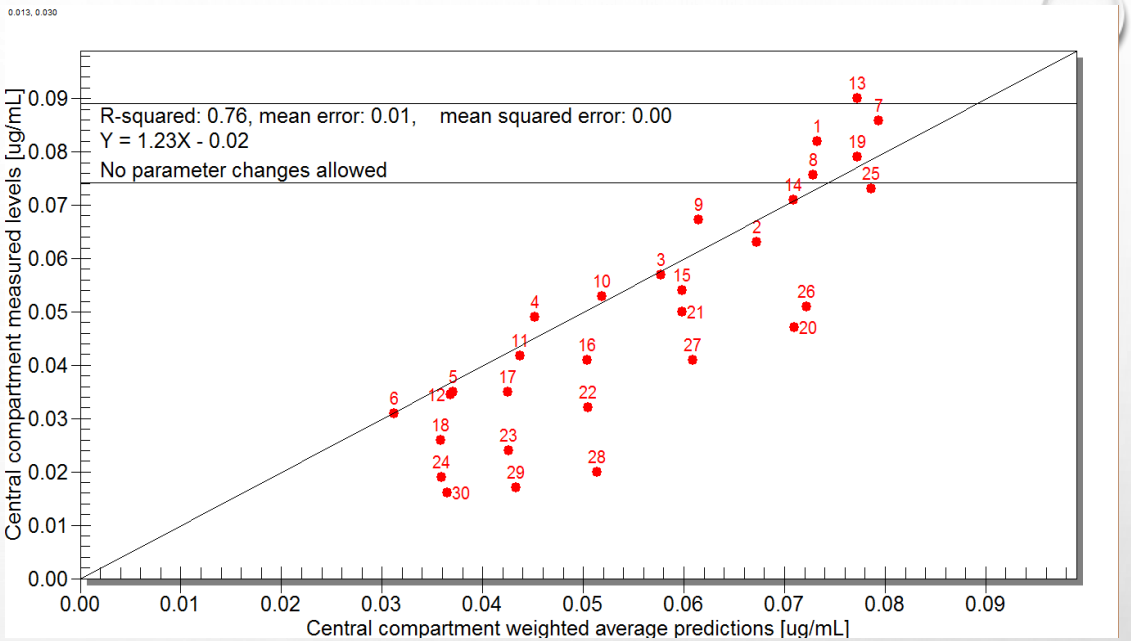
Hiemke C et al. Pharmacopsychiatry 2018;51:9.

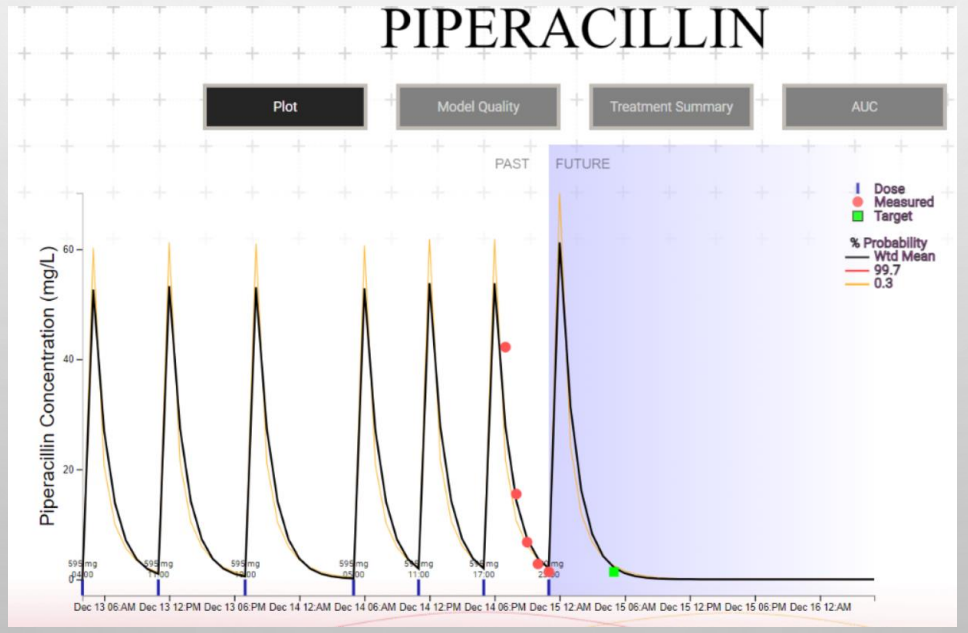
AZ ADAPTÍV VEZÉRLÉSŰ TERÁPIA MODELL



EGYÉNI GYÓGYSZERKINETIKAI MODELL ÉS TERÁPIA TERVEZÉS







EGYÉNI TERÁPIA TERVEZÉS: VANCOMYCIN

Step 1: Patient Data

Sex:

Male | Female

Weight: 75 kg

Height: 175 cm

Age: 25 years

Serum Creatinine: 1 mg/dL

Reset | Next

Step 2: Previous Doses

Previously Administered Dose: 2000 mg

Infusion Length: 2 hours

Dosing Frequency: q12h

Number Doses Given: 1 times

Back | Next

Step 3: Concentrations

Last Vancomycin Concentration: 12 mcg/mL

Hours Drawn Prior to Subsequent Dose: 0.25 hours

Level Drawn Prior To: 2nd Dose

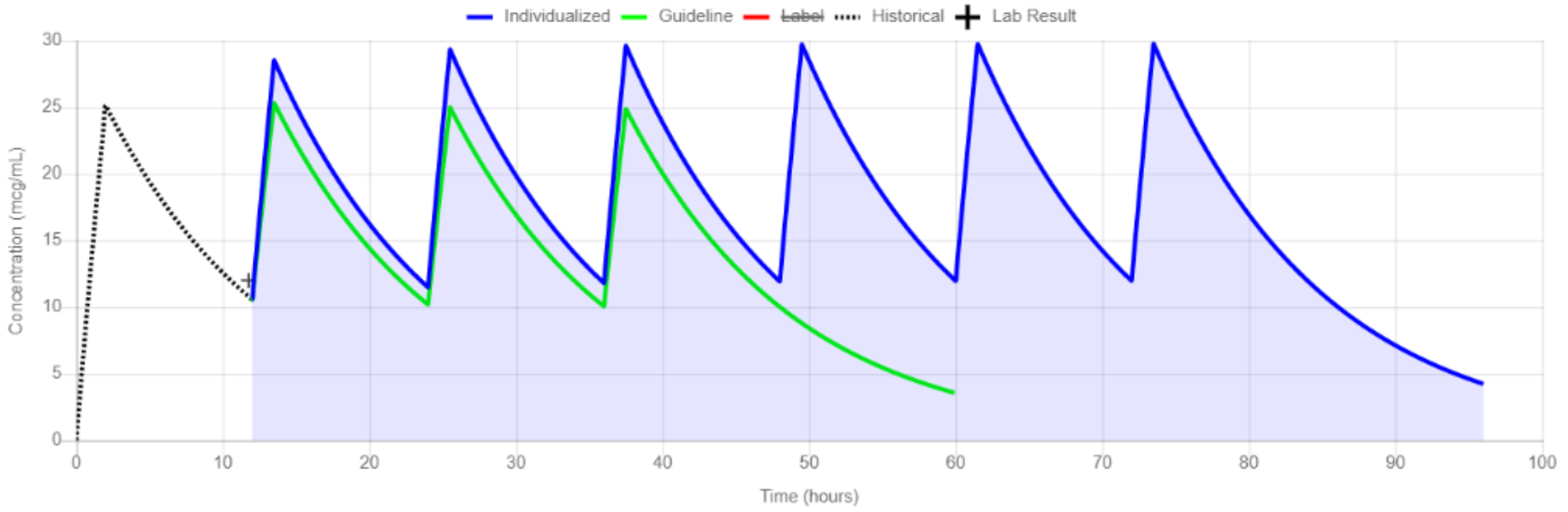
Target AUC:

AUC: 450 mc.h/L

Back | Calculate

AUC Target	Guideline	Label
1500 mg over 1.5 hours twice daily for 3 days	1250 mg over 1.5 hours twice daily for 3 doses	1000 mg over 2 hours twice daily for one day
Peak 29.77 mg/L	Peak 24.87 mg/L	Peak 20.15 mg/L
Trough 11.98 mg/L	Trough 10.01 mg/L	Trough 8.46 mg/L
AUC24 473.52 mg.h/L	AUC24 395.78 mg.h/L	AUC24 328.39 mg.h/L

Get My Free Target AUC Report



Az adatvezérelt klinikai laboratórium modellje

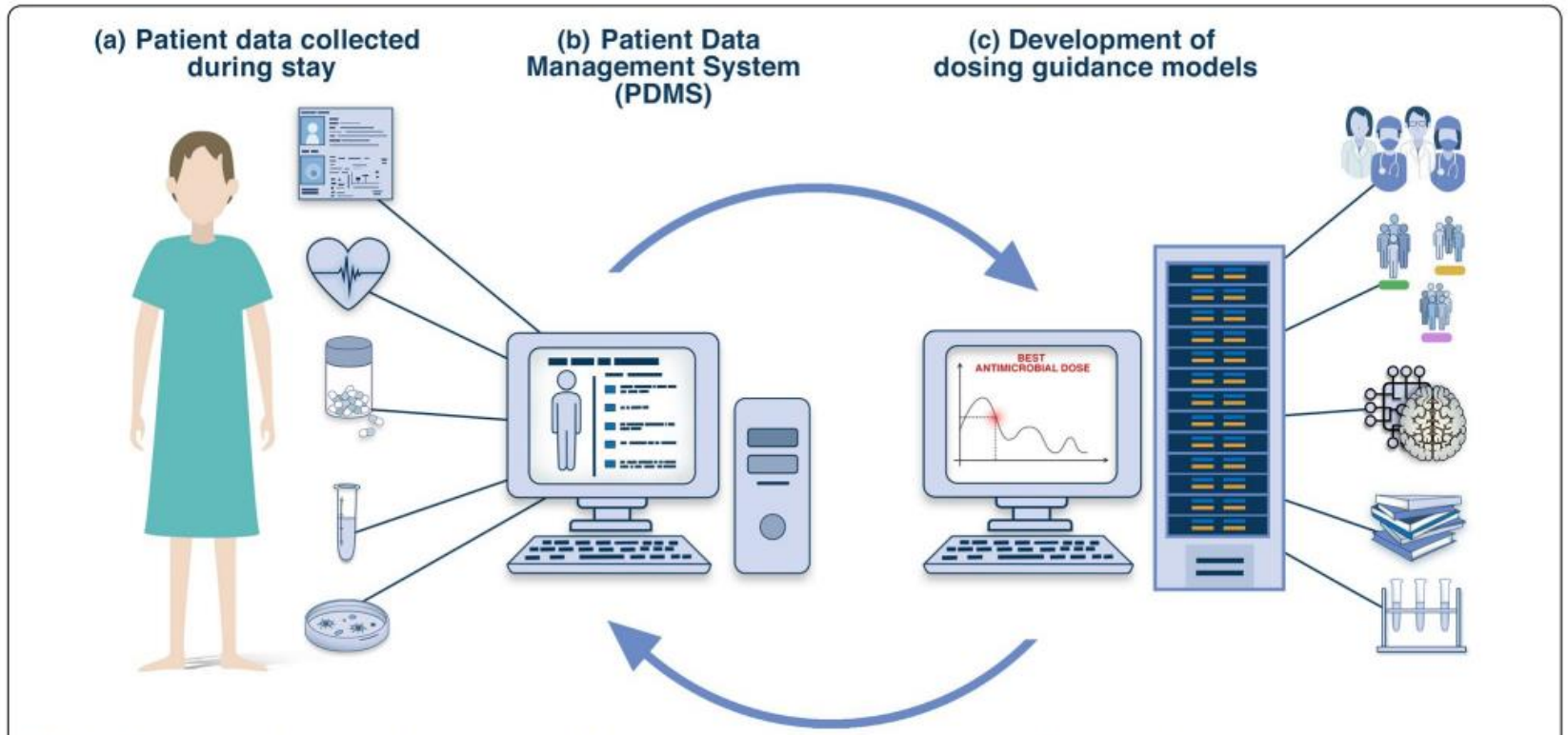


Fig. 1 **a** The variety of data produced during a patient's stay is centrally collected and updated in **b** the patient data management system (PDMS). **c** Dosing guidance models are developed by physicians, pharmacometric modellers and data scientists by combining medical background knowledge, pharmacometrics and machine learning. For baseline model development, already available routinely collected health care data (either from historic datasets or the PDMS) are used. These models are preferably made available through the PDMS, which automatically integrates all the necessary data in the model and produces dosing advice for the patient (**b** → **a**). The generated advice and consequent impact can also be fed back to the model's training set via the PDMS to continuously improve the model (**a** → **b** → **c**)

De Corte T et al. Intensive Care Med 2021;47:1481.

KÖSZÖNÖM A MEGTISZTELŐ FIGYELMET!