Klinische Praxis trifft pharmazeutische Forschung

Möglichkeiten der wissenschaftlichen Zusammenarbeit

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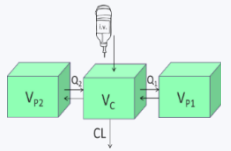
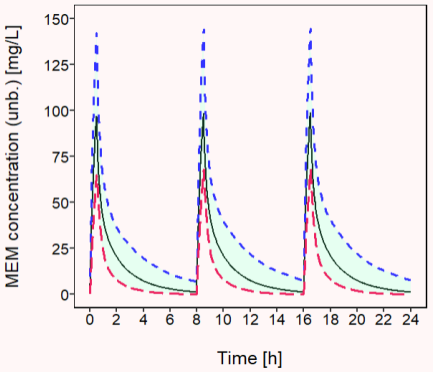
13. Linzer Sommergespräche, 6. Juli 2023





AKH
NYCOMED
Ordens klinikum Linz
Barmherzige Schwestern Elisabethinen

universität wien

Pharmaziestudium
Dipl.arbeit: Klinische Pharmazie

MEDIZINISCHE UNIVERSITÄT WIEN

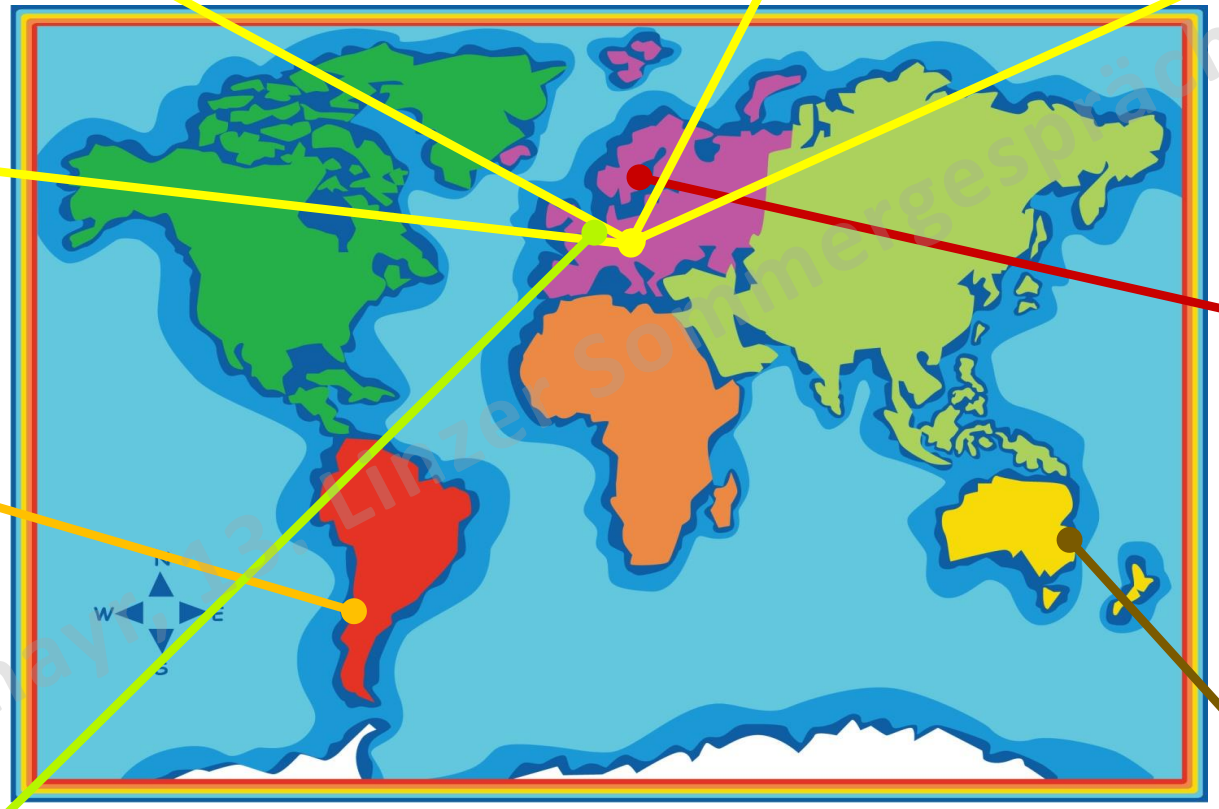
'Research associate'

MEDIZINISCHE UNIVERSITÄT WIEN

Univ.Klinik Klin. Pharmakologie

Assistenzprofessur (ten.)
'Clinical Pharmacometrics'

Apothekerin (Wien)



UNIVERSIDAD DE CHILE
CLINICA DAVILA

UPPSALA UNIVERSITET

'Researcher'
Dept. für Pharmazie
Pharmacometrics, PK/PD group

Freie Universität Berlin

Dept. Klinische Pharmazie

Pharmacometrics PharMetrX & Computational Disease Modelling

Doktoratsprogramm in Pharmakometrie,
Lehre in Klinischer Pharmazie

2 Forschungsaufenthalte:

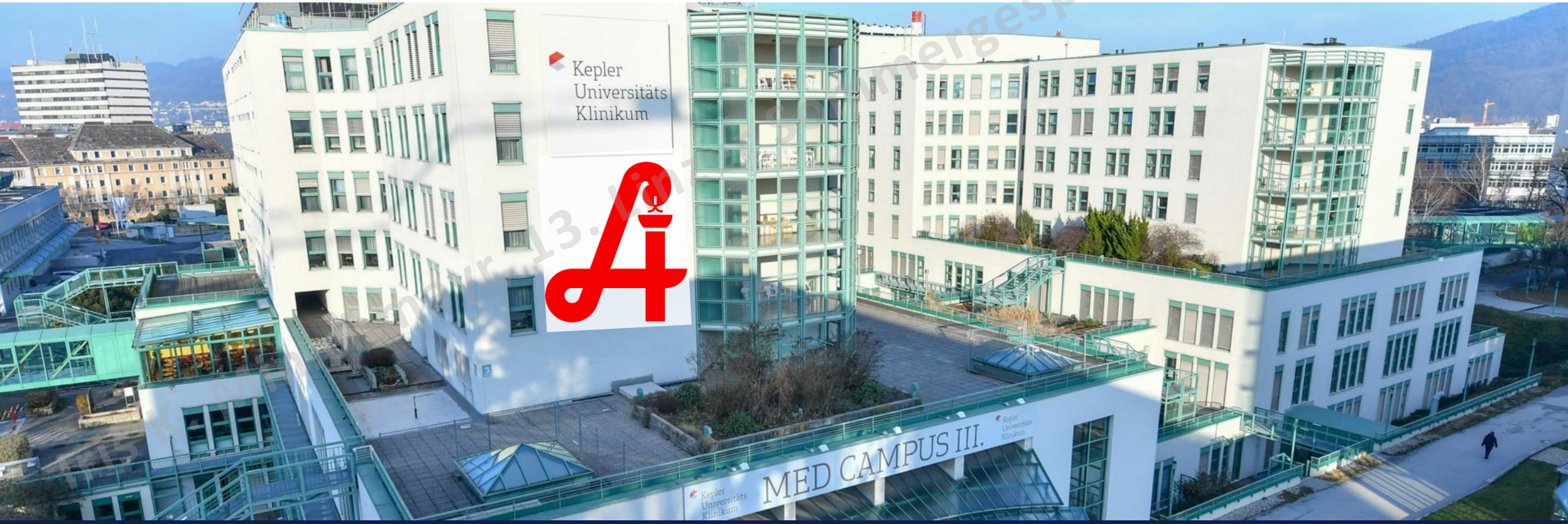
THE UNIVERSITY OF QUEENSLAND AUSTRALIA

RBWH Royal Brisbane and Women's Hospital

Burns, Trauma & Critical Care Research Centre
(Prof. Jason Roberts)

Klinische Praxis

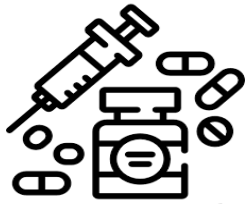
Pharmazeutische Forschung



Klinische Praxis

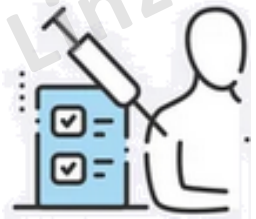
Pharmazeutische Forschung

***Medikations*optimierung**



***Dosis*optimierung und -individualisierung**

Klinische Studien



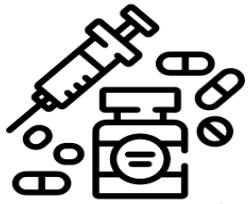
‘Real World’

Arzneimitteltherapiesicherheit, Outcome, Kosteneffektivität

Klinische Praxis

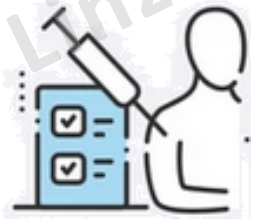
Pharmazeutische Forschung

***Medikations*optimierung**



***Dosis*optimierung und -individualisierung**

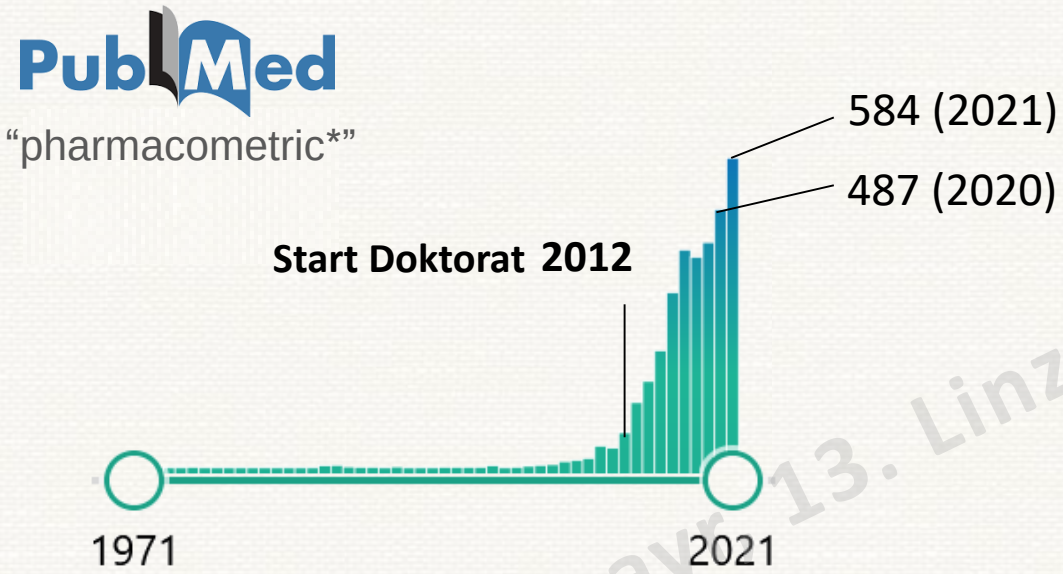
Klinische Studien



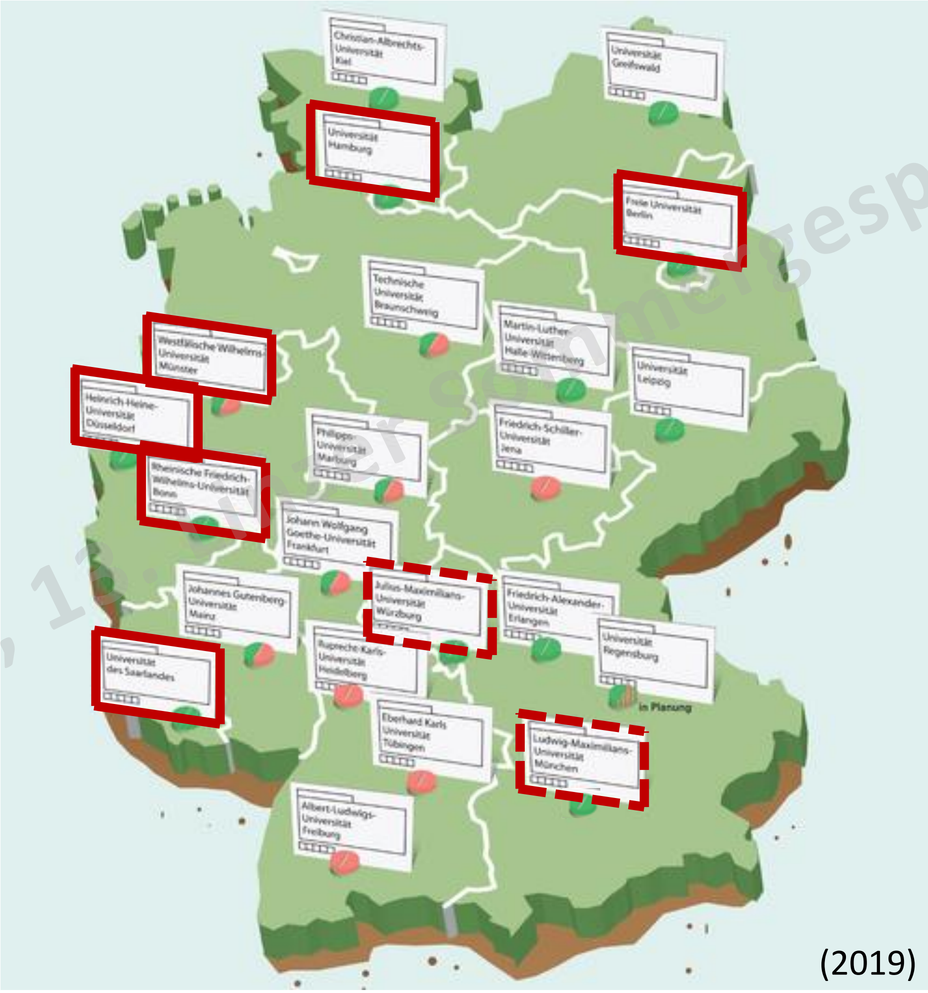
‘Real World’

Pharmakometrie

Pharmakometrie



Klinische Pharmazie ↔ Pharmakometrie



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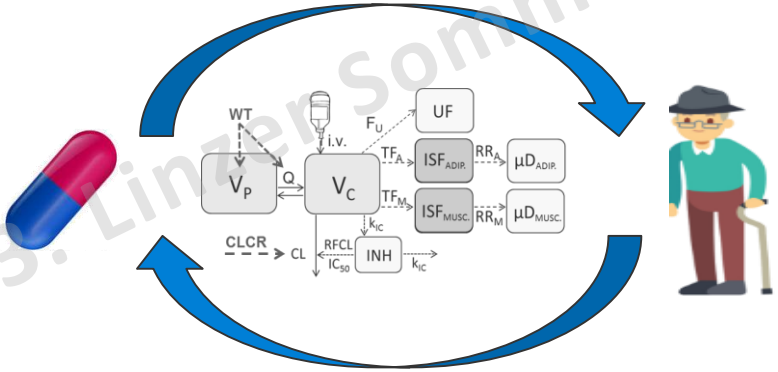
Pharmakometrie

- **Entwicklung** und **Anwendung** von mathematischen/statistischen Modellen

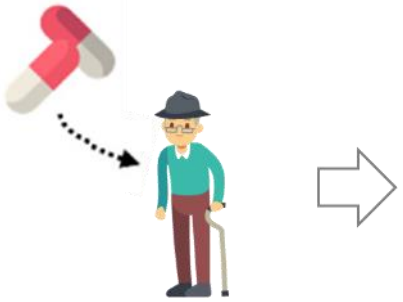
➢ **Quantifizierung** und **Vorhersage** von
Interaktionen zwischen **Arzneistoff – Patient – Krankheit**

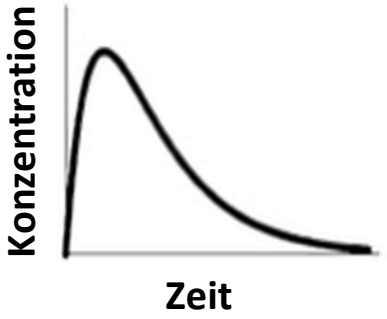


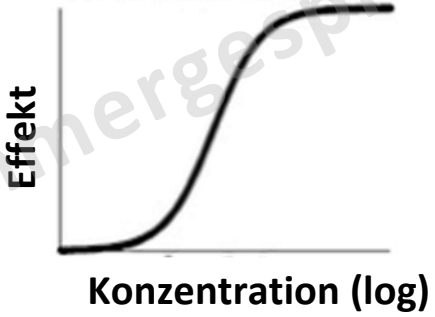
- **Wirksamkeit**
- **Toxizität**
- **Krankheitsverläufe**

Besseres Verständnis von **pharmakokinetischen, pharmakodynamischen** und **Krankheit**s-Aspekten

PK ↔ PD ↔ PKPD



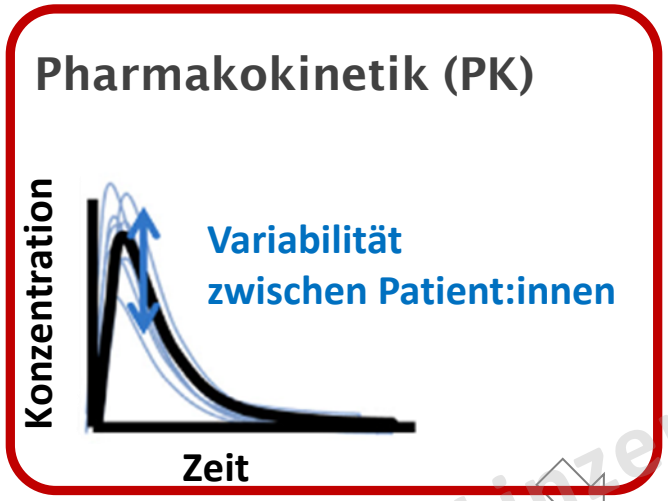


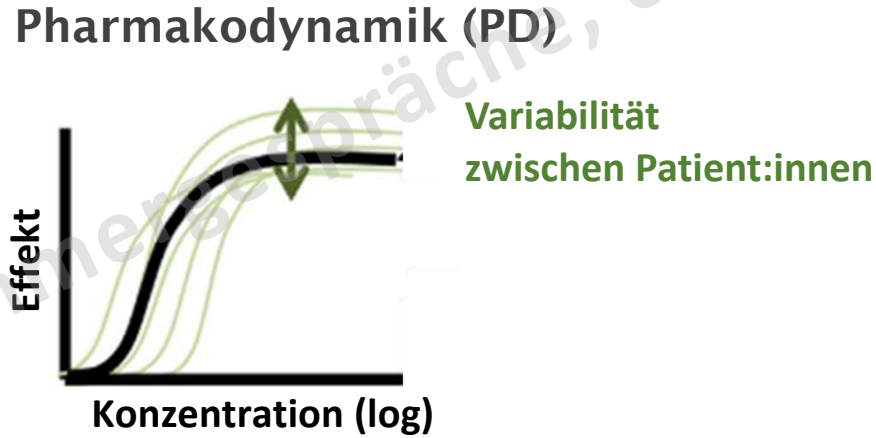


PK/PD

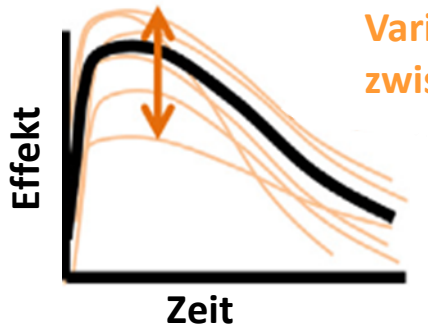
Source: Derendorf and Meibohm 1999

PK ↔ PD ↔ PKPD



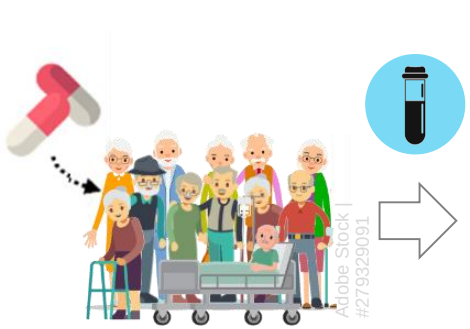


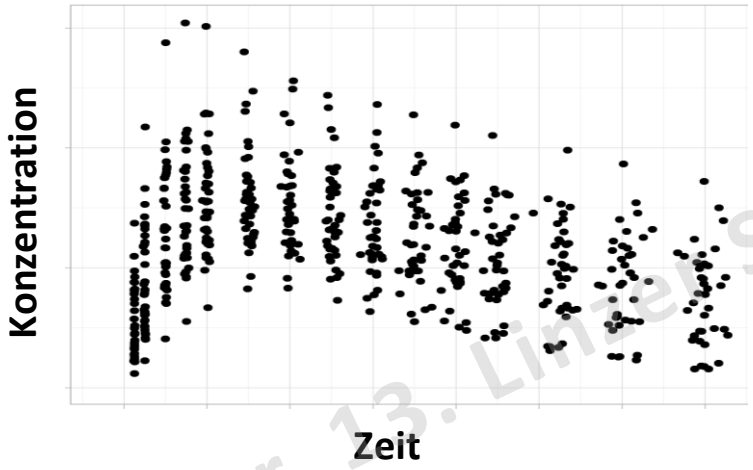
PK/PD



Irurzun-Arana. Trends Pharmacol. Sci. 41: 882 (2020)

Populationspharmakokinetisches Modell





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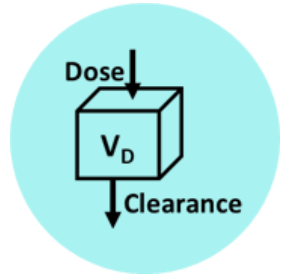
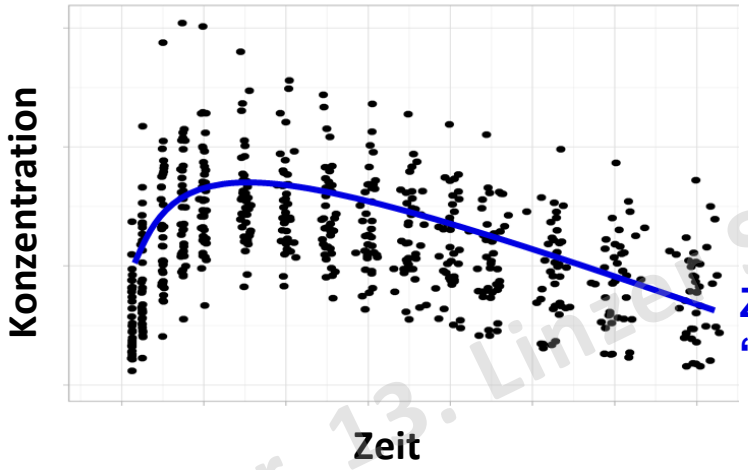
Populationspharmakokinetisches Modell



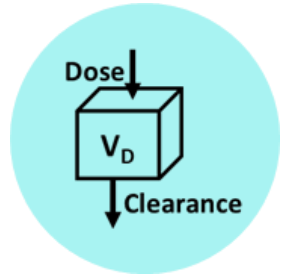
Modell beschreibt Daten

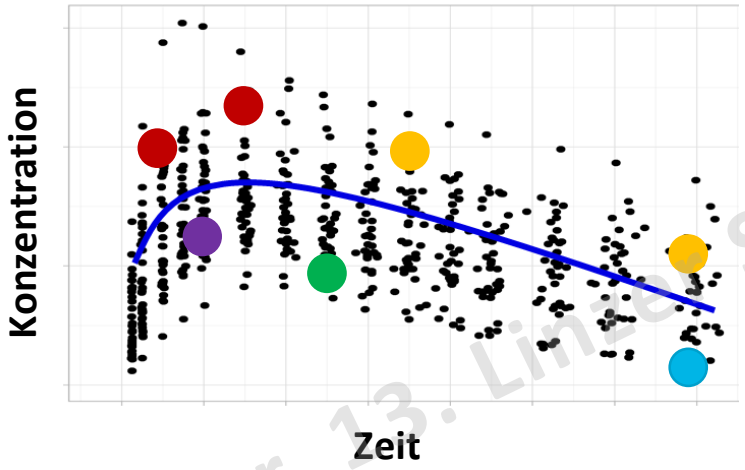


- **Gleichzeitige** Analyse **aller Daten aller Patient:innen**

Zentrale Tendenz,
“Typischer Patient”

Populationspharmakokinetisches Modell

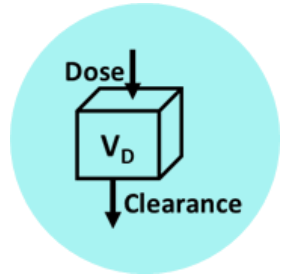


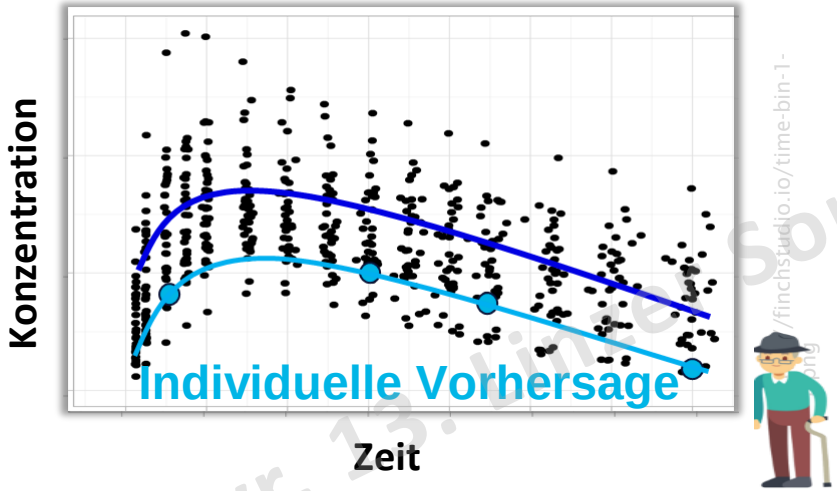


https://finchstudio.io/time-bin-1-1.png

- **Gleichzeitige** Analyse **aller Daten aller Patient:innen**
  - **Dichte und spärliche Daten**
    - → **Klinische Routinedaten (!)**

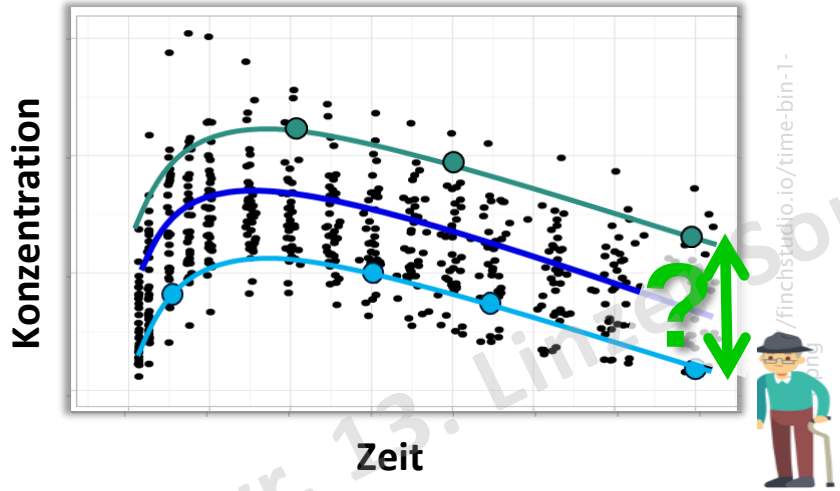
Populationspharmakokinetisches Modell





- **Gleichzeitige** Analyse **aller Daten aller Patient:innen**
- **Information über individuelle:n Patient:in bleibt erhalten**
- **Quantifizierung von Variabilität** zwischen Patient:innen

Populationspharmakokinetisches Modell



- **Gleichzeitige** Analyse **aller Daten aller Patient:innen**
- **Information über individuelle:n Patient:in bleibt erhalten**

- **Erklärung von Variabilität** zwischen Patient:innen mit **Kovariaten**

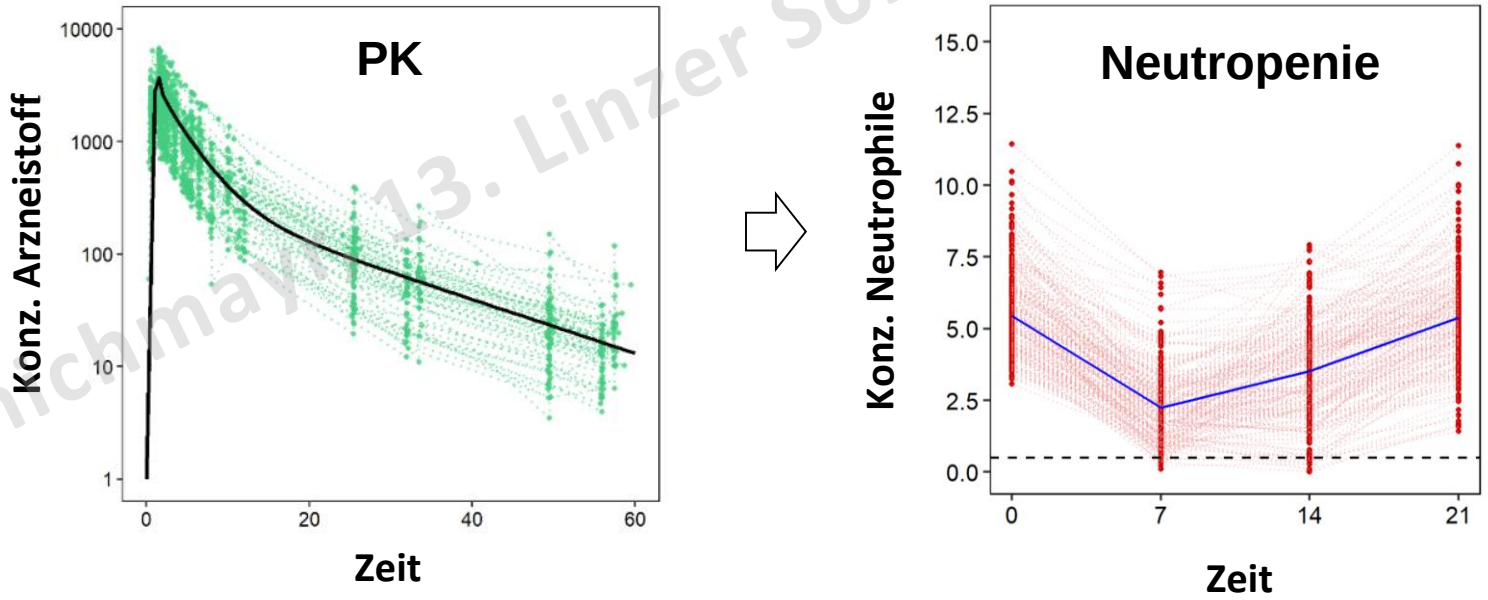
→ **Dosisindividualisierung**

Alter
Nierenfunktion
Geschlecht
Körpergewicht

PopulationsPK/**PD (pharmakodynamische) Modelle**

- **Erwünschte und unerwünschte Wirkungen**
- Verlauf von Biomarkern

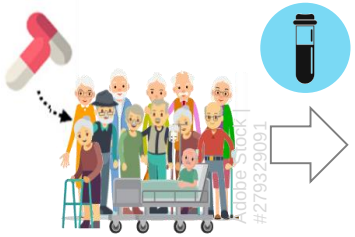
Neutropenie nach Chemotherapie

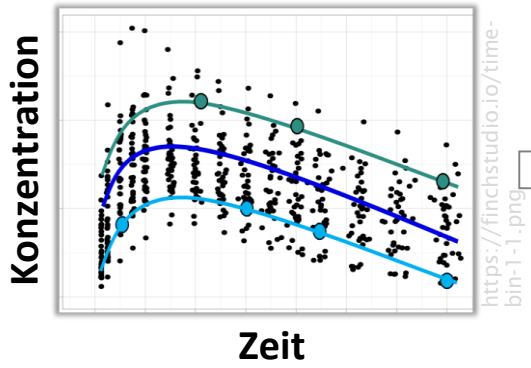


Minichmayr IK, Karlsson MO, Jönsson S. Pharm Res. 2021 Apr;38(4):593-605.

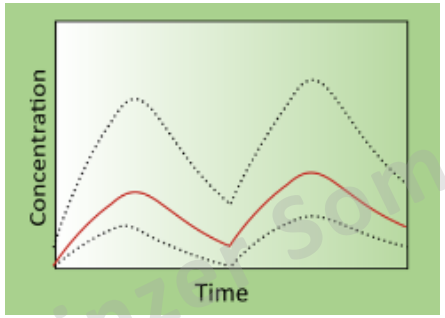
PopPK Modellierung **und Simulation**

Populations-PK Modell





Simulationen
“Was wäre wenn...?”



Vorhersage
neuer Szenarien

Studie:

- Oral Gabe
- 500 mg
- Alle 12 Stunden

Was wäre wenn **i.v. Gabe**?

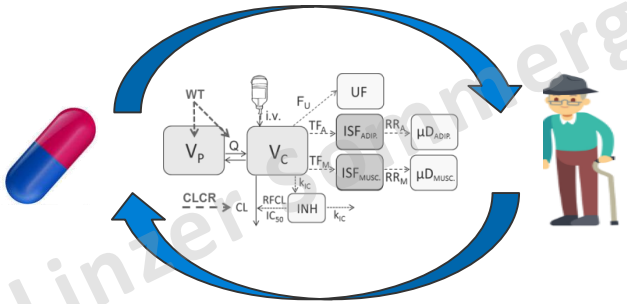
Was wäre wenn **Nierenfunktion** ↓?

Was wäre wenn **alle 8 Stunden**?

Was wäre wenn **750 mg**?

Pharmakometrie

➢ **Quantifizierung** und **Vorhersage** von
Interaktionen zwischen **Arzneistoff – Patient – Krankheit**



Entwicklung
***neuer* Arzneistoffe**

Zulassung
***neuer* Arzneistoffe**

Bessere Anwendung
***zugelassener* Arzneistoffe**

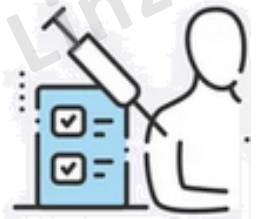
Klinische Praxis

Pharmazeutische Forschung

*Medikations*optimierung

***Dosis*optimierung und -individualisierung**

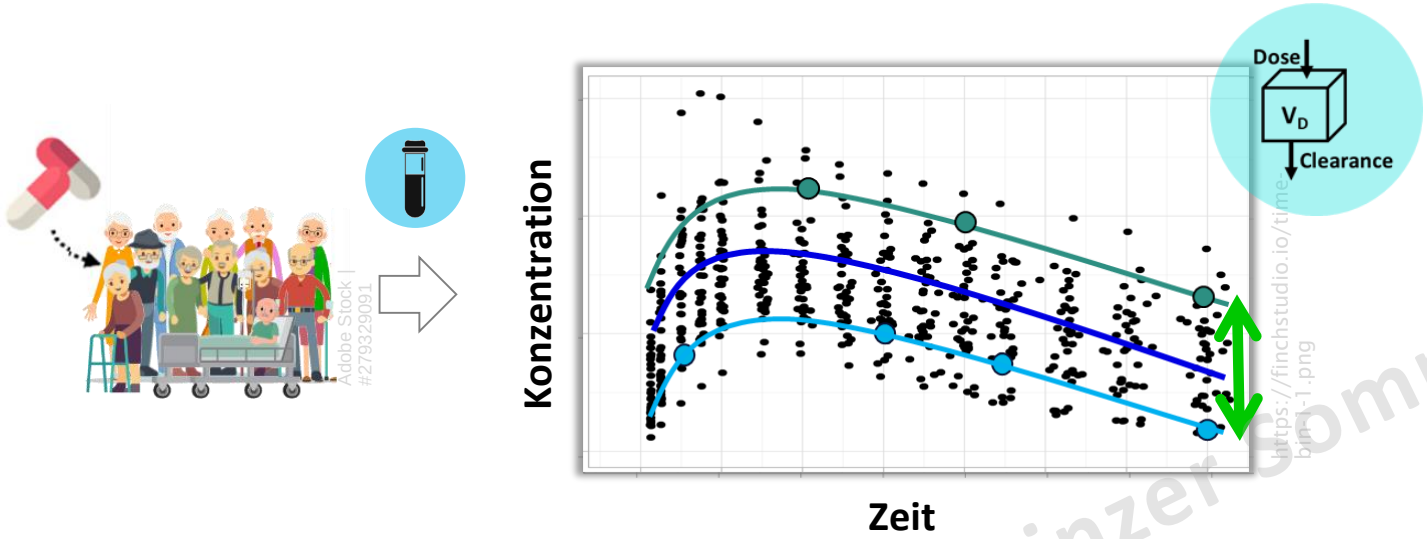
Klinische Studien



‘Real World’

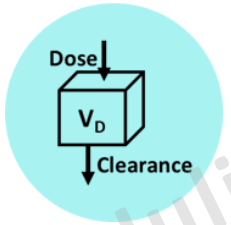
Arzneimitteltherapiesicherheit,
Outcome, Kosteneffektivität

Dosisoptimierung bei speziellen Patientenpopulationen



- Pathophysiologische Veränderungen
- Veränderte PK
  → Veränderte AST-Konzentrationen + Wirkung
- **Dosierungsempfehlungen** für **Patient:innen(sub-)gruppen**

Dosierung bei speziellen Patient:innengruppen

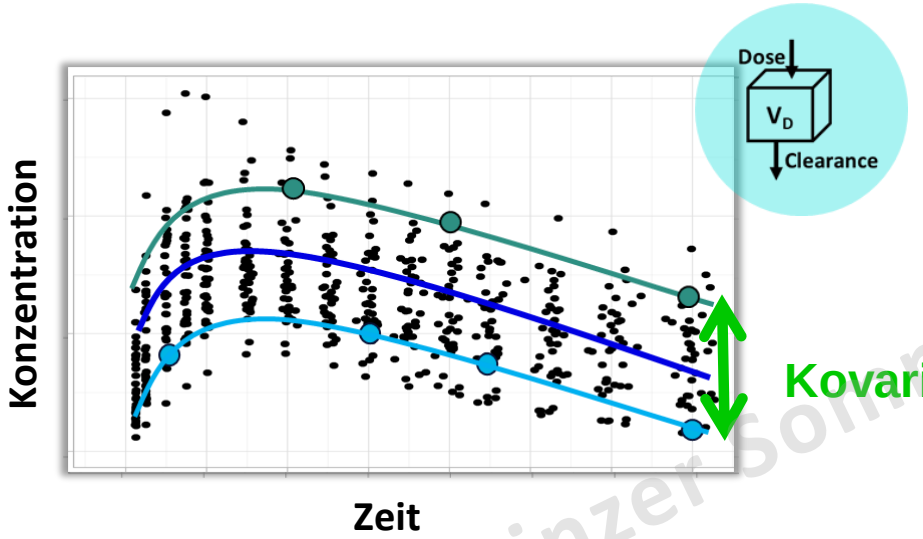


- z.B. Bestimmte Infektion, Kinder, Intensivstation, etc.

Treatment frequency	Tazocin 4 g / 0.5 g
Every 6 hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
Every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Skin and soft tissue infections (including diabetic foot infections)

Summary of product characteristics Tazocin 2 g / 0.25 g powder for solution for infusion
https://www.ema.europa.eu/en/documents/referral/tazocin-article-30-referral-annex-iii_en.pdf

Dosisierung bei speziellen Patientenpopulationen

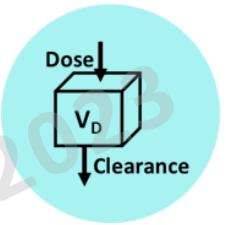


Kovariaten

- Alter
- Nierenfunktion
- Geschlecht
- Körpergewicht

- **Dosierungsempfehlungen** für bestimmte **Patient:innencharakteristika**

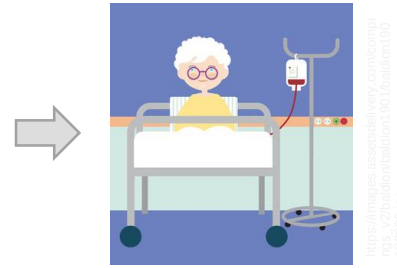
Dosierung bei bestimmten Patient:innencharakteristika



- z.B. Körpergewicht, Nierenfunktion, Nierenersatzverfahren

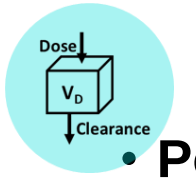
Creatinine clearance (ml/min)	Tazocin (recommended dose)
> 40	No dose adjustment necessary
20-40	Maximum dose suggested: 4 g / 0.5 g every 8 hours
< 20	Maximum dose suggested: 4 g / 0.5 g every 12 hours

Summary of product characteristics Tazocin 2 g / 0.25 g powder for solution for infusion
https://www.ema.europa.eu/en/documents/referral/tazocin-article-30-referral-annex-iii_en.pdf



Dosierung bei bestimmten Patient:innencharakteristika

- **Dosisnomogramme**, z.B.
  - Kontinuierliche Infusion von Meropenem bei Intensivpatient:innen

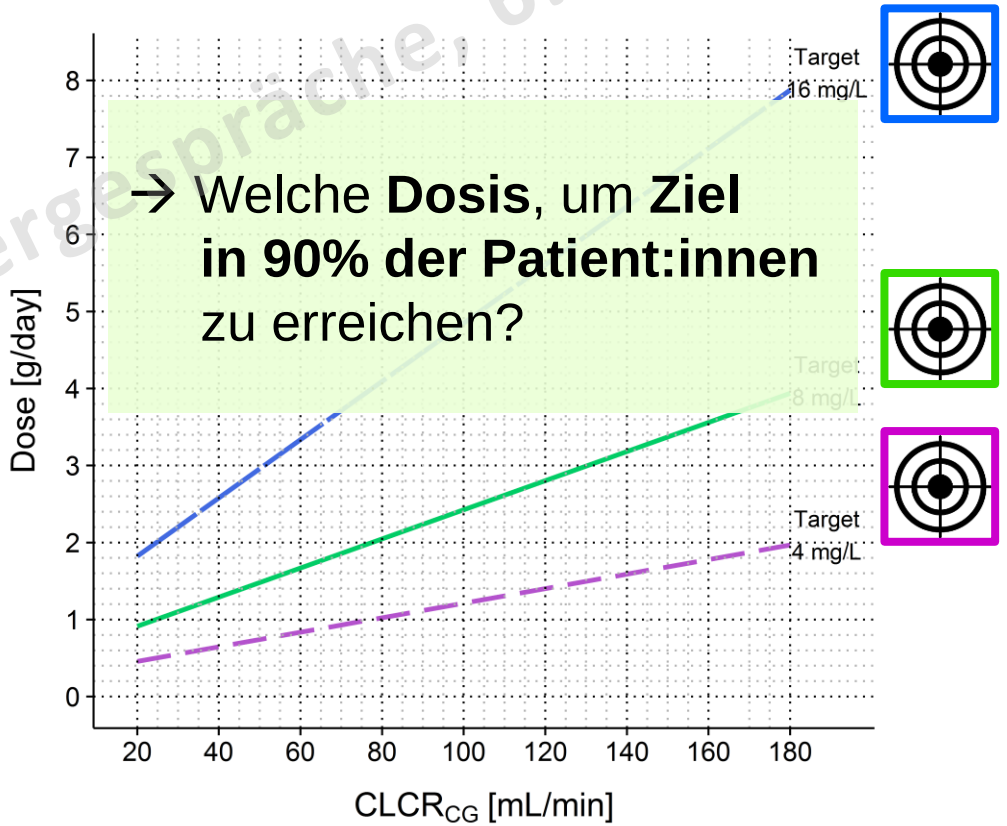


- **Populationsmodell** bas. auf klin. Daten

→ Welcher **Nierenfunktionsmarker** für Meropenem-Dosierung am besten geeignet?

($CLCR_{Cockcroft/Gault}$, MDRD, CKDEPI etc.)

Tages-Dosis

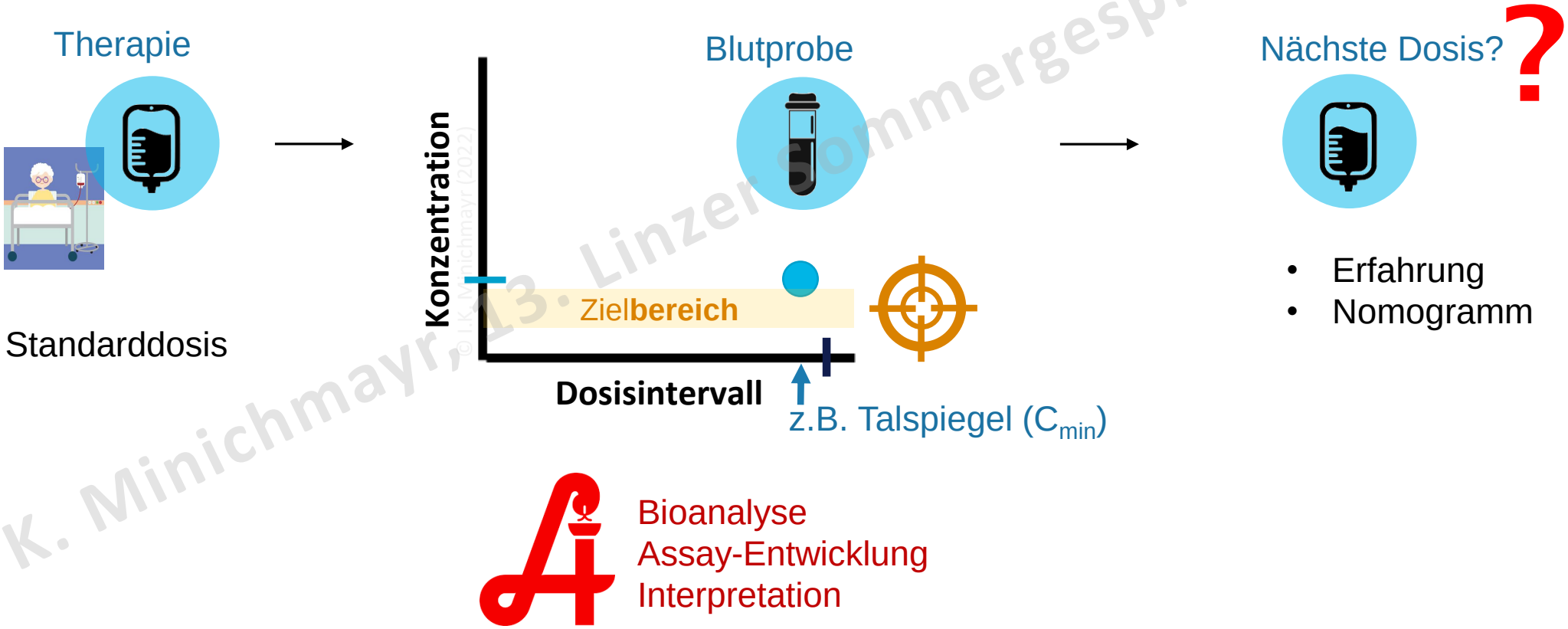


Nierenfunktion

Minichmayr IK et al. J Antimicrob Chemother. (2018)

Dosisindividualisierung

- **‘Traditionelles’ Therapeutisches Drug Monitoring** (TDM)



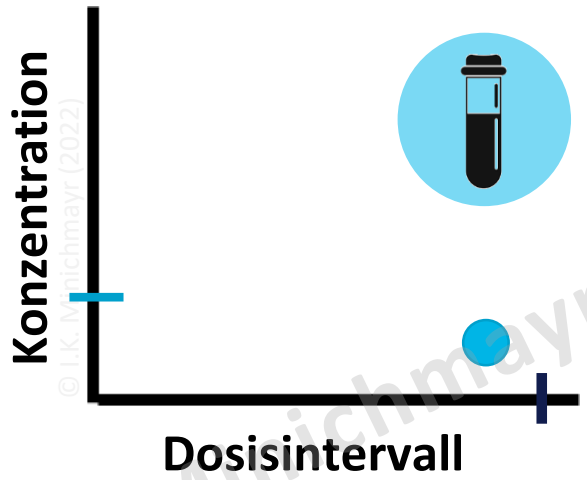
- Standarddosis

- Erfahrung
- Nomogramm

Bioanalyse
Assay-Entwicklung
Interpretation

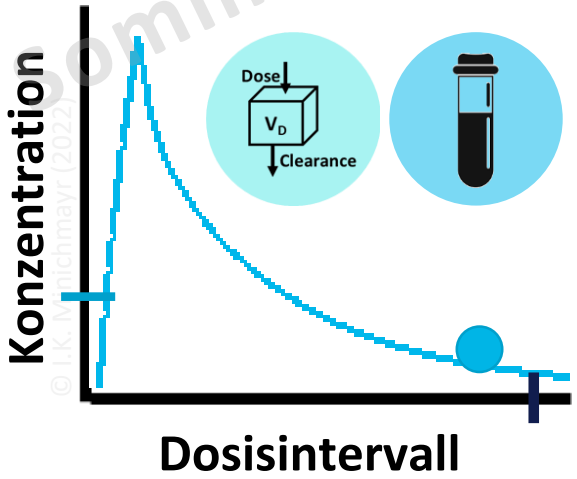
Dosisindividualisierung

- ‘Traditionelles’ TDM



- **‘Modell-basiertes’ TDM**

→ Model-informed precision dosing



Model-informed precision dosing (MIPD)

Nutzung eines **pharmakometrischen** (z.B. populationsPK) **Modells**...

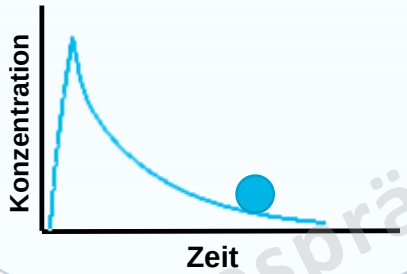
...um **individuelle Dosis vorherzusagen**

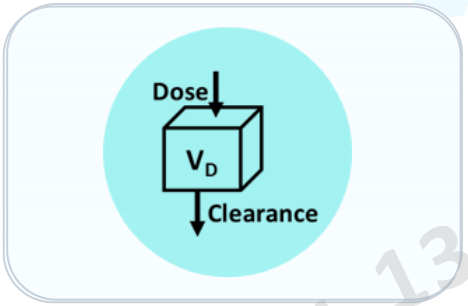
Patient:innen-Information

Dosierung (bisher)

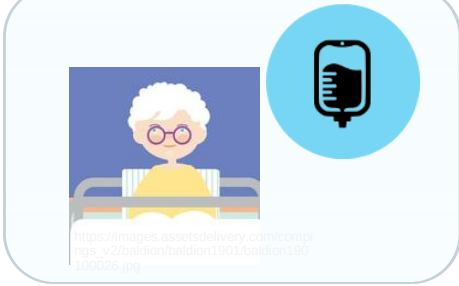
Patient:innen-charakteristika

TDM





Modell



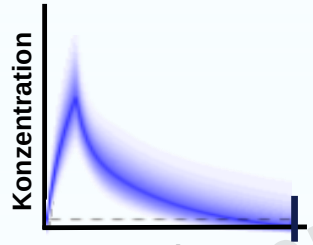
- Vorhersage einer **individuellen Dosierung**, um **bestimmtes Ziel** zu erreichen
  - z.B. $C_{min,}$ AUC, etc.

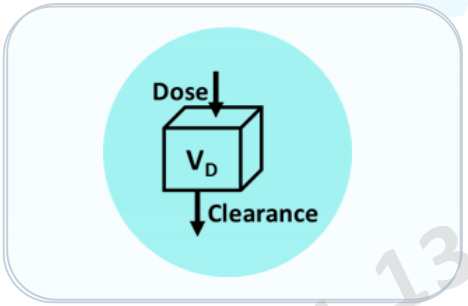
Patient:innen-Information

Dosierung (bisher)

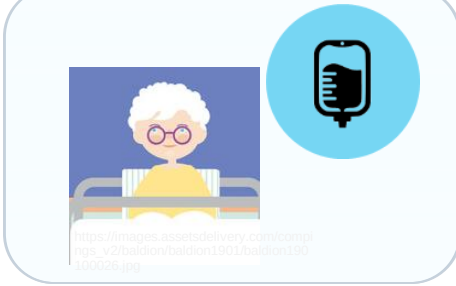
Patient:innen-charakteristika

X





Modell



- **Dosierung** mit **hoher Wahrscheinlichkeit**, **bestimmtes Ziel** zu erreichen

Patient:innen-Information

Dosierung (bisher)

Patient:innen-charakteristika

x

Konzentration

Zeit

Dose

V_D

Clearance

Modell

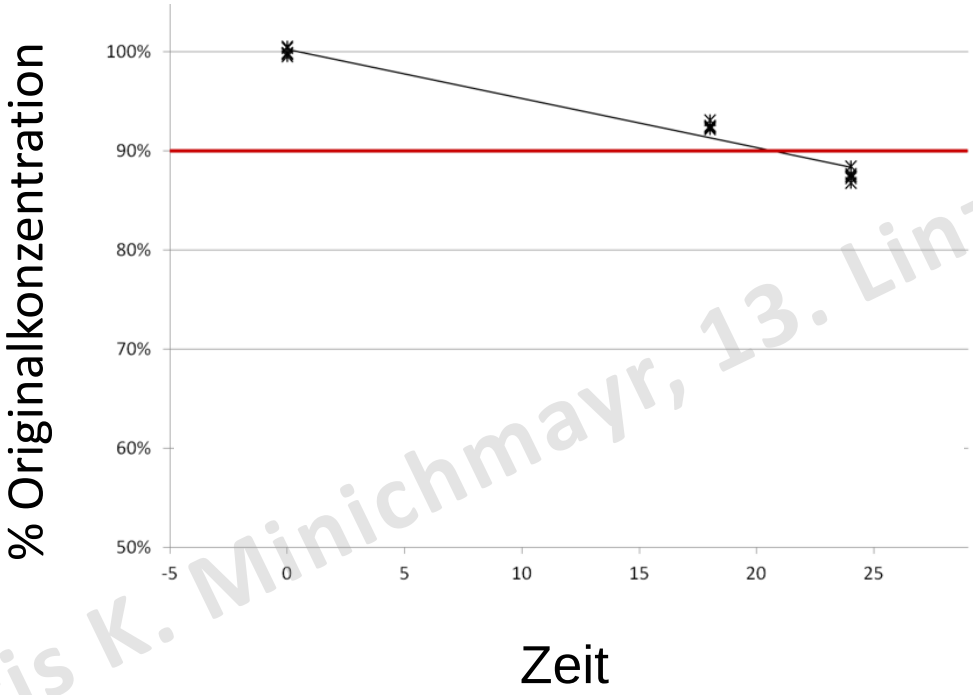
Welches Modell?

Modellevaluierung

Patient:innen-Information

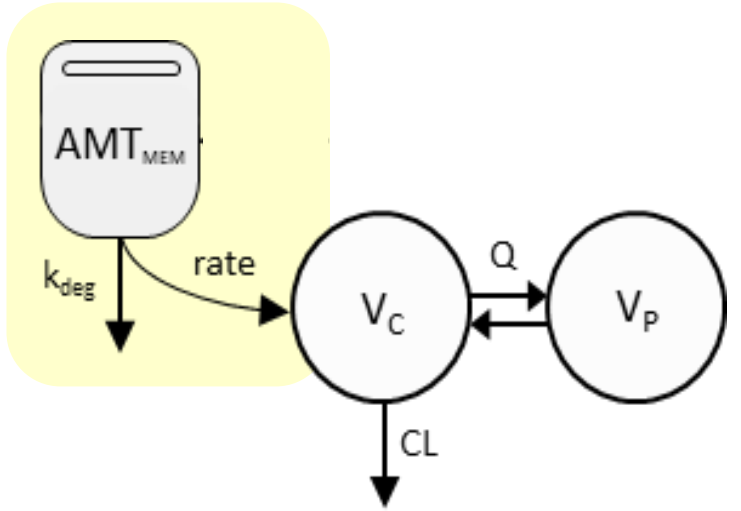
Stabilität von Meropenem während kontinuierlicher Infusion

- Stabilitätstests



Minichmayr et al. J Antimicrob Chemother 2018; 73: 1330–1339, Supplement

- Modell



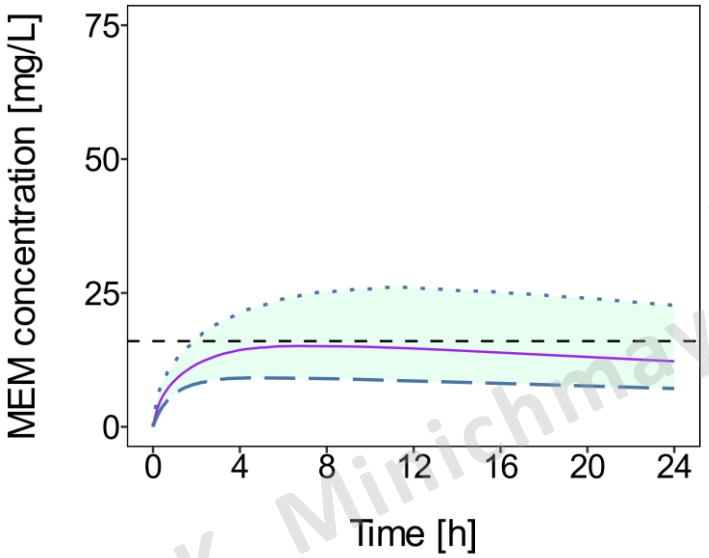
Minichmayr et al. Int J Antimicrob Agents 2023 (in submission)

Stabilität von Meropenem während kontinuierlicher Infusion

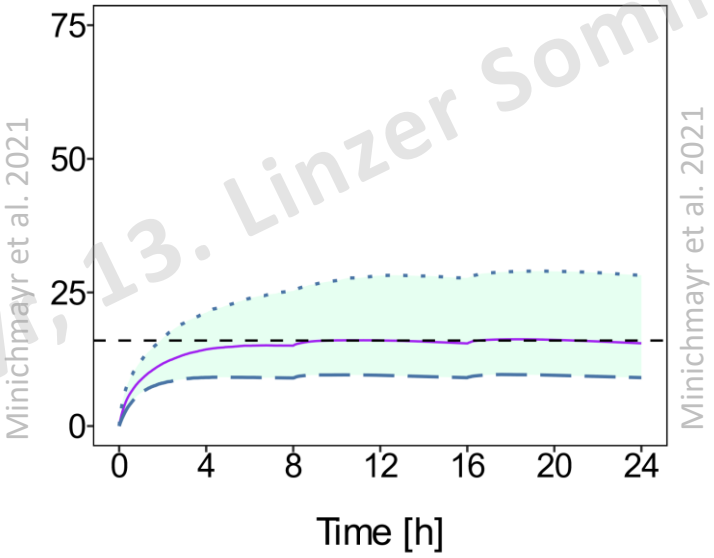
- **Simulationen**

- Modell

q24h Infusionswechsel

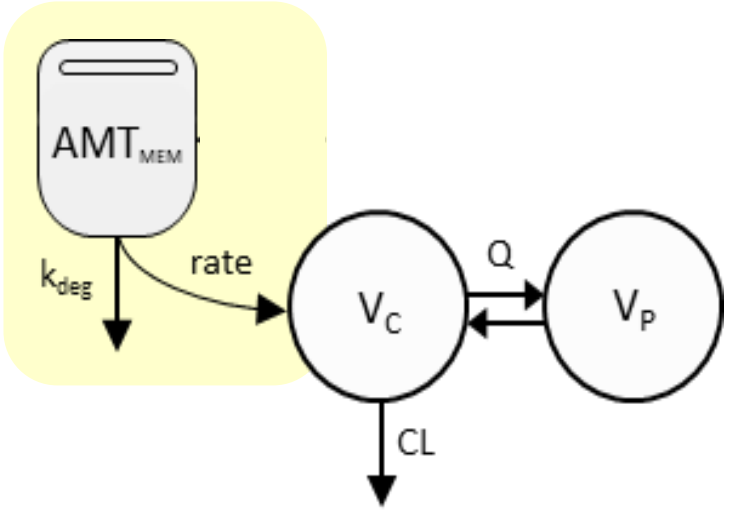


q8h Infusionswechsel



Minichmayr et al. 2021

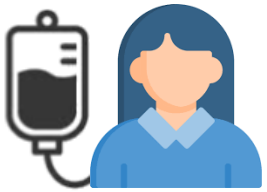
Minichmayr et al. 2021



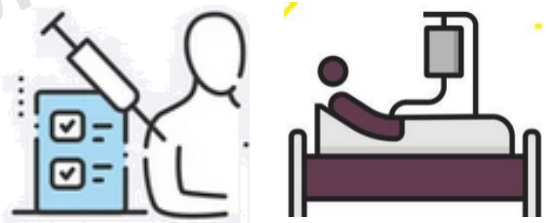
Minichmayr et al. Int J Antimicrob Agents 2023 (in submission)

Klinische Praxis

Pharmazeutische Forschung

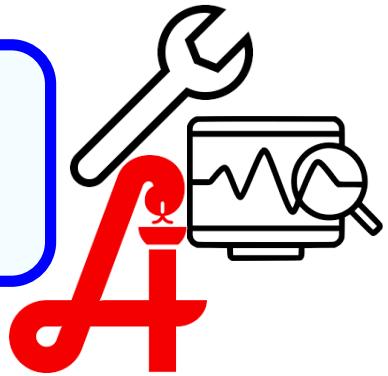


***Dosis*optimierung und -individualisierung**



Wissenslücke, Problem

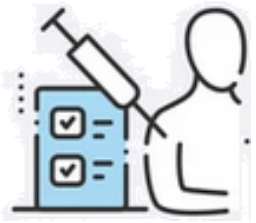
Studie, Analyse



Arzneimitteltherapiesicherheit,
Outcome, Kosteneffektivität

Klinische Praxis

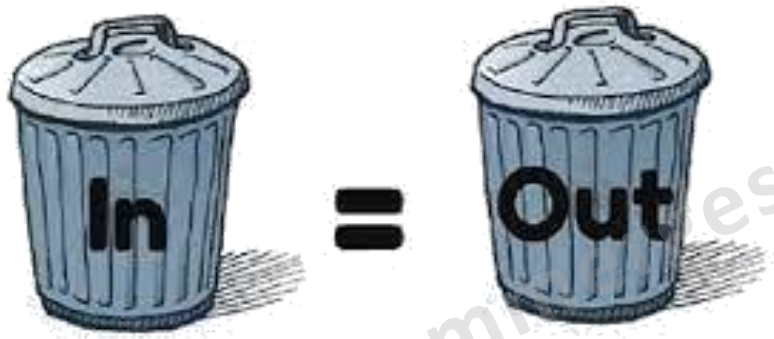
Pharmazeutische Forschung



- Herstellung der Studienmedikation, Warenlogistik, Verblindung, Vernichtung, Dokumentation, etc. (GMP, GCP)

- Datenerhebung, Dokumentation

Akkurate Dokumentation von Daten (!)



https://miro.medium.com/max/609/1*KtnIrZ4AIwgB-7tZMobcFA.png

→ **Tatsächliche Zeitpunkte (nicht nur geplante Zeitpunkte)**

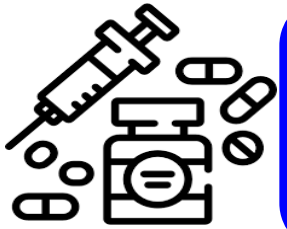
- **Dosierung**
- **Sampling** (z.B. Konzentrationsmessung)

→ **Tatsächliche Dosierung (nicht nur geplante Dosierung)**

- Dosis, Intervall, Infusionsdauer

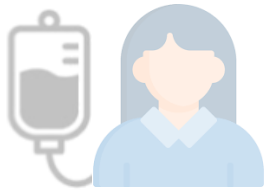
Klinische Praxis

Pharmazeutische Forschung



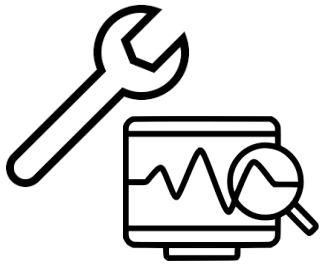
_Medikations_optimierung

_Dosis_optimierung und -individualisierung

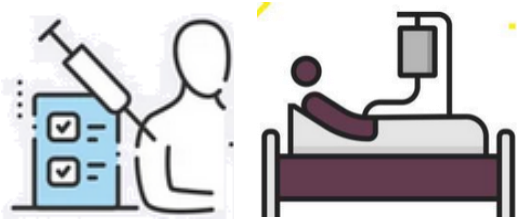


Status-quo Erhebung

Intervention, Evaluierung



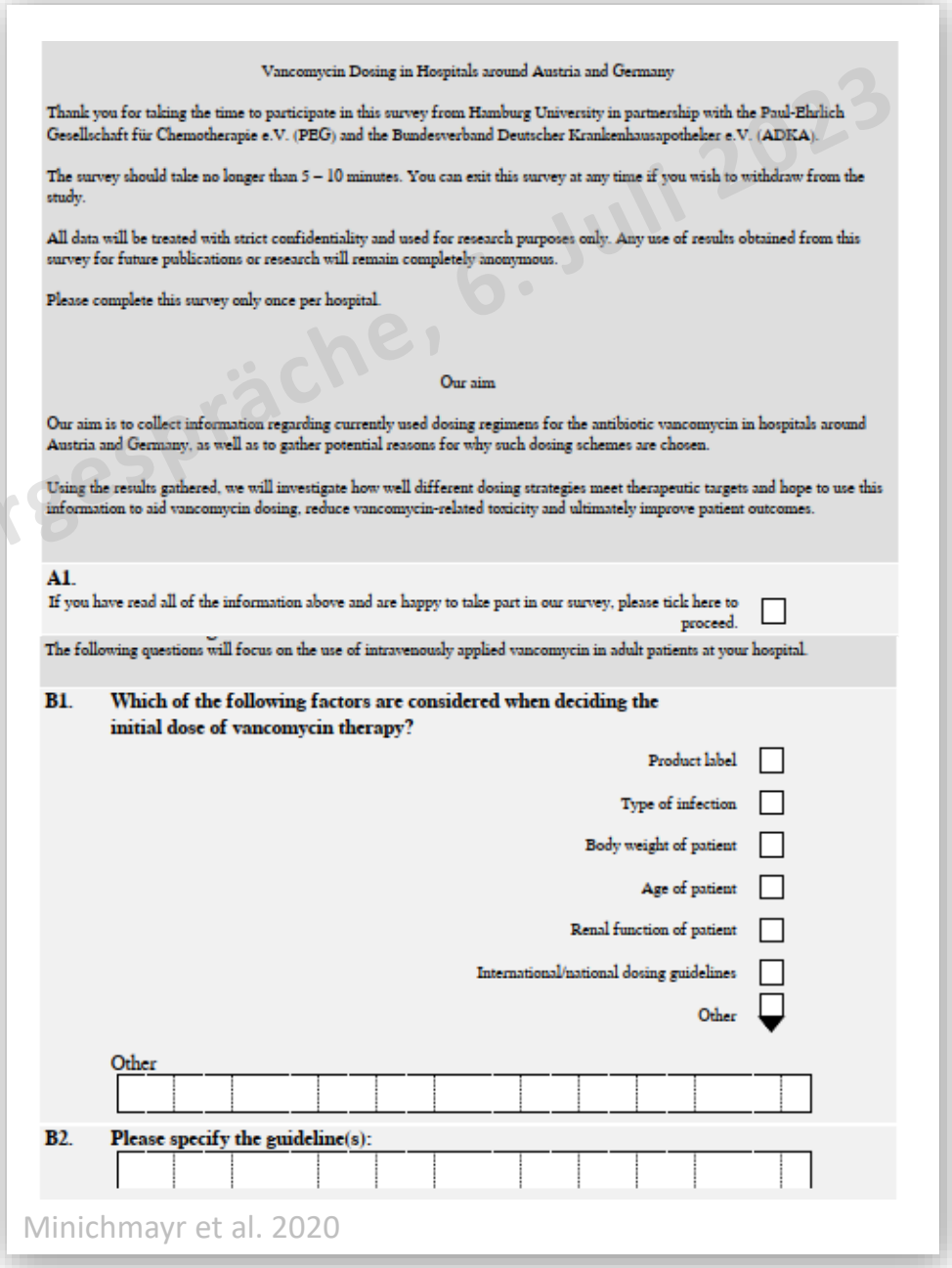
Arzneimitteltherapiesicherheit, Outcome, Kosteneffektivität



Klin. Studien Real-World

Umfragen

- **Vancomycin-Dosierung bzw. TDM in AT und DE**
  - Online, anonymisierter Fragebogen (2020)
  - Krankenhausapotheker:innen,
    ÖGIT Mitglieder



Vancomycin Dosing in Hospitals around Austria and Germany

Thank you for taking the time to participate in this survey from Hamburg University in partnership with the Paul-Ehrlich Gesellschaft für Chemotherapie e.V. (PEG) and the Bundesverband Deutscher Krankenhausapotheker e.V. (ADKA).

The survey should take no longer than 5 – 10 minutes. You can exit this survey at any time if you wish to withdraw from the study.

All data will be treated with strict confidentiality and used for research purposes only. Any use of results obtained from this survey for future publications or research will remain completely anonymous.

Please complete this survey only once per hospital.

Our aim

Our aim is to collect information regarding currently used dosing regimens for the antibiotic vancomycin in hospitals around Austria and Germany, as well as to gather potential reasons for why such dosing schemes are chosen.

Using the results gathered, we will investigate how well different dosing strategies meet therapeutic targets and hope to use this information to aid vancomycin dosing, reduce vancomycin-related toxicity and ultimately improve patient outcomes.

A1.
If you have read all of the information above and are happy to take part in our survey, please tick here to proceed. ☐

The following questions will focus on the use of intravenously applied vancomycin in adult patients at your hospital.

B1. Which of the following factors are considered when deciding the initial dose of vancomycin therapy?

- Product label ☐
- Type of infection ☐
- Body weight of patient ☐
- Age of patient ☐
- Renal function of patient ☐
- International/national dosing guidelines ☐
- Other ☐

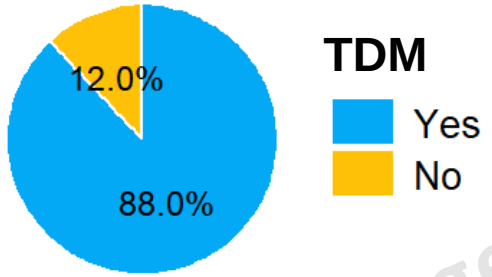
Other

B2. Please specify the guideline(s):

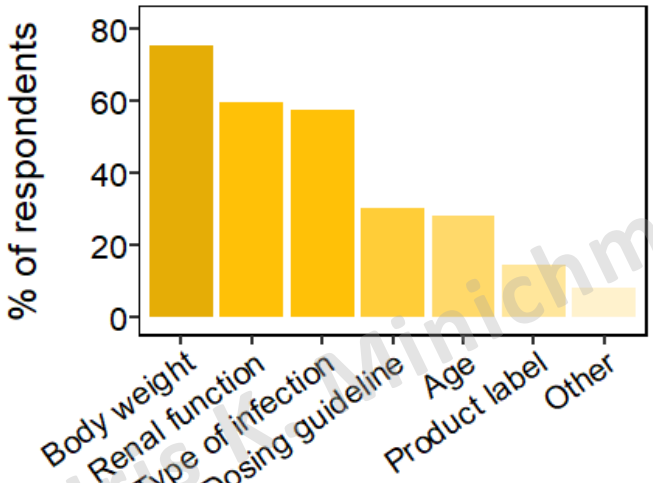
Minichmayr et al. 2020

Umfrage (Vancomycin)

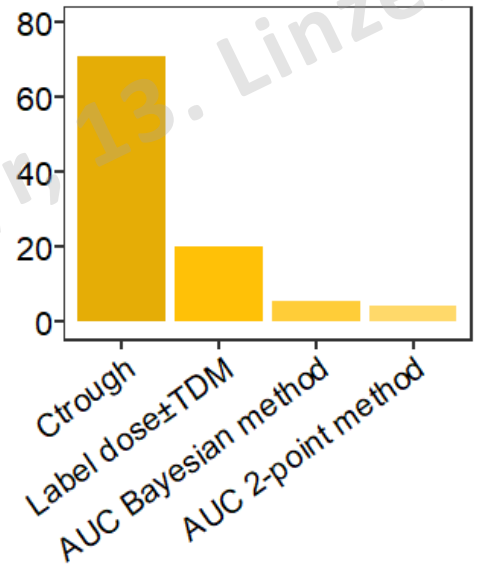
- **Diverse Dosierungsschemata**
  - 86% Intermittierende Gabe
  - 31% Kontinuierliche Infusion



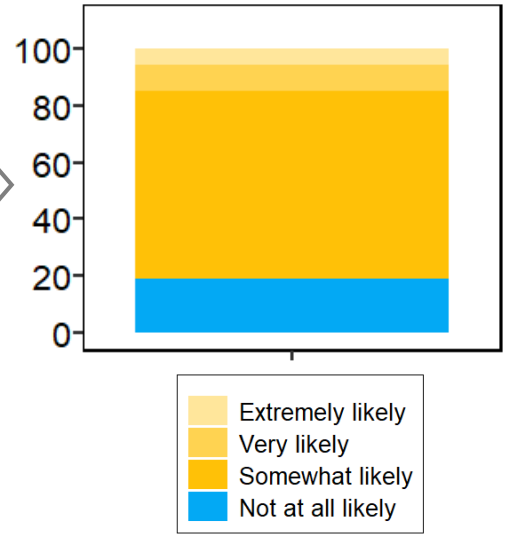
Basis für Initialdosis

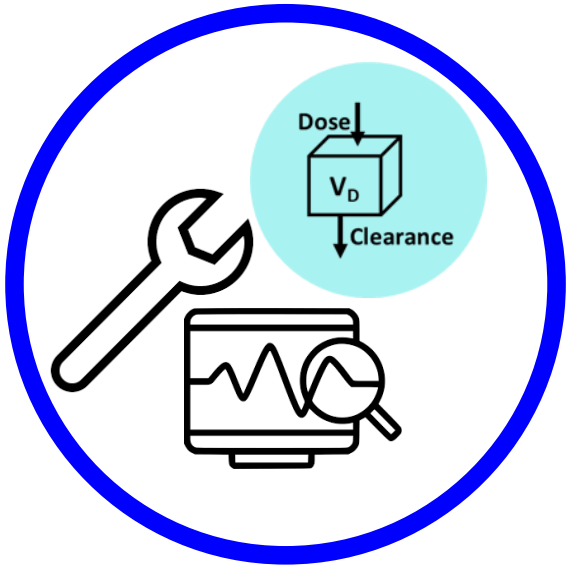


Basis für nächste Dosis



AUC-basierte Dosierung, wenn Training?





Minichmayr et al. IATDMCT conference 2020

Umfragen

Umfragen

Williams *et al. Critical Care* (2023) 27:241
https://doi.org/10.1186/s13054-023-04527-1

Critical Care

RESEARCH Open Access

International survey of antibiotic dosing and monitoring in adult intensive care units

Affiliations

Pharmacy Department, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.
Pharmacy Department, Sunshine Coast University Hospital, Birtinya, QLD, Australia.
Pharmacy Department, Parc de Salut Mar, Barcelona, Spain
Department of Pharmacy, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.
Department of Pharmacy, Saint Clare's Health, Denville, NJ, USA

Interaktionen

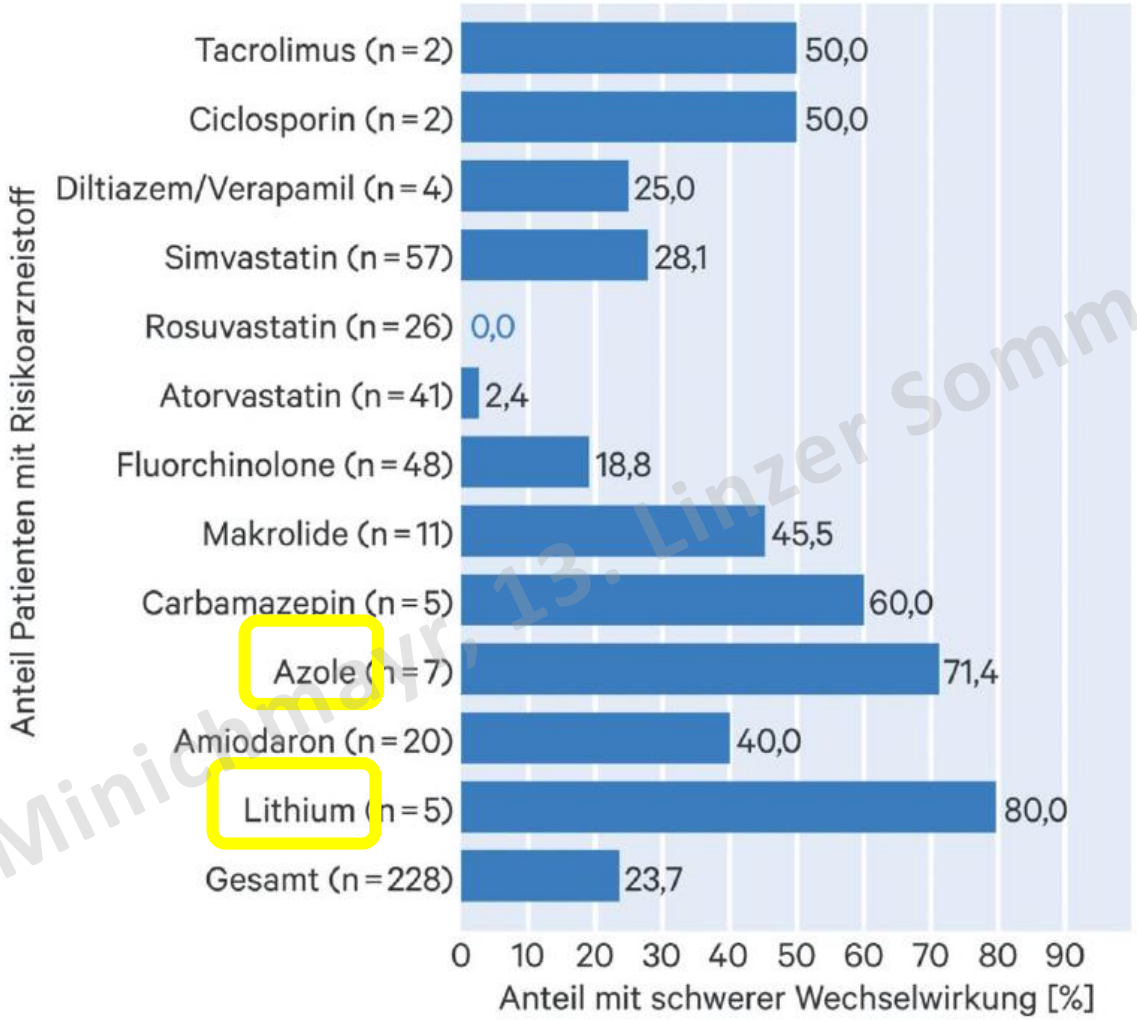
Clinically Relevant Interactions with Anti-Infectives on Intensive Care Units—A Multicenter Delphi Study

Table 2. DDIs (n = 65) including anti-infectives and rated clinically relevant by expert panel.

Group	Drug 1	Drug 2	Mode Category	Additional Strategies to Reduce Patient Risk from Interaction
Cephalosporins	Ceftriaxone	Calcium (intravenous)	3	separate administration
Carbapenems	Imipenem	Valproic acid	5	TDM for valproic acid
	Meropenem	Valproic acid	5	
Azithromycin		Citalopram	3	QTc-monitoring, high-normal serum levels of potassium and magnesium
		Haloperidol	3	

Köck et al. Antibiotics 2021, 10, 133

Wechselwirkungen – should we care?



Pointinger, Schneider; Krankenhauspharmazie 40. Jahrgang Heft 11, November 2019

Arzneimittelbezogene Probleme

A Standardized, Structured Approach to Identifying Drug-Related Problems in the Intensive Care Unit: FASTHUG-MAIDENS

Letter	Definition	Letter	Definition
F	Feeding	M	Medication reconciliation
A	Analgesia	A	Antibiotics or anti-infectives
S	Sedation	I	Indications for medications
T	Thromboprophylaxis	D	Dosing
H	Hyperactive or hypoactive delirium*	E	Electrolytes, hematology, and other
U	Stress ulcer prophylaxis	N	No drug interactions, allergies, duplications, side effects
G	Glucose control	S	Stop dates

*In the original version of the FASTHUG mnemonic, H was for "head of the bed elevated".[1]

Art, Häufigkeit, Erhebungsmechanismen

Mabasa et al. CJHP 65: 366 (2011)

Intervention, Evaluierung

Research in Social and Administrative Pharmacy 15 (2019) 1309-1316

A case study of the implementation and sustainability of medication reviews in older patients by clinical pharmacists

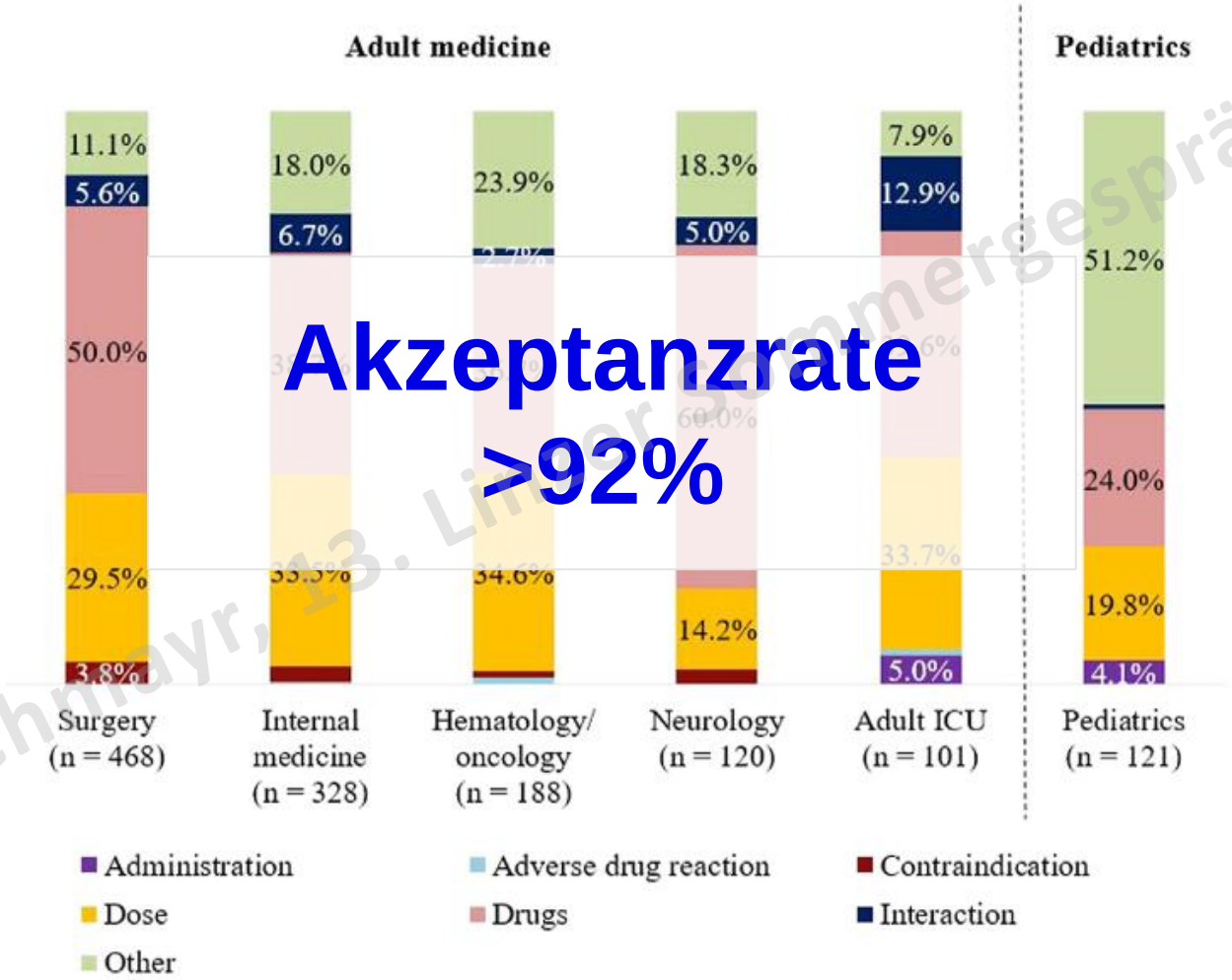
Thomas G.H. Kempen[a,b,*], Ulrika Gillespie[a], Maria Färdborg[c], Jennifer McIntosh[d], Alpana Mair[e], Derek Stewart[f]

Kempen et al. Res Social Adm Pharm. 2019 Nov;15(11):1309-1316

- **Versorgungsforschung**
- **Adhärenzforschung**
  - Einfluss von Beratungsvideos auf Wiedereinweisungsrate
- **...**

universität innsbruck

Intervention, Evaluierung

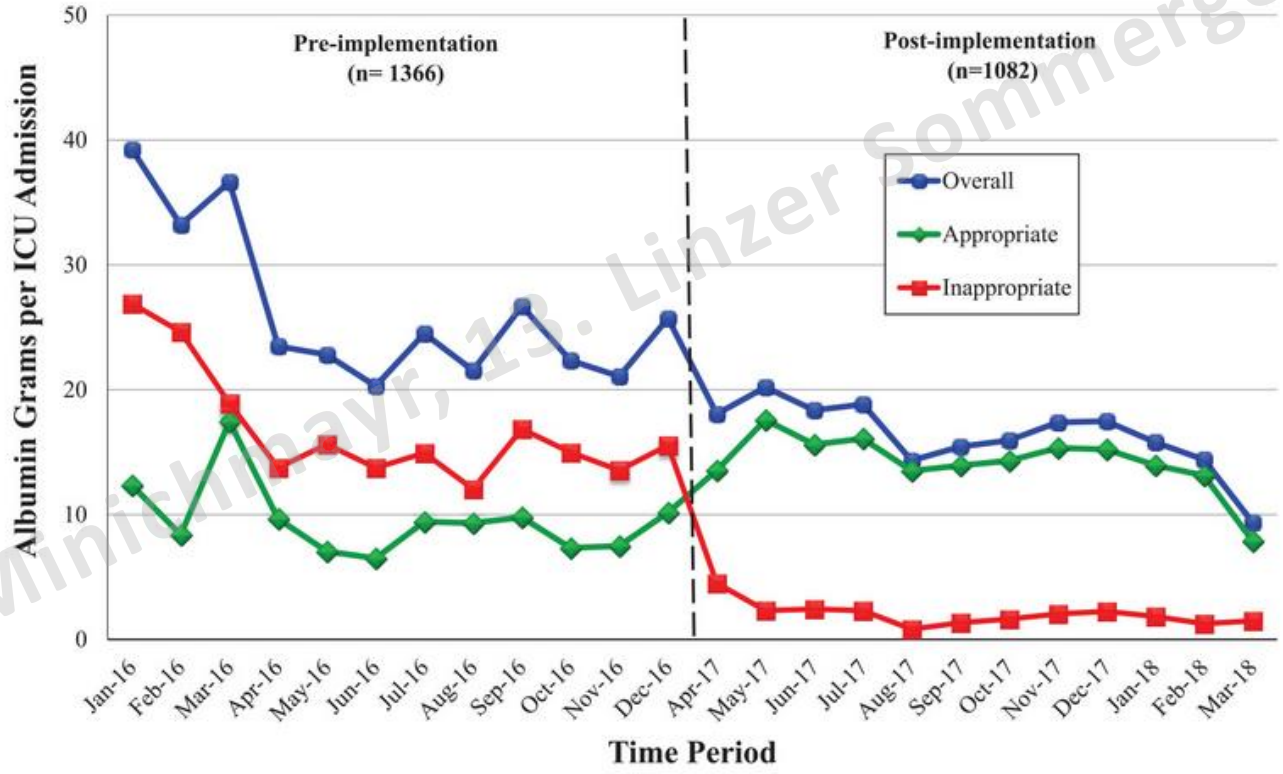


Akzeptanzrate >92%

Berger et al. Front. Pharmacol. 13:1030406.

Pharmakoökonomische Interventionen

Clinical Pharmacist–Led Impact on Inappropriate Albumin Use and Costs in the Critically Ill



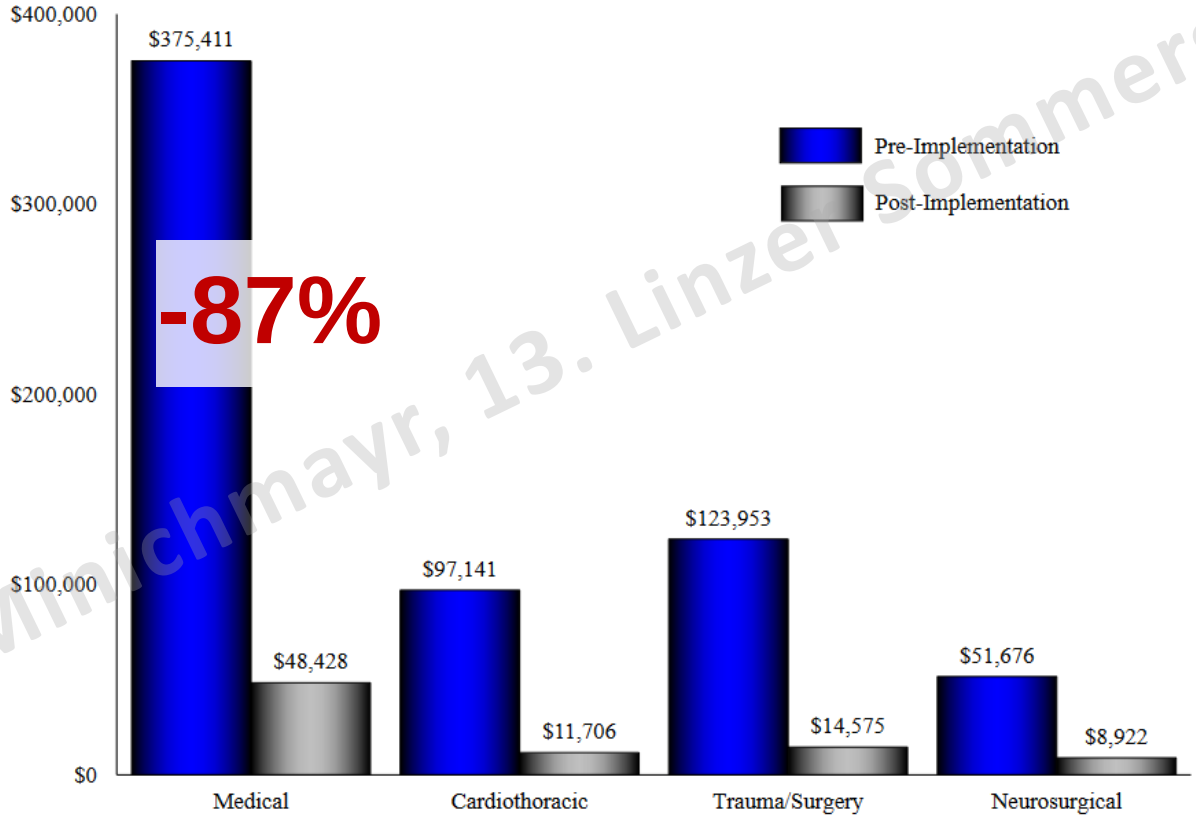
Appropriate use:
- HRS
- > 5L Aszites
- gefäßchirurgische Patienten
- Plasmapherese
- ....

Inappropriate use:
- Kombination mit Diuretika
- Hypoalbuminämie
- ....

Buckley et al. Ann Pharmacother 54, 105-112 (2020)

Pharmakoökonomische Interventionen

Clinical Pharmacist–Led Impact on Inappropriate Albumin Use and Costs in the Critically Ill



- Bewertung des **Medikamentenge-/verbrauchs**
- Analyse der **Medikamentenausgaben**

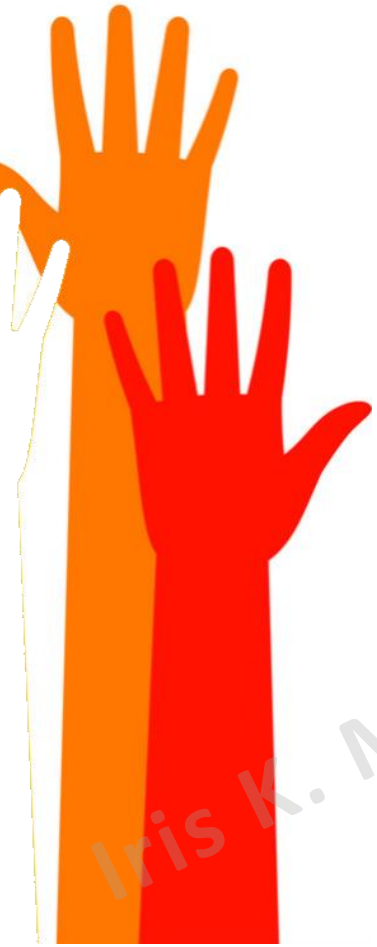
Buckley et al. Ann Pharmacother 54, 105-112 (2020)

Entwicklung und Umsetzung von Leitlinien

- **Praxis-Leitlinie** über Medikamente mit **Delir**-Risiko
  - Bestimmung des relativen Delir-Risikos verschiedener Anästhetika bei post-OP Patient:innen
    - Einfluss von Patient:innenencharakteristika

universität innsbruck

Beitrag



- **Dokumentation, Monitoring**
- **Kooperationen, Netzwerke**
  - Lokal
  - National
  - International

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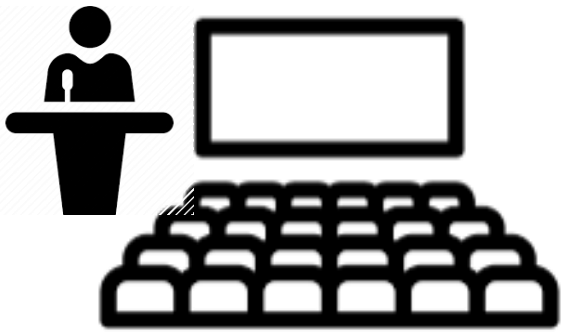

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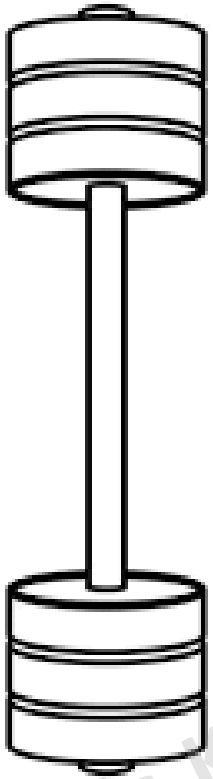
‘Fit für’s Krankenbett’



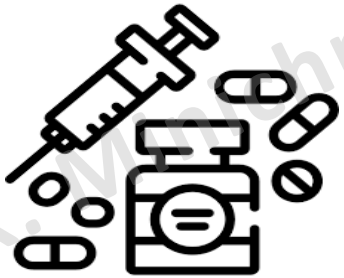
- **Fortbildung**
- **Kooperationen, Netzwerke**
  - Lokal
  - National
  - International
- **Fachliteratur**

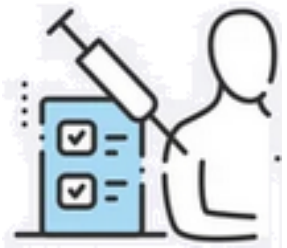
Kapitel zu
- **Pharmakometrie**
- **Dosisindividualisierung**

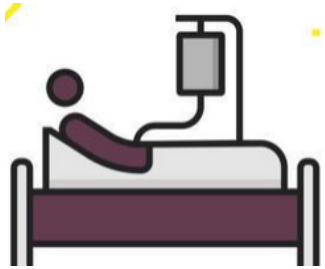
https://st3.depositphotos.com/1007566/33947/v/450/depositphotos_339479236-stock-illustration-weight-lifting-dumbbell-isolated-icon.jpg

Klinische Praxis

Pharmazeutische Forschung







Danke

- Allen Projektpartner:innen und Studienteilnehmer:innen

Fragen!?