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Schweizerische Akademie Perinatale Pharmakologie SAPP
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Herzlich willkommen zur Jahrestagung der SAPP in Zusammenarbeit mit dem UKBB

Thema: «Wenn Schwangere und ihre Kinder Medikamente benötigen-Hotspots»

Zürich 2.11.23

SAPP

- Seit 16 Jahren: kontinuierlicher interdisziplinärer Beitrag zur Sicherheit der Anwendung von Arzneimitteln in Schwangerschaft und Stillzeit (Fortbildungen, Dokumente zur prakt. Anwendung).
- Fokus: Gleichsetzung Population der Schwangeren und Stillenden mit derjenigen der Kinder. Der heutige Anlass gemeinsam mit der pädiatrischen Pharmakologie soll dies symbolisieren.

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Programm

12.00 Uhr **Registrierung**

13.00 Uhr **Eröffnung**
SAPP Vorstand

13.05 Uhr **Grusswort**
Christoph Meier, Prof. Dr., Departement Pharmazeutische Wissenschaften, Universität Basel

13.15 Uhr **Impulsreferat: Persönliche Erfahrungen der Frauen- und Kindermedizin in armen Ländern**
Marcel Tanner, Prof. em., Swiss TPH, Universität Basel

1. Moderation Olav Lapaire

13.35 Uhr **Pharmakotherapie bei der Frau, Schwangeren, Stillenden – mehr als eine Gender Frage**
Ursula von Mandach, Prof. Dr. pharm., SAPP

14.00 Uhr **Praktische Dosierungsanpassungen in Schwangerschaft und Stillzeit: Dialo**
Verena Gotta, PhD, Pädiatrische Pharmakologie, UKBB
Andrea Burch, MSC, FPH Klinische Pharmazie, Kantonsapotheke Zürich

14.45 Uhr **Diskussion**

15.00 Uhr **Kaffeepause und Posterbesichtigung**

2. Moderation Marc Pfister

15.50 Uhr **Vom Früh- zum Termingeborenen: Medikamentöse Therapien sind komplex**
Roland Gerull, Dr. med., Neonatologie, UKBB

16.15 Uhr **In welchem Alter wie dosieren: Lösungsansatz von SwissPedDose**
Elisabeth Giger, Dr. sc. ETH, SwissPedDose

16.40 Uhr **Probleme und medikamentöse Ansätze bei Schwangeren und ihren Neugeborenen in Entwicklungsländern**
Daniel H. Paris, Prof. Dr. med., Swiss TPH, Universität Basel

17.05 Uhr **Diskussion**

3. Roundtable mit Vertreter:innen aus Behörden und Politik

17.20 Uhr **Off-label use, HMG, Medikamentenversorgung Patientensicherheit u.a.**
Unter Mitwirkung von NR Yvonne Feri, Dr. pharm. Enea Martinelli, dipl. pharm. Martine Ruggli, dipl. pharm. Monika Schäublin, lic. phil. Erika Ziltener
Leitung: Stephanie Vollenweider, Dr. phil.

18.15 Uhr **Posterpreis und Schlussbemerkungen**

18.30 Uhr **Apéro**

Grusswort Jahrestagung 2.11.23

«Wenn Schwangere und ihre Kinder Medikamente benötigen-Hotspots»

Prof. Dr. Chr. Meier
Vorsteher Dept. Pharmazeutische Wissenschaften, Univ. Basel

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Impulsreferat
Erfahrungen der Frauen-, und Kindermedizin in armen Ländern

Prof. em. Marcel Tanner

Swiss Tropical & Public Health Institute

Swiss Academy of Arts and Sciences

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Deklaration Interessenskonflikte
Marcel Tanner

- Finanzielle oder Eigentümerinteressen: keine
- Tätigkeiten für die pharmazeutische Industrie und andere Firmen des Gesundheitssystems: keine aktuell
- Drittmittel / Spenden: keine mehr
- Persönliche Beziehungen: keine in Bezug auf SAPP
- Sonstige Mitgliedschaften:1.Board Member Botnar Foundation 2018 - today. 2. Consultant EDCPT 2017- to today. 3. Member different committees of Swiss Agency for Development & Cooperation since 1985 until today. 3. Board Member, University Hospital, Basel, Switzerland, 2016 – today. 4. President of Swiss Academies of Arts and Sciences a+ 2019 – today. 5. Präsident Förderverein Universität Basel, 2022 – today. 6. Board Member FAIRMED 2008 – today. 7. Chair Leprahilfe, 2014 – today. 8. Chair Federal Commission of Sexually transmitted Infections (EKSI), 2017 – today.

Foederatio Pharmaceutica Helvetiae FPH Fortbildungsprogramme

Inhalt

1. Herausforderungen der MNCH*

   Erlebte Beispiele:

   Malariaprävention – Intermittent Preventive Treatment During Infancy (IPTi)

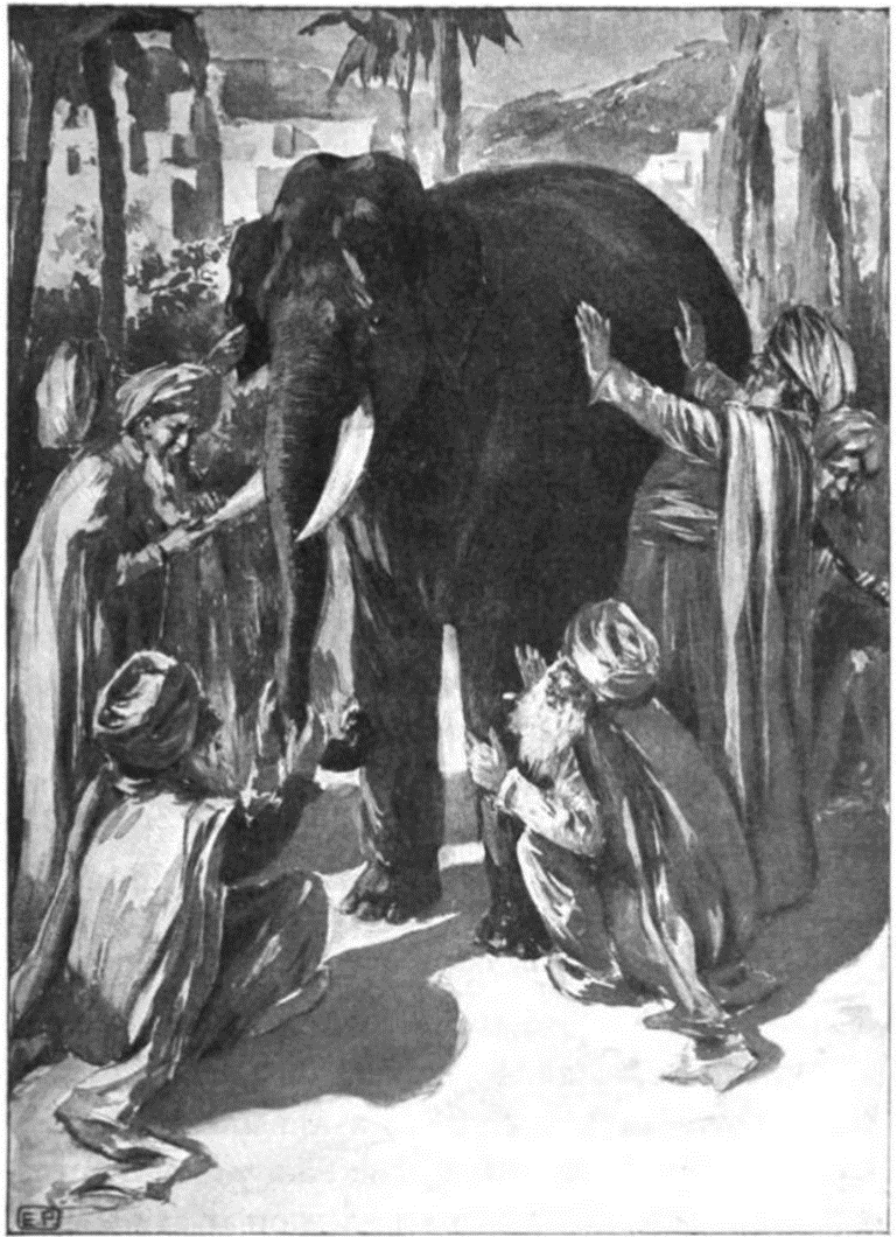
   HIV / Prevention of mother-to-child transmission of (PMTCT)

   One-Stop Clinic

   Continuum of Care (CoC)

2. *“The past lies ahead of us”* und neue Herausforderungen

3. Ausblicke



*MNCH: Maternal, Newborn and Child Health

https://pmnch.who.int/docs/librariesprovider9/governance/2023022122-workplanning-retreat-mnch-advocacy-strategy.pdf?sfvrsn=fc799bcf_5

MNCH im Kontext des öffentlichen Gesundheitswesens: Instrumente / „Produkte" zur Diagnose, Behandlung, Prävention...

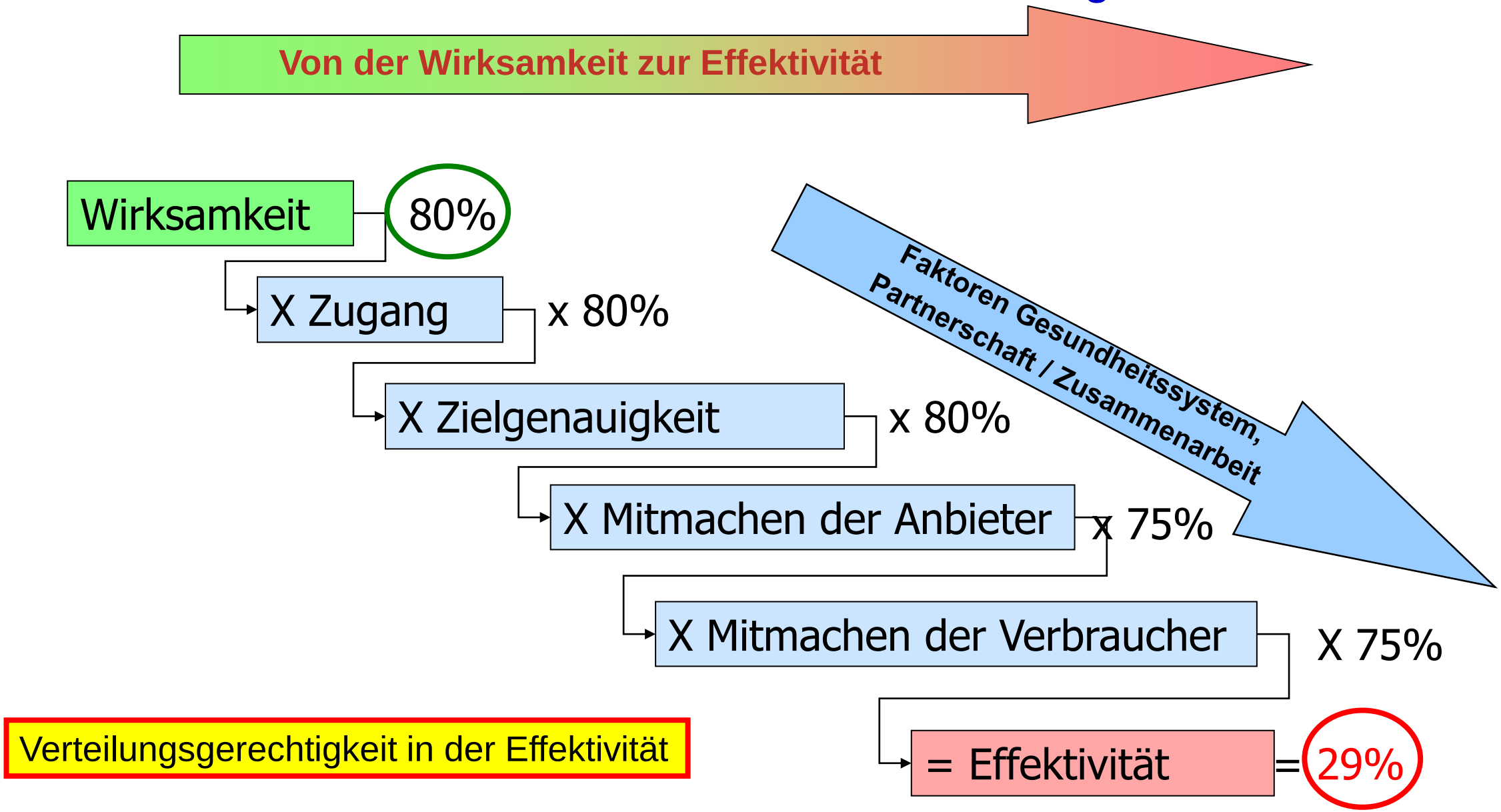
Handlungsbedarf

- Annehmbare, geeignete Werkzeuge definieren Diagnose- und Servicepakete
- Strategien für die Anwendung (wann, welche und wie)
- Strategien für die Überwachung – Reaktion
- Hochskalierung auf die nationale Ebene und Effektivität, um UHC zu erreichen:

- **HIV** ⇒ **Antiretrovirale Therapie (ART)**
- **TB** ⇒ **Direct Observed Therapy (DOT)**
- **Malaria** ⇒ **Insecticide-Treated Net (ITN)**
  Intermittend Preventive Treatment (IPTi),
  Combination Therapy (CT)
- **Neglect Tropical Diseases (NTDs)** ⇒ **Mass Drug Administration (MDA)**

Systemische Ansätze zugeschnitten
auf das jeweilige soziokulturelle und sozio-ökologische Umfeld

Von der Wirksamkeit zur Effektivität auf Bevölkerungsebene - effektiv sein



Erkenntnisse und Aussichten für MNCH – Schwerpunkt öffentliche Gesundheit

Globale Gesundheit

- Vermeidung von Fragmentierung und damit von Effektivitätsverlusten
  - Systemische (funktionale und strukturelle) Ansätze
  - Werkzeuge - Triple A: Angemessenheit, Akzeptanz, Zugang
  - Der Prozess der Leistungserbringung bestimmt die Qualität der Versorgung
  - Dienstleistungen aus einer Hand - Kliniken aus einer Hand
  - Kommunikation >> Information / Propaganda: „kreatives Zuhören“
- Von Risiko/Verwundbarkeit zu Resilienz wechseln, um Dienstleistungen zu fokussieren
- Wichtigste Ergebnismassnahme: verteilungsgerechte Effektivität
- Prozesse und Interventionspakete - Kontinuität der Versorgung - wahrgenommene Qualität der Versorgung

Grundlagenforschung und Validierung

- Pädiatrische Formulierungen
- Individuelle Pk/Pd

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Pharmakotherapie bei der Frau, Schwangeren, Stillenden – mehr als eine GENDER Frage

Prof. Dr. pharm. Ursula von Mandach
Klinische Pharmazeutin
Präsidentin SAPP
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Deklaration Interessenskonflikte
Ursula von Mandach

- Finanzielle oder Eigentümerinteressen: keine
- Tätigkeiten für die pharmazeutische Industrie und andere Firmen des Gesundheitssystems: Swissmedic (ext. Expertin)
- Drittmittel / Spenden: keine
- Persönliche Beziehungen: Präsidentin SAPP
- Sonstige Mitgliedschaften: SAPhW (Co-Präsidentin), SAMW (Vertreterin SAPhW), pS, GSASA, AAV

Foederatio Pharmaceutica Helvetiae FPH Fortbildungsprogramme

Medikamentenkonsum bei Schwangeren

97% (n= 9272) mind. 1 Medikament

(exkl. Vit., Min. stoffe)

Haas DM et al. Obstet Gynecol 2018;135:789-98.

50% mind. 4 Medikamente

Mitchell AA et al. Am J Obstet Gynecol 2011;205:51.e1-8.

→ Tendenz steigend

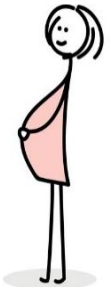
Gründe:

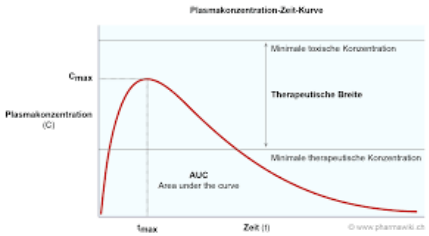
- Beschwerden und Komplikationen während Schwangerschaft, Geburt, Stillzeit

  Zunehmendes ALTER!

  Schwangere mit **vorbestehenden** Krankheiten
- Umwelteinflüsse, Ernährung

Unterschiede





Progesteron	(+)	+++	+++++
		Abnahme Motilität des GI	→ *Absorption*
Östrogene	(+)	+++	+++++
		Veränderte Aktivität der Phase I und II Leberenzyme	→ *Metabolismus*
Fett	+	++	+++
Muskulatur	++	+	++
Blutvolumen	++	+	++
Plasmavolumen	++	+	++
		Körperwasser Proteine	→ *«Verteilungsvolumen»* *Distribution*
Blutfluss	++	+	++
Cardiac Output	++	+	++
Renale Clearance	++	+	++
			→ *Elimination*

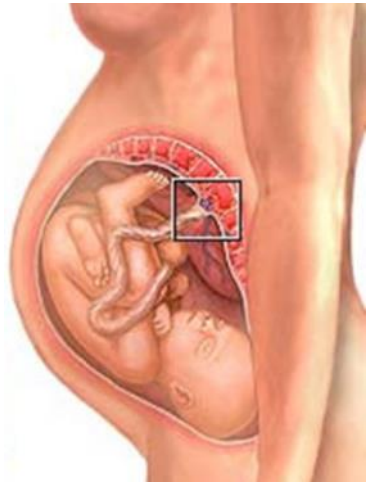
Weiterführend: Eke AC. J Basic Clin Physiol Pharmacol 2021;33:581-98.

Medikamente für Schwangere und Stillende:

ein weiter Weg

Therapieansatz – Forderung:

Verträglich UND wirksam für Mutter UND Kind(er)!

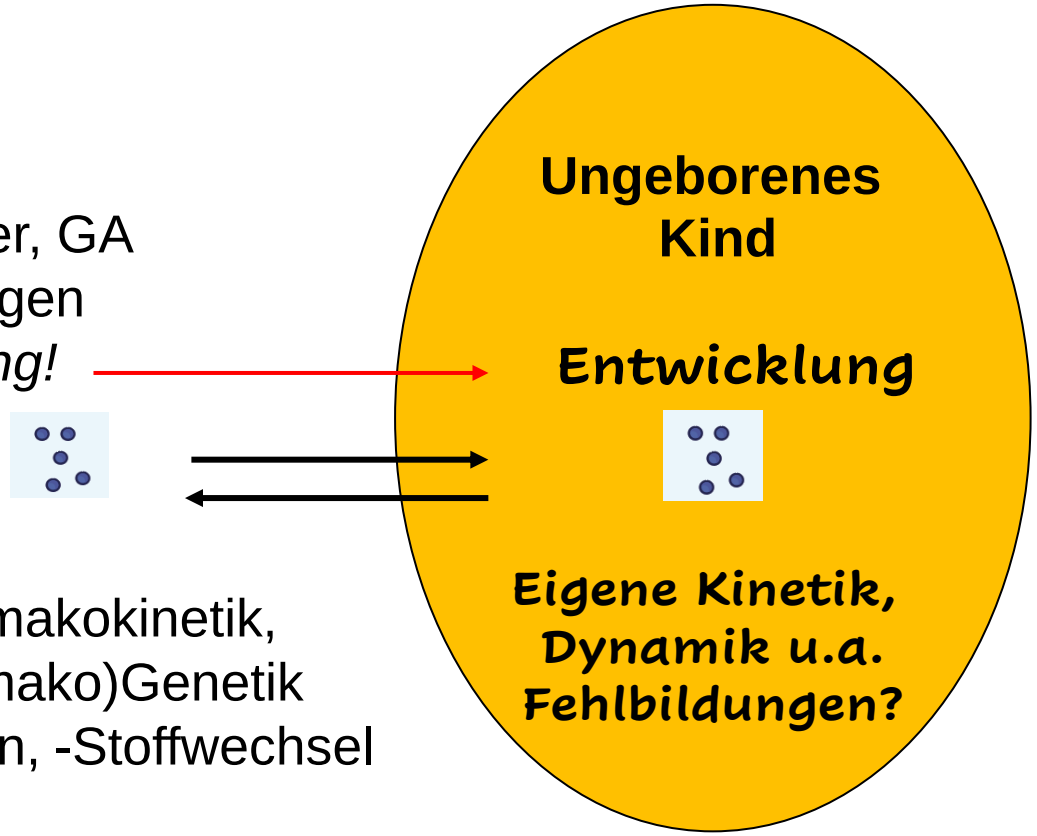


Pinheiro EA, Stika CS. Drugs in pregnancy: Pharmacologic and physiologic changes that affect clinical care. Semin Perinatol 2020;44:151221.

Schicksal ungeborenes Kind

Mutter
Physiologie, Alter, GA
Begleiterkrankungen
Fetal programming!

Arzneimittel
Eigenschaften
Dosierung, Pharmakokinetik,
-dynamik, (Pharmako)Genetik
Plazenta-Funktion, -Stoffwechsel



Take home messages

oder wofür sich das interdisziplinäre Netzwerk SAPP einsetzt:

Die Arzneimitteltherapie bei Schwangeren und Stillenden ist komplex und benötigt

- ✓ Ausbau des Netzwerks: Sammeln von **Evidenz UND Erfahrung**
- ✓ Zusammenarbeit der Gesundheitsversorger
- ✓ Förderung der universitären **Forschung und Lehre** (Aus- und Fortbildung)

Translation von der Forschung in den praktischen Alltag

- ✓ Angepasste Dosierungen, **klare Empfehlungen** auf bestehenden gesetzlichen Grundlagen (Art. 67a HMG) →
- ✓ **Offizielles Arzneimittelverzeichnis** für Schwangere und Stillende

UND bei HMG Revision: Gleichstellung zur Situation in der Pädiatrie

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Praktische Dosierungsanpassungen in Schwangerschaft und Stillzeit

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Dr. Verena Gotta
FPH Klinische Pharmazie/SGKPT Klinische Pharmakologie
Leiterin Klinische Pharmazie Pädiatrie
Pädiatrische Pharmakologie & Pharmakometrie
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Deklaration Interessenskonflikte
Andrea Burch

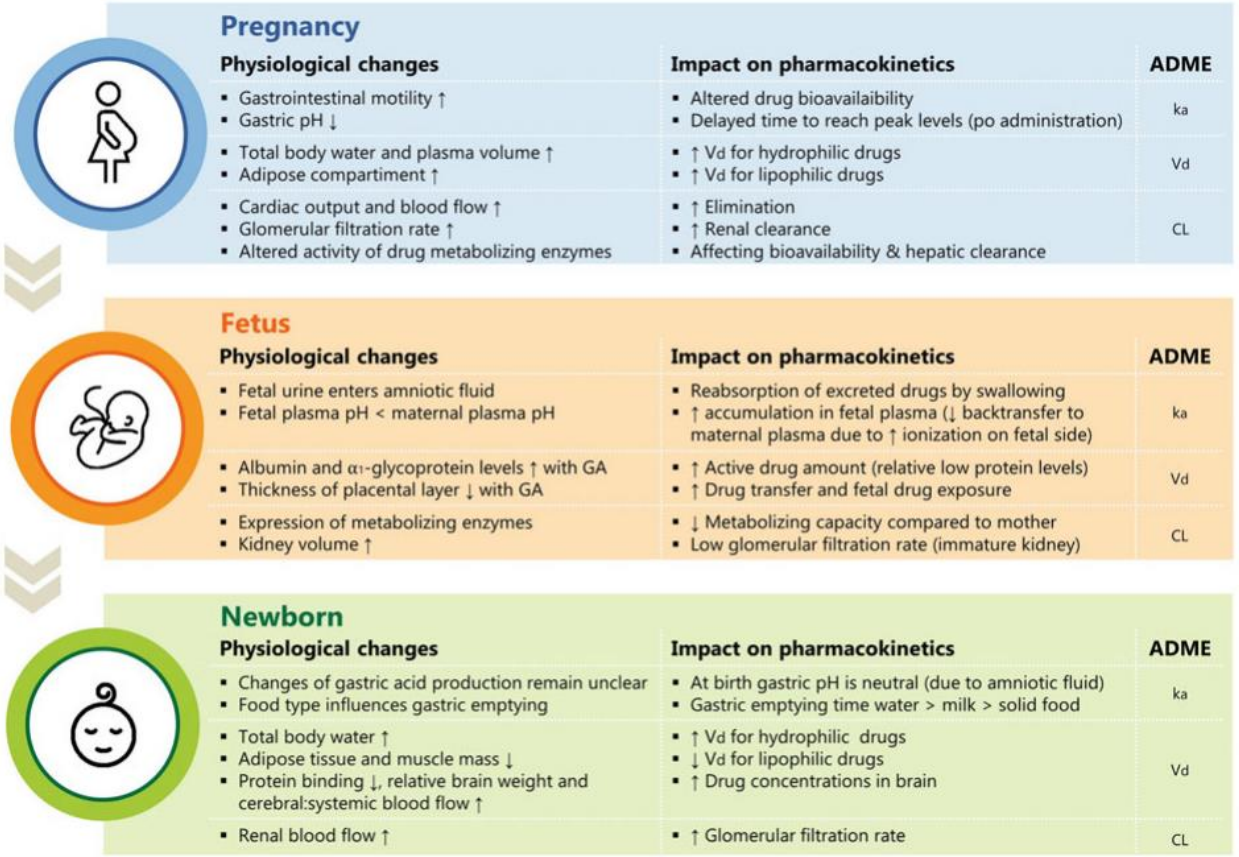
- Finanzielle oder Eigentümerinteressen: keine
- Tätigkeiten für die pharmazeutische Industrie und andere Firmen des Gesundheitssystems: keine
- Drittmittel / Spenden: keine
- Persönliche Beziehungen: Vizepräsidentin SAPP
- Sonstige Mitgliedschaften: pS, SAPhW

Deklaration Interessenskonflikte
Verena Gotta

- Finanzielle oder Eigentümerinteressen: -
- Tätigkeiten für die pharmazeutische Industrie und andere Firmen des Gesundheitssystems: -
- Drittmittel / Spenden: B. Braun Stiftung im Rahmen einer Ausschreibung zu «Arzneimittelsicherheit“ , Universität Basel
- Persönliche Beziehungen: -
- Sonstige Mitgliedschaften: GSASA, SGKPT, pharmaSuisse, ESDPPP, SGP, DPhG

Pharmakokinetische Änderungen während der Schwangerschaft (SS) und postpartal

1. SS-bedingte Medikation: **Absetzen? Timing?**
2. Weiterführen peripartaler Medikation: **Dosierung?**
3. SS-unabhängige Medikation: **Dosisanpassung? Wiederaufnahme? Stillen?**



Pregnancy

Physiological changes	Impact on pharmacokinetics	ADME
▪ Gastrointestinal motility ↑ ▪ Gastric pH ↓	▪ Altered drug bioavailaibility ▪ Delayed time to reach peak levels (po administration)	ka
▪ Total body water and plasma volume ↑ ▪ Adipose compartiment ↑	▪ ↑ Vd for hydrophilic drugs ▪ ↑ Vd for lipophilic drugs	Vd
▪ Cardiac output and blood flow ↑ ▪ Glomerular filtration rate ↑ ▪ Altered activity of drug metabolizing enzymes	▪ ↑ Elimination ▪ ↑ Renal clearance ▪ Affecting bioavailability & hepatic clearance	CL

Fetus

Physiological changes	Impact on pharmacokinetics	ADME
▪ Fetal urine enters amniotic fluid ▪ Fetal plasma pH < maternal plasma pH	▪ Reabsorption of excreted drugs by swallowing ▪ ↑ accumulation in fetal plasma (↓ backtransfer to maternal plasma due to ↑ ionization on fetal side)	ka
▪ Albumin and α_1-glycoprotein levels ↑ with GA ▪ Thickness of placental layer ↓ with GA	▪ ↑ Active drug amount (relative low protein levels) ▪ ↑ Drug transfer and fetal drug exposure	Vd
▪ Expression of metabolizing enzymes ▪ Kidney volume ↑	▪ ↓ Metabolizing capacity compared to mother ▪ Low glomerular filtration rate (immature kidney)	CL

Newborn

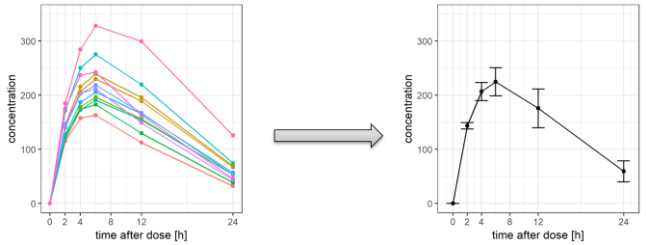
Physiological changes	Impact on pharmacokinetics	ADME
▪ Changes of gastric acid production remain unclear ▪ Food type influences gastric emptying	▪ At birth gastric pH is neutral (due to amniotic fluid) ▪ Gastric emptying time water > milk > solid food	ka
▪ Total body water ↑ ▪ Adipose tissue and muscle mass ↓ ▪ Protein binding ↓, relative brain weight and cerebral:systemic blood flow ↑	▪ ↑ Vd for hydrophilic drugs ▪ ↓ Vd for lipophilic drugs ▪ ↑ Drug concentrations in brain	Vd
▪ Renal blood flow ↑	▪ ↑ Glomerular filtration rate	CL

Van Donge T et al. Handb Exp Pharmacol 2020;261:325-37.

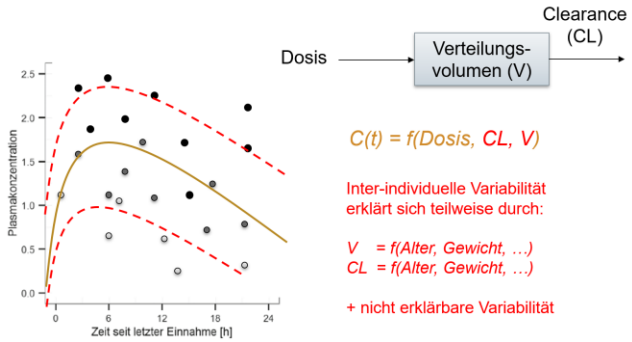
→ Voraussetzung für Entscheidung: prospektives Management ab Kinderwunsch resp. bei Beginn der Therapie in der Schwangerschaft

Modell-basierte Pharmakometrische Ansätze

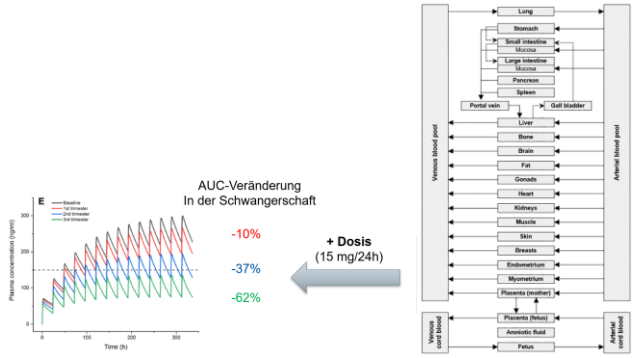
zur Vorhersage/Quantifizierung von PK-Änderungen während/nach der Schwangerschaft



Nicht-Kompartimentelle Analyse (NCA)
(z.B. Plasma Mutter)
Viele Konzentrationsbestimmungen pro Patient notwendig



Populations-Pharmakokinetik (PopPK)
(z.B. Plasma Mutter ±Muttermilch)
Wenige Konzentrationsbestimmungen pro Patient notwendig



Physiologisch-basierte Pharmakokinetik (PBPK)
(zB. Plasma Mutter, Fetus, Muttermilch…)
Keine Konzentrationsbestimmungen erforderlich

Komplexität

Annahmen

Interpolations- & Vorhersage-Möglichkeiten

Van Hasselt JG et al. BJCP 2012;74:932-9. Dallmann A et al. Clin Pharmacokinet 2017;56:1303-30. Gotta V et al. Ther Umschau 2015;72:679-86.

Dosisanpassungen gemäss Therapeutic Drug Monitoring (TDM) *(patientinnenindividuell)*		
	während Schwangerschaft	**postpartal**
Lamotrigin *(EURAP Study Group 2016; Sabers A, Acta Neurol Scand 2012;126:e1-4.)*	Erhöhung (siehe Algorithmus)	Reduktion, erste postpartale Messung spätestens nach 2 Wochen
Lithium *(Wesseloo R et al. Br J Psychiatry. 2017;211:31-6.)*	Erhöhung, zu Beginn der Wehen reduzieren/pausieren für 24-48 Std.	Reduktion, sofort präkonzeptionelle Dosis mit TDM alle paar Tage
Dosisanpassungen gemäss klinischem Ansprechen *(patientinnenindividuell)*		
Thyroxin *(Soldin OP et al. Ther Drug Monit 2010;32:265-8.)*	Erhöhung ab 2. Trimester abh. von TSH	abh. von TSH
Citalopram, Sertralin *(O'Brien L. et al. Forensic Sci Int 2010;196:93–6.; Freeman MP et al. J Clin Psychopharmacol 2008;28,646–53.; Sit DK et al. J Clin Psychiatry 2008;69:652-8.)*	Erhöhung ab 2. Trimester	Reduktion rasch postpartal
Methadon *(Ke AB et al. Br J Clin Pharmacol 2014;77:554-70.)*	Erhöhung	Reduktion rasch postpartal
Dosisanpassungen gemäss Richtlinien *(für die gesamte Population)*		
Amoxicillin (Betalaktame) *(Andrew MA et al. Clin Pharmacol Ther 2007;81:547–56.)*	Intervallverkürzung	Intervallverkürzung auch noch während erster Wochen postpartal
Metoprolol *(Roston TM et al. Heart Rhythm 2020;17:341-8. Haas DM et al. Obstet Gynecol 2012;120:1176-9.)*	Evtl. Intervallverkürzung und/oder Erhöhung	Indikation Arrhythmie: ab Geburt Dosis maximal wie UAWs tolerierbar
Nifedipin *(ter Laak MA et al. Int J Clin Pharmacol Ther 2015;53:84-91.; Silberschmidt AL et al. BJOG 2008;115:480-5.)*	Intervallverkürzung	Indikation Hypertonie: Intervallverlängerung

TSH: Thyroidea stimulierendes Hormon; UAW: unerwünschte Arzneimittelwirkung

Zusammenfassung

- ✓ Die Kinetik von Arzneimitteln kann (!) in der Schwangerschaft verändert sein
  - → Auch postpartal findet eine Veränderung in der Arzneimittelkinetik statt
  - → Möglicherweise Dosis(intervall)anpassung
  - → Monitoring nach Möglichkeit

- ✓ Modell-basierte Pharmakometrische Ansätze können die quantitative Vorhersage von Kinetik-Änderungen (+ deren Variabilität) in der Schwangerschaft unterstützen
  - → Evaluation des Bedarfs einer Dosisanpassung / klinischen Studien
  - → Möglich, selbst wenn noch keine klinischen Kinetik-Daten vorliegen

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Vom Früh- zum Termingeborenen: Medikamentöse Therapien sind komplex

Dr. med. Roland Gerull

Leitender Arzt Neonatologie
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Deklaration Interessenskonflikte
Roland Gerull

- Finanzielle oder Eigentümerinteressen: keine hier relevanten
- Tätigkeiten für die pharmazeutische Industrie und andere Firmen des Gesundheitssystems: keine
- Drittmittel / Spenden: keine hier relevanten
- Persönliche Beziehungen: keine hier relevanten
- Sonstige Mitgliedschaften: keine hier relevanten

Frühgeborene – Steroide pränatal

- **Betamethason 2 x 12mg 24h; Dexamethason 4 x 6mg 12h**
- Frühgeborene
  - Neonatale Morbidität / Mortalität ↓
  - Perinatale Mortalität ↓
  - Kindliche Entwicklungsverzögerung ↓

→ Frühgeborene profitieren von pränatalen Steroiden

- Spät Frühgeborene / Termingeborene
  - Respiratorische Morbidität ↓
  - Hypoglykämie ↑
  - Neurologische Entwicklung ↓ (?)

→ kurzfristiger Benefit aber langfristiges Risiko

McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for *women at risk of preterm birth. Cochrane Database Syst Rev 2020;12(12):CD004454*
Ninan K, Liyanage SK, Murphy KE, Asztalos EV, McDonald SD. Evaluation of long-term outcomes associated with preterm exposure to antenatal corticosteroids: A systematic Review and meta-analysis. JAMA Pediatr 2022;176(6):e220483

Frühgeborene – Steroide postnatal

Dexamethason systemisch (< 7 Lebenstag), 0.5mg/kg absteigend 12d

- Respiratorische Morbidität ↓
- Kindliche Entwicklungsverzögerung ↑
- Cerebralparese ↑

Budesonid inhalativ (2x 200µg 14d, dann 1x200µg)

- Respiratorische Morbidität → / ↓
- Mortalität ↑

→ Corticosteroide bei Frühgeborenen: kurzfristiger respiratorischer Benefit auf Kosten erhöhten Risikos für schlechte neurologische Entwicklung

Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2017 Oct 24;10(10):CD001146
Bassler D, Shinwell ES, Hallman M, Jarreau PH, Plavka R, Carnielli V, Meisner C, Engel C, Koch A, Kreutzer K, van den Anker JN, Schwab M, Halliday HL, Poets CF; Neonatal European Study of Inhaled Steroids Trial Group. Long-term effects of inhaled budesonide for bronchopulmonary dysplasia. N Engl J Med. 2018;378:148-57.

Frühgeborene – Coffein

- **Coffeincitrat**: Ladedosis 20mg/kg, Erhalt 5mg/kg
- Respiratorische Morbidität ↓
  - Reduktion Beatmung, CPAP, Sauerstoffbedarf, BPD
- Neurologie

2 Jahre	- Cerebralparese	0.58; 95% CI 0.39 - 0.87; P = 0.009
	- Entwicklungsverzögerung	0.81; 95% CI 0.66 - 0.99; P = 0.04
11 Jahre	- Motorische Einschränkung	0.66; 95% CI 0.48 - 0.90; P = 0.009
	- Intelligenz	0.89; 95% CI 0.62 - 1.27; P = 0.43
	- Aufmerksamkeit	1.02; 95% CI 0.62 - 1.67; P = 0.89

Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W; Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006:2112-21.
Mürner-Lavanchy IM, Doyle LW, Schmidt B, Roberts RS, Asztalos EV, Costantini L, Davis PG, Dewey D, D'Ilario J, Grunau RE, Moddemann D, Nelson H, Ohlsson A, Solimano A, Tin W, Anderson PJ; Caffeine for Apnea of Prematurity (CAP) Trial Group. Neurobehavioral Outcomes 11 years after neonatal caffeine therapy for apnea of prematurity. Pediatrics 2018;141(5):e20174047.

Frühgeborene – Coffein

- Metabolisierung / Ausscheidung steigt nach Geburt
- Dosisanpassung in ersten Lebenswochen für gleichbleibenden Spiegel notwendig

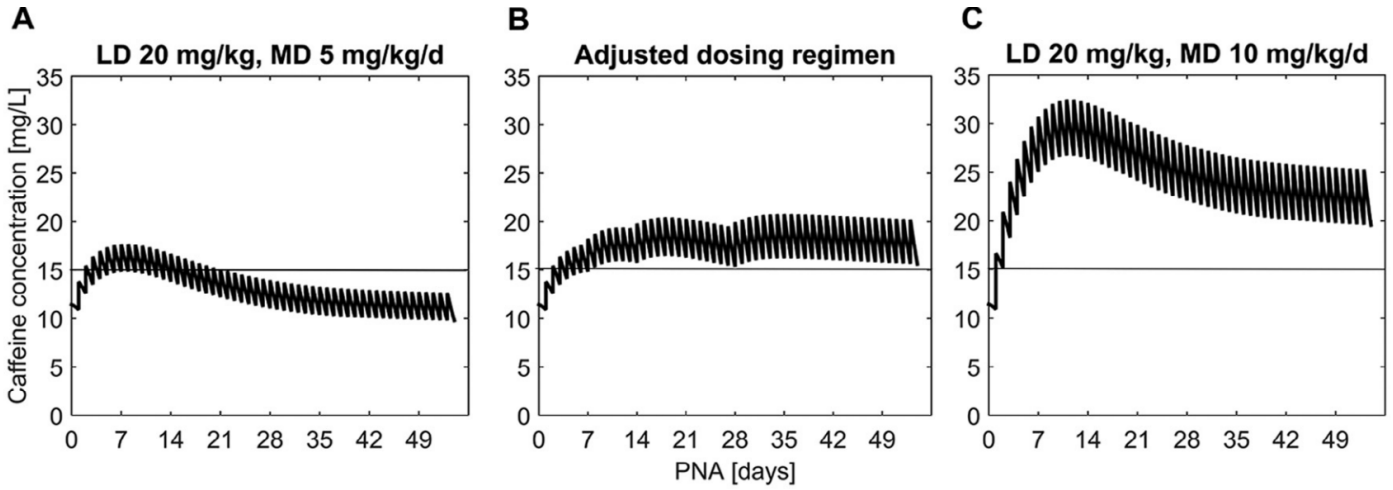

Figure 2. Prediction of caffeine concentration based on the integrated model with **A,** the standard caffeine citrate dosing regimen, **B,** an adjusted dosing regimen to produce a trough concentration of approximately 15 mg/L, and **C,** a maintenance dose (*MD*) of 10 mg/kg/day.

Koch G, Datta AN, Jost K, Schulzke SM, van den Anker J, Pfister M. Caffeine citrate dosing adjustments to assure stable caffeine concentrations in preterm neonates. J Pediatr 2017;191:50-56.e1.

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Académie Suisse Pharmacologie Périnatale ASPP
Academia Svizzera Farmacologia Perinatale ASFP
Swiss Academy Perinatal Pharmacology SAPP

Jahrestagung 2.11.2023

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In welchem Alter wie dosieren: Lösungsansatz von SwissPedDose

Dr. sc. ETH Elisabeth Giger

Fachperson Harmonisierung Neonatologie SwissPedDose
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Deklaration Interessenskonflikte
Elisabeth Giger

- Finanzielle oder Eigentümerinteressen: Keine
- Tätigkeiten für die pharmazeutische Industrie und andere Firmen des Gesundheitssystems: Keine
- Drittmittel / Spenden: SwissPedDose ist finanziert durch das Bundesamt für Gesundheit (BAG)
- Persönliche Beziehungen: Fachperson Harmonisierung Verein SwissPedDose
- Sonstige Mitgliedschaften: Keine

DOSIERUNGS-ANFRAGE

Spitalinterne Dosierungsabfrage
Datenexpertinnen- und experten (Spital-apotheker/in aus den 8 beteiligten Kinderspitälern)

Literaturrecherche
Harmonisierungsspezialist/in von SwissPedDose

Dosierungsvorschlag
Harmonisierungsspezialist/in von SwissPedDose

Harmonisierung
Dissens/Konsens der Harmonisierungs-expertinnen und Harmonisierungsexperten (Fachärztin und Facharzt aus den 8 Kinderspitälern)

Nationale pädiatrische Arzneimitteldosierung

Generelles Vorgehen

- Erstellung eines Dosierungsvorschlags aufgrund von Literaturdaten und aktuell verwendeten Dosierungen (hier: Auszug Fluconazol, invasive Candidiasis)

Fach-information	<14 days: 6-12 mg/kg every 72 h 14-28 days: 6-12 mg/kg/dose every 48 h
BNFc	<14 days: 6-12 mg/kg/dose every 72 h 14-28 days: 6-12 mg/kg/dose every 48 h
NNF7	<14 days: 6-12 mg/kg/dose every 72 h 14-28 days: 6-12 mg/kg/dose every 48 h
Nelson's	12 mg/kg/day q24h, after a load of 25 mg/kg/day
Kinder-formularium	Start: 25 mg/kg/dose Maintenance: <14 days: 12 mg/kg/dose every 72 h 14-28 days: 12 mg/kg/dose every 48 h
Leroux et al 2018	loading dose: 25 mg/kg/dose maintenance dose: <30 weeks PMA: 12 mg/kg/day >30 weeks PMA: 20 mg/kg/day

- Diskussion mit Experten. Ladedosis: 25 mg/kg/dose, Erhalt: 12 mg/kg/dose 1x tgl
- Publikation

Daten SwissPedDose Datenbank

	Total	Neonatologie
Wirkstoffe	212	88
Dosierungsempfehlungen (Wirkstoff, Indikation, Verabreichungsweg)	648	157
Zulassungsstatus Off-label Unlicensed Licensed	 n.a. n.a. n.a.	 80% 11% 9%

Stand: Oktober 2023

Zusammenfassung

- Bestimmung von Arzneimitteldosierungen für Kinder ist eine Herausforderung
- Für Neugeborene gibt es sehr wenige zugelassene Arzneimittel
- Dosierungsempfehlungen unter Einbezug von Literatur und Experten der grössten Schweizer Kinderkliniken (via online Tool)
- www.swisspeddose.ch/datenbank: National harmonisierte Arzneimitteldosierungen

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Swiss TPH

Probleme und medikamentöse Ansätze bei Schwangeren und ihren Neugeborenen in Entwicklungsländern

Daniel H. Paris, MD PhD DTM&H

Leiter, Departement Medizin, Swiss TPH

Deklaration Interessenskonflikte
Daniel H. Paris

- Finanzielle oder Eigentümerinteressen: Keine Interessenskonflikte
- Tätigkeiten für die pharmazeutische Industrie und andere Firmen des Gesundheitssystems: Involviert in klinische Forschungsprojekte und Dienstleistungen für Medikamentenentwicklung in Zusammenarbeit mit Novartis, Merck, MMV und Sanofi.
- Drittmittel / Spenden: Keine
- Persönliche Beziehungen: Keine
- Sonstige Mitgliedschaften: Keine

Übersicht

Ausgangslage und Probleme

- Studien über die Ursachen von «Fieber in der Schwangerschaft» in den Tropen
- Aktuell wichtige Probleme in SE-Asien und Afrika
- Zugang zu «Drugs, Diagnostics and Vaccines» in LMICs (Low and Middle Income Countries)
- Schwangere Frauen und Kinder – zu wenig wahrgenommene vulnerable Populationen

Medikamente für Mütter und ihre Neugeborenen

- Erfahrungen aus der Malariaforschung
- Medikamente für die Kleinsten
  (Lehren der CALINA Studie, DR Congo)
- Zugang zu Medikamenten für Mütter und Kinder
  (Lehren der CARAMAL Studie, aus 3 Afrikanischen Ländern)

Screening und Zukunft

Regional wichtige endemische Krankheiten

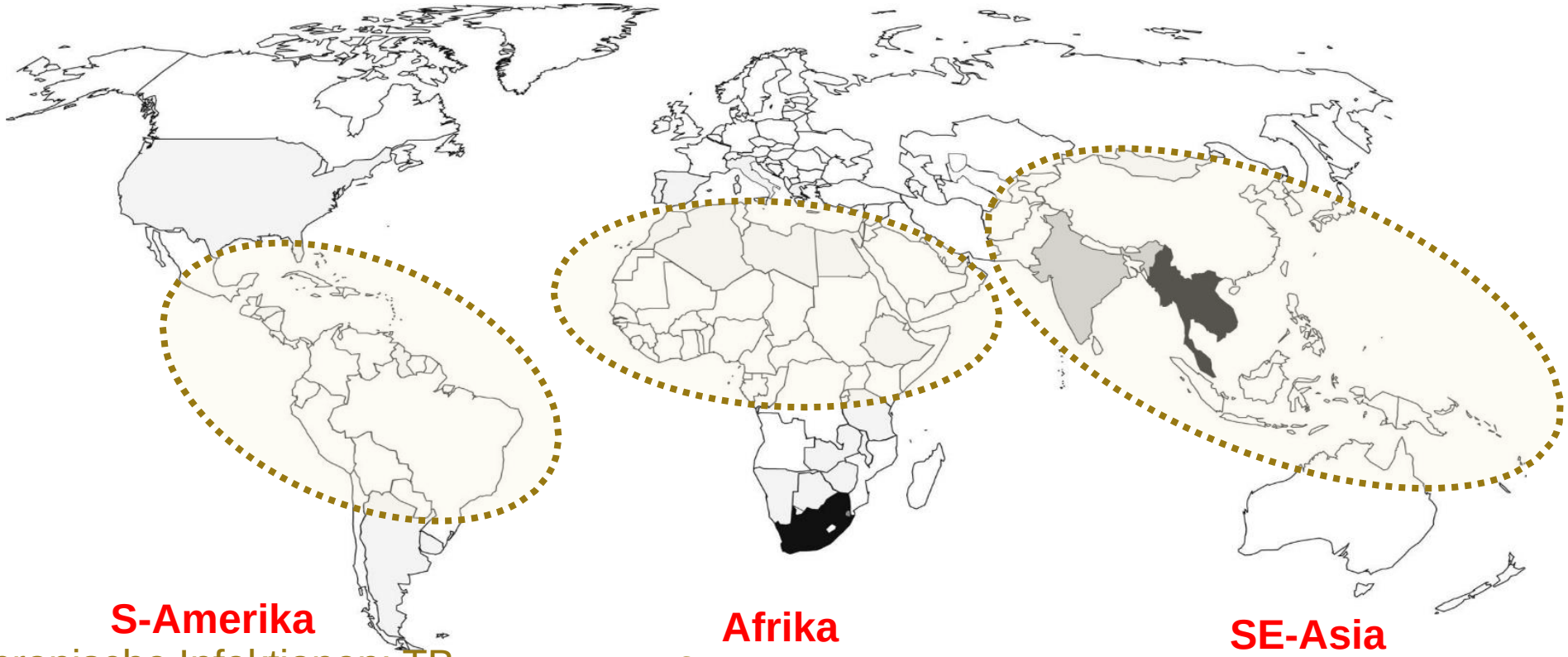
Klinisch relevante Infektionskrankheiten

- Tuberkulose
- Malaria
- HIV

- Dengue (Flaviviren)
- Influenza
- Chikungunya
- Zika Virus

- Rickettsiosen
- Q Fieber
- Brucellose
- Leptospirose
- Abdominaltyphus
- Melioidose

- Schistosomiasis
- Strongyloidiasis
- Leishmaniosen
- Trypanosomiasis



S-Amerika
Chronische Infektionen; TB, Leishmaniasis, fungale Infection.; undiagnost. HIV

Afrika
W-Afrika ≠ E-Afrika
Malaria, NTDs (Helminthen and Protozoen), Zoonosen, HIV und TB hoch prävalent

SE-Asia
Malaria, Dengue, Rickettsiosen, Leptospirose, Abd.typhus u.a.

Delord M et al. Travel Med Infect Dis 2014;12:443-58.

Zugang zu Medikamenten für Mütter und Neugeborene

«In Ländern mit niedrigem Einkommen ist die Verfügbarkeit von wichtigen Medikamenten in Gesundheitseinrichtungen schlecht, die Qualität der Behandlungen mangelhaft, es kommt häufig zu Lieferengpässen und zu einer suboptimalen Verschreibung und Verwendung von Medikamenten»
WHO, AfricaRenewal, 2020

Beispiele zu Malaria Medikamente

Papua NeuGuinea: Artemether/Lumefantrin (Mala-1, 2017-2019)

Jahrelange Lieferengpässe hatten zur Folge, dass nicht-zugelassene Medikamente oder Artemether als Mono-Therapie benutzt wurden. PNG lief Gefahr, die hart erkämpften Erfolge im Kampf gegen die Malaria der letzten Jahre zu verlieren, und zu einer Quelle der Resistenzbildung gegen Artemisinin-Medikamente zu werden.

Weltweit: Chloroquin and Hydroxychloroquin Engpass (2020-2021, COVD-19 Pandemie)

Initial nicht beabsichtigte schädliche Folgen bei der Umwidmung von Malariamitteln gegen SARS-CoV-2 ohne ausreichenden Nachweis des Nutzens machten deutlich, wie wichtig es ist, auch im Zusammenhang mit einer Pandemie wissenschaftliche Strenge zu wahren.

Zusammenfassung

Anhand von aktuellen Studien am Swiss TPH werden Erkenntnisse wird die Versorgung von Schwangeren und Neugeborenen in Entwicklungsländern präsentiert und im Zusammenhang mit Medikamenten und der Malaria besprochen:

- Zugang zu Medikamenten (Artemether/Lumefantrin, Chloroquin)
- Resistenzen von Medikamenten (ACT; Artemisinin Kombination
- Neugeborenen Formulierungen und pre-referral Strategien(Supp.)

Zum Schluss wird ein kurzer Einblick in die Entwicklung von gezielten Gen Transkriptionspanels im Blut gegeben. Diese erlauben zunehmend eine Überwachung der immunologischen Veränderungen während der Schwangerschaft und tragen zur Früherkennung von Schwangerschaftskomplikationen bei.

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Poster-Abstracts

NR.1

TITLE	**Mobile application to support a nutrient-rich diet during pregnancy and breastfeeding: development of a beta version**
	Grünenfelder L (1), Huwyler J (1), von Mandach U (2) (1) Department of Pharmaceutical Sciences, Division of Pharmaceutical Technology University of Basel, Switzerland (2) SAPP, Department of Obstetrics, University Hospital Zurich, Switzerland
ABSTRACT	**Purpose:** During pregnancy and breastfeeding, the need for micro- and macronutrients increases. Normally the increased nutritional requirement can be covered by a balanced diet. Adequate intake of vitamins and minerals not only contributes to the positive course of pregnancy, but also supports the healthy development of the fetus/newborn and the health of the mother. The development of the beta version of a mobile application is intended to support women in pregnancy and during breastfeeding who are striving for optimal nutrition. The mobile application is designed to provide to types of information: (I) information on the nutritional content of foods and (II) key information for healthy diet during these two life stages. **Methods:** Three different methods were followed: (I) A market analysis identified already available applications dealing with the topic of healthy nutrition and/or micro- and macronutrient supply during pregnancy and lactation. (II) Based on the Swiss nutritional database, a separate study database was created with the aim of using it as the data basis for the development of the beta version. (III) In addition, to obtain information on the importance of nutrients during pregnancy and lactation, a literature review was conducted. **Results**: Through predefined selection criteria, 14 already available applications for the nutrition of pregnant and breastfeeding women, each with different functions, could be identified within the market analysis. The market analysis also showed that none of the existing mobile applications allowed searching for and finding information in the way that was planned for the beta version. In order to use the created study database as the data foundation for the beta version, it was compiled in a multi-stage process from 49 variables and 1`215 records. The results of the literature research were prepared in such a way that they could be incorporated into the beta version as information modules, where they are available to users as sources of information. **Conclusion:** It can be assumed that the application developed in this work serves a market niche, which enables an unrivaled existence and also offers potential for future development. To confirm this assumption, the next step would be to survey the suitability and usefulness of the beta version by women belonging to the target audience. The results of the survey will be used for the further development as well as the improvement of the beta version. The present work/beta version is intended to make a further contribution to the practical implementation for the user (pregnant woman, nursing mother) of the theoretical knowledge on the positive influence of an adequate nutrient supply on the course of pregnancy. The application should serve women as an instrument to influence the positive course of their pregnancy and breastfeeding individually and self-determined. REFERENCES Ernährung während der Schwangerschaft. Bern: Schweizerische Gesellschaft für Ernährung SGE; 2015 Zimmermann M, Schurgast H, Burgerstein UP. Burgerstein Handbuch Nährstoffe. 13. Aufl. Stuttgart: TRIAS; 2018 **Scan to check the beta version!**
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NR.2

TITLE	**Utilization of prescribed drugs in pregnancy between 2015 and 2021 in Switzerland: A retrospective analysis of Swiss healthcare claims data**
	Marxer CA (1,2), Graber S (3), Surbek D (4), Huber C (3), Panchaud A (5,6,7), Meier CR (1,2), **Spoendlin J** (1,2) (1) Hospital Pharmacy, University Hospital Basel, Basel, Switzerland (2) Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland (3) Department of Health Sciences, Helsana Insurance Group, Zurich, Switzerland (4) Department of Obstetrics and Gynaecology, University Hospital, University of Bern, Switzerland (5) Institute of Primary Health Care (BIHAM), University of Bern, Switzerland (6) Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Switzerland (7) Materno-fetal and Obstetrics Research Unit, Department “Femme-Mère-Enfant”, University Hospital, Lausanne, Switzerland
ABSTRACT	**Purpose** The use of prescribed drugs during pregnancy in Switzerland is not well understood. Therefore, we aimed to evaluate the utilization of prescribed drugs during pregnancy in outpatient care in Switzerland. **Methods** We conducted a population-based descriptive study using anonymized healthcare claims data of one of the biggest health insurance companies in Switzerland, the insurance group Helsana (2015-2021). We established a cohort of pregnancies by identifying deliveries and estimating the date of the last menstrual period. We quantified the utilization of drugs (≥1 and ≥5 filled distinct drug prescriptions) during pregnancy overall, by trimester (T), and by age category. We also quantified the prevalence of exposure to the most frequently filled drug prescriptions during pregnancy and by trimester. Results were weighted based on the demographic distribution of the Helsana population relative to the Swiss population. **Results** We identified a weighted pregnancy population of 502’100 pregnancies with a median maternal age at delivery of 32 years (IQR=28-35). During pregnancy, 87.7% of women filled ≥1 drug prescription (97.8% when including vitamins, minerals, iron preparations, iodide, and vaccinations) with the largest proportion in T3 (vs 67.2%/59.5% in T1/T2) and among women <26 years of age (90.6% vs. 87.3% in 26-35, 87.5% in ≥35). Overall, 30% of pregnant women filled ≥5 distinct drug prescriptions during pregnancy, and 8.2% filled ≥5 distinct drug prescriptions during T1 alone, when organogenesis takes place. During T1, progesterone was claimed by the largest proportion of women (10.9%), followed by antiemetics (9.9%; 8.6% metoclopramide and 1.3% ondansetron), and paracetamol (8.2%). However, the first-line antiemetics (antihistamines) were not captured because they were not covered by health insurance during the study period. In T2, paracetamol (9.9%) was followed by the vaginal desinfectant dequalinium chloride (4.1%), levothyroxine (4.0%), and amoxicillin with clavulanic acid (2.8%). In T3, paracetamol (7.0%), anti-D immunoglobulins (3.7%), and drugs for the treatment of gastroesophageal reflux (proton pump inhibitors: 7.0%, mineral antacids: 3.6%, ranitidine: 1.5%) represented the top 3 most frequently filled drug claims. Other drugs among the most commonly claimed drugs during pregnancy were acetylsalicylic acid, fosfomycin, fluconazole, clotrimazole, estriol, nifedipine, and insulin. **Conclusion** Most of the frequently used drugs during pregnancy in Switzerland are considered safe. However, the observed large drug burden during pregnancy underlines the importance of evidence on the benefit-risk profile of individual drugs used during pregnancy. This is especially important for controversial drugs, such as the antiemetic ondansetron during trimester 1. Reference Gerbier E, Graber SM, Rauch M, Marxer CA, Meier CR, Baud D, Winterfeld U, Blozik E, Surbek D, Spoendlin J, Panchaud A. Use of drugs to treat symptoms and acute conditions during pregnancy in outpatient care in Switzerland between 2014 and 2018: analysis of Swiss healthcare claims data. Swiss Med Wkly. 2021;151:w30048.
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NR.3

TITLE	**Exposure to teratogens in pregnancy and in women of childbearing age between 2015 and 2021 in Switzerland: A retrospective analysis of Swiss healthcare claims data**
ABSTRACT	Marxer CA (1,2), Graber S (3), Surbek D (4), Huber C (3), Panchaud A (5,6,7), Meier CR (1,2), **Spoendlin J** (1,2) (1) Hospital Pharmacy, University Hospital Basel, Basel, Switzerland, (2) Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland, (3) Department of Health Sciences, Helsana Insurance Group, Zurich, Switzerland, (4) Department of Obstetrics and Gynaecology, University Hospital, University of Bern, Switzerland, (5) Institute of Primary Health Care (BIHAM), University of Bern, Switzerland, (6) Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Switzerland, (7) Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland **Purpose** Exposure to teratogens during pregnancy and by women of childbearing age in Switzerland is not well investigated. Therefore, we aimed to evaluate the exposure to teratogens during pregnancy and by women of childbearing age in outpatient care in Switzerland. **Methods** We conducted a population-based descriptive study using anonymized healthcare claims data of one of the biggest health insurance companies in Switzerland, the insurance group Helsana. We quantified the prevalence of exposure to weak, proven, and unequivocally potent teratogens[1] in women of childbearing age in 2021 as well as in pregnant women during trimester 1 (T1) and during a 9-month period before the estimated date of the last menstrual period (LMP) between 2015-2021. Results were weighted based on the demographic distribution of the Helsana population relative to the Swiss population. Our results were then compared to teratogen exposure in Germany quantified by the health insurance BARMER[2]. **Results** We identified a weighted pregnancy population of 502'100 pregnancies (median maternal age=32 years (IQR=28-35) and 1'413'519 women of childbearing age (median age=33, IQR=25-41). In total, 14.4% of women of childbearing age were exposed to ≥1 potentially teratogenic drug in 2021 (vs. 7.8% in Germany in 2020). In total, 11.5% were exposed to weak teratogens, most frequently (9.5%) systemic glucocorticoids, for which teratogenicity is debated until today (vs 6.8% and 4.6% in Germany). Proven teratogens and unequivocally potent teratogens were dispensed to 1.2% and 2.5% of women of childbearing age (vs 0.8% and 0.6% in Germany). In Switzerland, the overall exposure to teratogens increased with age (<26 years: 12.2%, ≥36 years: 16.8%), but unequivocally potent teratogens were most frequently used among women aged <26 years (4.7% vs. <2% in other age groups). This was mainly driven, by exposure to systemic retinoids (4.1%), whereas the second most frequent potent teratogen was valproate (0.2%). Before pregnancy and during T1, women were less frequently exposed to teratogens (7.0% and 1.3%). The proportion of women exposed to weak and proven teratogens during T1 was higher in Switzerland vs Germany (1.2% vs. 0.9% and 0.10% vs. 0.05%), with the most frequent teratogens being systemic glucocorticoids (weak, 104/10'000), cotrimoxazole (weak, 22/10'000), thiamazole/carbimazole (weak, 3.2/10'000), carbamazepine (proven, 2.6/10'000), and topiramate (proven, 2.6/10'000). The proportion of women exposed to unequivocally potent teratogens during T1 was similar in Switzerland (0.04%) and Germany (0.03%). Valproate was the most frequently claimed potent teratogen during T1 (1.2/10'000), but exposure decreased after the introduction of a pregnancy prevention program in 2018 (0.9-1.1/10'000 in 2019-2020 vs. 1.9-4.1/10'000 in 2016-2018). Concerningly, 25/10'000 women claimed systemic retinoids within 9 months before pregnancy, and 1.2/10'000 claimed systemic retinoids during T1. While the estimated LMP may not be entirely exact in all women, this number shows exposure to systemic retinoids very close to the date of conception. **Conclusion** The majority of women in Switzerland stopped teratogenic drugs before pregnancy. However, exposure to teratogens in women of childbearing age and during T1 was higher in Switzerland than in Germany. Especially, use of systemic retinoids close to the date of conception warrants further investigation. Systemic retinoids lead to malformations in >50% of T1-exposures, and, unlike valproate, they are almost never absolutely indicated (treatment of acne vulgaris). Our results further suggest that the pregnancy prevention program for valproate may have helped to reduce exposure during T1, but further studies are needed. References 1. Dathe K, Schaefer C. The Use of Medication in Pregnancy. *Dtsch Arztebl Int* 2019;116:783-90. 2. Grandt D, Lappe V, Schubert I.Arzneimitteltherapie in der Schwangerschaft und bei Frauen im gebärfähigen Alter. BARMER Arzneimittelreport 2021. https://www.barmer.de/presse/infothek/studien-und-reporte/arzneimittelreporte
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NR.4

TITLE	**Transplacental passage of hyperforin and hypericin**
ABSTRACT	Spiess D (1,2), Abegg VF (2), **Kuoni S** (1), Chauveau A (2), Reinehr M (3), Oufir M (2), Potterat O (2), Hamburger M (2), Simões-Wüst AP (1) (1) Department of Obstetrics, University Hospital Zurich, University of Zurich, Zurich, Switzerland (2) Division of Pharmaceutical Biology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland (3) Department of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland **Purpose** Mild depressions are common during pregnancy and can lead to complications like preterm birth if left untreated. Most medications for depression may not only cause side effects in the mother, but also easily cross the placental barrier and reach the foetus. Concerns on tolerability, teratogenicity and impact on neonatal outcomes exist. Pregnant women in need of antidepressants therefore face a dilemma between using and refraining from using them. Safe medications for mild mental diseases in pregnancy are therefore needed. In the treatment of mild to moderate depression, the herb St. John's wort (*Hypericum perforatum* L.) has become an alternative to already established pharmacological antidepressants. However, the use of St. John's wort during pregnancy is not recommended due to insufficient toxicological data. **Methods** To find out whether the main compounds St. John's wort can cross the placental barrier, the transplacental transport of hyperforin and hypericin was evaluated using the human *ex vivo* placental perfusion model. This model is the gold-standard among placental transfer models, and we have recently shown its usefulness for studying the transplacental transfer of phytochemicals in comparison with that of the connectivity marker, antipyrine. All samples were quantified by a newly developed and validated U(H)PLC-MS/MS bioanalytical method. **Results** Perfusion data obtained with donated term placentae showed that only minor amounts of hyperforin passed into the foetal circuit, reaching maximal FM (foetal-maternal concentration) ratio of 0.18 after 180 minutes. Hypericin, on the contrary, did not cross the placental barrier, resulting in FM ratios of zero. None of the two compounds affected significantly metabolic, functional, and histopathological parameters of the placenta. **Conclusion** Since the *ex vivo* perfusion model mimics the placental barrier structure at term, where transplacental transfer is known to be maximal, the potential foetal exposure to hypericin and hyperforin is likely expected to be minimal throughout the pregnancy. References Spiess D et al. Transplacental passage of hyperforin, hypericin, and valerenic acid. Front Pharmacol 2023;14:1123194. Spiess D et al. Placental Passage of protopine in an ex vivo human perfusion system. Planta Med 2023;89:194-207.
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NR.5

TITLE	**PEDeDose – Impact of Clinical Decision Support on Pediatric Drug Dose Prescribing**
	Higi L (1,2), Käser K (1), Wälti M (1), Bravo S (1), Skilandat M (1), Vonbach P (1) (1) PEDeus Ltd., Zurich, Switzerland (2) Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland
ABSTRACT	**Purpose** Drug dosing errors are among the most frequent causes of preventable harm in pediatrics. The manual calculation by healthcare professionals (HCP) is a well-described source of error. To prevent calculation errors, we developed a clinical decision support system (CDSS). PEDeDose supports HCP by calculating the dosage for the individual patient. In order to evaluate the impact of PEDeDose, a simulation trial was conducted. Additionally, new modules are being developed to further increase the safety of pharmacotherapy in children. **Methods** In a randomized within-subject trial, we compared: (I) the calculation with the CDSS PEDeDose (with built-in dose calculator) with either (II) a pocket calculator and the PEDeDose dosing data only or (III) a pocket calculator and the Summary of Product Characteristics (SmPC). For this, HCP were asked to derive dosages for 18 hypothetical patient cases. We assessed the number of dose calculation errors and the calculation time. In order to develop additional algorithms to support HCP, we defined the user requirements for new PEDeDose modules and functionalities together with clinical specialists. **Results** A total of 52 HCP participated in the simulation trial and calculated 932 dosages. Overall, there was a 77% reduction of calculation errors when (I) the CDSS PEDeDose was used as compared to (III) the pocket calculator and the SmPC. Furthermore, we found that the dose derivation step with the (I) CDSS PEDeDose was twice as fast as compared to (III) the pocket calculator and the SmPC. An exploratory analysis revealed that using (II) the PEDeDose data only but without the built-in calculator did not substantially reduce errors. Three new PEDeDose module will be available in the near future, with the following aims: (1) adjustment of dosages in patients with impaired kidney function, (2) a module for the preparation and the administration of parenteral drugs, and (3) a mobile app for emergency care. **Conclusion** Our results provide robust evidence that the use of the CDSS PEDeDose is safer and more efficient than manual dose derivation in pediatrics. Interestingly, only consulting a dosing database was not sufficient to substantially reduce errors. Based on these results, we are confident that the use of the CDSS PEDeDose ensures a higher safety and speeds up the prescribing process in practice. The success of PEDeDose enabled us to move forward by providing HCP with additional functionalities for the safe and efficient pharmacotherapy in children. References Gates PJ, Meyerson SA, Baysari MT, Westbrook JI. The Prevalence of Dose Errors Among Paediatric Patients in Hospital Wards with and without Health Information Technology: A Systematic Review and Meta-Analysis. Drug Saf 2019;42:13-25. Higi L, Käser K, Wälti M, Grotzer M, Vonbach P. Description of a clinical decision support tool with integrated dose calculator for paediatrics. Eur J Pediatr 2022;181:679-89. Higi L, Schmitt R, Käser K, Wälti M, Grotzer M, Vonbach P. Impact of a clinical decision support system on paediatric drug dose prescribing: a randomised within-subject simulation trial. BMJ Paediatrics Open 2023;7(1):e001726.
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NR.6

TITLE	***Bryophyllum pinnatum* attenuates oxytocin-induced pro-inflammatory signalling pathways in human myometrial cells**
	Zurfluh L (1),, Santos S (1,2), Mennet M (3), Potterat O (2), von Mandach U (1), Hamburger M (2), Simões-Wüst AP (1) (1) Department Obstetrics, University Hospital Zurich, Zurich (2) Division of Pharmaceutical Biology, University Basel, Basel (3) Weleda AG, Arlesheim
ABSTRACT	**Purpose** Preterm birth is one of the leading causes of neonatal morbidity and mortality. Preterm myometrial contractions are a common cause of preterm labor and are treated with tocolytic agents. Over the past few years, the potential of anti-inflammatory substances in the treatment of preterm labor has become apparent. *Bryophyllum pinnatum* - a traditional medicinal plant with, among others, anti-inflammatory properties - has been used in the treatment of preterm labor, first in anthroposophic hospitals and, recently, in conventional settings. The main advantage of *B. pinnatum* compared to synthetic tocolytic agents is the rare occurrence of side effects. Furthermore, *in vitro* work with human myometrial cells has shown that *B. pinnatum* leaf press juice (BPJ) inhibits intracellular calcium signaling induced by oxytocin, a hormone known to play a major role in labor. The aim of this work was therefore to characterize the effect of *B. pinnatum* on the pro-inflammatory MAPK cascade of the oxytocin-signaling pathway. **Methods** Experiments were performed with an immortalized human myometrial cell line (hTERT-C3). Cells were treated with either BPJ, corresponding fractions, single compounds or just medium and stimulated with oxytocin (for 5 min in phosphorylation experiments and 6 h for enzyme expression experiments). As a positive control, the tocolytic agent atosiban was used. Activation of the MAPK proteins p38, SAPK/JNK and ERK1/2 by phosphorylation was analyzed by immunoblotting. The effect of BPJ-compounds on COX-2 expression was analyzed with ELISA. **Results** BPJ and a bufadienolide-enriched fraction inhibited the oxytocin-driven activation of the MAPKs SAPK/JNK and ERK1/2, but not of p38. Some BPJ-compounds inhibited the oxytocin-induced expression of COX-2. The effects on the MAPK signaling cascade were comparable to those of the oxytocin-receptor antagonist and tocolytic agent atosiban. **Conclusion** BPJ, the bufadienolide-enriched fraction and some single compounds attenuate inflammatory processes triggered by oxytocin. In a next step, the effect of *B. pinnatum* on further downstream processes in the MAPK cascades (e.g. prostaglandin production) needs to be investigated. Our findings further substantiate the use of *B. pinnatum* as a well-tolerated treatment for preterm labor. References Fürer K, Simões-Wüst A P, von Mandach U, Hamburger M, & Potterat O. Bryophyllum pinnatum and related species used in anthroposophic medicine: constituents, pharmacological activities, and clinical efficacy. Planta Med 2016;82:930-41. Santos S, Zurfluh L, Mennet M, Potterat O, Von Mandach U, Hamburger M, & Simões-Wüst A P Bryophyllum pinnatum compounds inhibit oxytocin-induced signaling pathways in human 2myometrial cells. Front Pharmacol 2021;12:632986.
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NR.7

TITLE	***In silico* studies to evaluate dosing intervals associated with low risk of amikacin accumulation in preterm neonates**
	Gotta V (1,2,3), Bielicki JA (4,5), Paioni P (1,6), Csajka C (1,7,8), Bräm DS (2), Berger C (6,9), Giger E (9), Buettcher M (1,2,10), Posfay-Barbe KM (11), van den Anker J (2), Pfister M (1,2) (1) SwissPedDose/SwissPedNet collaboration expert team (2) Pediatric Pharmacology and Pharmacometrics, University of Basel Children's Hospital, Basel, Switzerland (3) Pediatric Clinical Pharmacy, University of Basel Children's Hospital, Basel Switzerland (4) Paediatric Research Centre and Paediatric Infectious Diseases and Vaccinology Division, University of Basel Children's Hospital, Basel, Switzerland (5) Centre for Neonatal and Paediatric Infection, St George's University, London, United Kingdom (6) Division of Infectious Diseaeses, University Children's Hospital Zürich, 8032 Zürich (7) Center for Research and Innovation, University Hospital and University of Lausanne, Lausanne, Switzerland (8) School of Pharmaceutical Sciences, University of Geneva and University of Lausanne, Geneva, Switzerland (9) SwissPedDose, Zürich, Switzerland (10) Paediatric Infectious Diseases, Lucerne Children's Hospital, Cantonal Hospital Lucerne, Switzerland and Faculty of Health Sciences and Medicine, University Lucerne, Switzerland (11) General Pediatrics & Pediatric Infectious Diseases Unit, Department of Woman, Child and Adolescent, University Hospitals of Geneva & Medical School of Geneva, Geneva, Switzerland
ABSTRACT	**Purpose** Pharmacometric approaches are frequently applied to guide dose decisions during the development of new medicines. We aim to demonstrate how pharmacometric modelling and simulation can provide a scientific rationale for optimizing drug dosing in the context of the Swiss national dose harmonization project in neonatology, based on the example of amikacin. **Methods** Amikacin neonatal dosing is stratified by post-menstrual age (PMA) and post-natal age (PNA) in Switzerland and many other countries across the globe. Clinical concerns have been raised for the subpopulation of neonates with a PMA of 30-35 weeks and a PNA of 0-14 days ("subpopulation of clinical concern") as potentially oto-/nephrotoxic trough concentrations (C_{trough} >5 mg/L) were observed with the dose of 15 mg/kg once daily. We applied an existing 2-compartmental population pharmacokinetic model (amikacin clearance depending on birthweight and PNA) to real-world demographic data from 1563 neonates receiving anti-infectives (median birthweight 2.3 kg, median PNA 6 days) and performed pharmacometric dose-exposure simulations to identify extended dosing intervals ensuring non-toxic C_{trough} (C_{trough} <5 mg/L) in most neonates. **Results** In the subpopulation of clinical concern, C_{trough} <5 mg/L was predicted in 59% versus 79-99% of cases in all other subpopulations following the current recommendations. Elevated C_{trough} values were associated with a PNA <7 days. Simulations revealed that extending dosing-interval to ≥36h in the subpopulation of clinical concern increased the frequency of a desirable C_{trough} below 5 mg/l to >90%. **Conclusion** Pharmacometric *in silico* studies with high-quality real-world demographic data can provide a scientific rationale for national neonatal dose optimization procedures and increase clinical acceptance of fine-tuned harmonized dosing recommendations, supporting their implementation, including in vulnerable subpopulations. Reference Cristea S, Smits A, Kulo A, Knibbe CAJ, van Weissenbruch M, Krekels EHJ, Allegaert K. Amikacin pharmacokinetics to optimize dosing in neonates with perinatal asphyxia treated with hypothermia. Antimicrob Agents Chemother 2017;61(12):e01282-17
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NR.8

TITLE	**Enhancing collaboration between clinical pharmacists and primary care providers in the neonatal acute care setting to promote medication safety**
	Vella G (1), Whittome E (1), Burch AR (1), Rüegger Ch (2), Cannizzaro V (2) (1) Cantonal Pharmacy of Zurich; Hospital Pharmacy of the University Hospital of Zurich (2) Department of Neonatology, University Hospital of Zurich
ABSTRACT	**Purpose** Supply shortages of medicines have become an increasing problem in Switzerland over recent years. In neonatal care, where there is a large amount of off-label usage of medications, the identification of suitable and safe substitutes is particularly challenging. In order to increase the safety of medicines supply for this vulnerable population, an inter-professional collaboration between neonatal specialists and clinical pharmacists has been introduced. **Methods/ measures** This collaboration started in early 2023 with the definition of two dedicated pharmacists as contact persons responsible for the neonatal department. Their tasks surrounding the medication processes in the neonatal intensive care unit (NICU) included: (1) optimising patient-specific prescriptions, (2) defining and maintaining the local medication stock, and (3), optimising the standard use of drugs by providing drug-related information regarding for example preparation, administration, drug interactions and compatibility. **Results** During 6 months (March-August 2023), 164 patients were visited and their medication reviewed (1'010 prescriptions). A total of 47 interventions to optimise prescriptions were made (acceptance rate of 96%) (1). Of the 239 medicines in the ward pharmacy (status January 2023), 83 were removed and 14 were added to the stock. Fifteen of these medicines, which are exclusively used in neonatal care, were included in the hospital wide list of formulary medications in order to increase their supply security. Since January 2023, 5 important supply shortages could be resolved quickly by defining a suitable alternative in close collaboration with the responsible pharmacists (2). In April 2023, the pharmacists also took over the creation and maintenance of prescription templates in the electronic prescription system. Since then 15 new templates have been created in consultation with the physicians and several adjustments have been made to the existing templates. In order to optimise the standard use of parenteral and enteral medicines, the existing pharmaceutical information was combined in a single document: This contains information about administration, storage and dosage of 95 active substances that are routinely used in neonatal care (3). **Conclusion** The first 8 months of this cooperation showed promising results. The definition of contact persons has lead to better decision-making, problem solving, and inter-professional communication. This collaboration has the potential to further improve both medication safety and outcomes for this vulnerable population. References Ziesenitz VC, Fox E, Zocchi M, Samiee-Zafarghandy S, van den Anker JN, Mazer-Amirshahi M. Prescription Drug Shortages: Impact on Neonatal Intensive Care. Neonatology 2019;115:108-15. Yalçın N, Kaşıkcı M, Çelik HT, Allegaert K, Demirkan K, Yiğit Ş. Impact of clinical pharmacist-led intervention for drug-related problems in neonatal intensive care unit a randomized controlled trial. Front Pharmacol 2023;14:1242779.
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NR.9

TITLE	**Administering beta-lactams and glycopeptides via extended infusion: barriers and enablers for a change of standard of care in paediatric care**
	von Arx LE (1,2), Neumeier VI (2), Burch AR (2) (1) Institute of Pharmaceutical Sciences ETH, 8049 Zürich (2) Cantonal Pharmacy of Zürich, 8006 Zürich
ABSTRACT	**Purpose** Optimizing antibiotic therapy is imperative with rising bacterial resistance and high infection mortality [1]. Previous findings suggest that extended administration of beta-lactams and glycopeptides leads to a reduction of mortality for paediatric patients compared to their intermittent administration (IA; unpublished systematic review). This study aimed to identify potential barriers and facilitators of clinical implementation of extended infusion of beta-lactams and glycopeptides in paediatric patients in Switzerland. **Methods/ measures** Adhering to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES; [2]), we designed and conducted an anonymous survey including 24 questions asked either with multiple answer choices or in an open manner. The target populations comprised nurses, clinical pharmacists and physicians. Extended infusion was defined as continuous infusion (COI; over 24 h) or at least the infusion in a prolonged manner (PI; over >1 h). The survey did contain questions related to (1) the current administration mode, (2) the subjective opinion of extended infusion and (3) the factors influencing clinical implementation. **Results** 39 participants completed the questionnaire, comprising 16 physicians (41%), 15 pharmacists (38.5%), and 8 nurses (20.5%). We received responses from 79% (15/19) of the selected hospitals. In all 15 hospitals, the current administration route of beta-lactams was IA. For glycopeptides, only 1 in 15 (7%) used PI as standard administration mode (1). Stated possible reasons for using IA of beta-lactams were adherence to existing guidelines, easier catheter-lumen management or fewer compatibility issues. Three participants mentioned a lack of better options as a possible reason. The reasons for using IA were equivalent to the reasons mentioned for beta-lactams. Four participants of the hospital using PI stated that PI was used to avoid adverse drug reactions (2). Anticipated barriers in the clinical implementation of extended infusion encompassed compatibility issues (n=11), insufficient or for the user inaccessible knowledge about the stability of drugs (n=5), and non-adherence of patients (n=2). Participants highlighted the need for training and new guidelines (n=9). Moreover, participants expected a higher likelihood of errors during the transition phase from IA to extended infusion (n=4) and an increased workload (n=4). Facilitators for clinical implementation of extended infusion included training provision (n=11), more robust evidence (n=10), guideline development (n=7), and additional human resources (n=3). (3) **Conclusion** Our findings suggest that knowledge about possible advantages of extended infusion vs. IA is lacking in Switzerland and the current standard of care in paediatrics is the IA of these antimicrobial substances. Most of the mentioned barriers for clinical implementation might be overcome by knowledge distribution through the development of harmonized guidelines including information about dosing, drug solution stabilities and compatibilities of concomitantly administered drugs. As a first reaction to these results, we developed a comprehensive German guideline for COI administration of beta-lactams and glycopeptides. Reference Eysenbach G. Improving the Quality of Web Surveys: The Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res 2004;6:e34.
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NR.10

TITLE	**Advanced Practice Nurse for patients and families affected by preeclampsia**
	Dreier J (1), Lapaire O (1) (1) Department of Obstetrics, University Hospital Basel, Switzerland
ABSTRACT	**Purpose** In the current care model at the University Hospital Basel (USB), patients/families affected by preeclampsia (PE) express significant uncertainty in handling and managing the condition/therapy. Additionally, the patients/families do not experience comprehensive and continuous care, leading to uncertainty and information loss for the caregiving team. Thus, the aim of this study was to evaluate the current and potentially develop a new care model to empower patients/families affected by PE to better navigate and manage their condition/therapy in their daily lives. **Methods** A participatory, evidence-based, patient-centred process (PEPPA) framework was used to evaluate the current, as well as potentially develop a new care model. For this analysis, steps 1-5 of the PEPPA framework were executed: Describing the patient population and context of care, identifying and engaging stakeholders, determining the need for a new model of care, identifying priority goals and issues, and synthesizing all information and defining the APN role within the new model of care. Within this framework, semi-structured individual interviews and focus group interviews were conducted with stakeholders (patients/families affected by PE, nursing staff, physicians, and other professional groups). Additionally, a literature review was conducted. Ultimately, the new care model was developed based on Hamric's competencies. **Results** An evaluation of the current care model for patients/families affected by PE revealed that a new care model should be implemented. Using the described method, specific competencies for the new care model were defined along with their corresponding outputs, as well as short, medium, and long-term outcomes. Competencies of direct clinical practice include, for example, blood pressure monitoring, adjustment of the medication plan after consultation with the responsible gynecologist and telephone follow-up after discharge (once a month for one year). One of the core competencies within the care model should be systematic promotion of self-management in terms of blood pressure measurement, medication management, sleep hygiene and stress reduction. To enable family-centered care, it is crucial to provide support for patients and families affected by PE throughout the entire continuum of care. To improve information flow and centralize care delivery, additional competencies within the care model include coordinating the treatment of patients with PE and collaborating with the interprofessional team. Possible outcomes of these activities may include increased patient and staff satisfaction, reduced hospitalization duration, lower complication rates, and improved blood pressure values in patients with PE. **Conclusion** By implementing this new care model, patients/families affected by PE receive structured self-management support through a continuous and easily accessible point of contact who is available across interfaces, leads cases, coordinates care, and remains consistently accessible in both inpatient and outpatient settings. An Advanced Practice Nurse (APN) is ideally suited for this care model because self-management support and continuous care both within and outside the hospital are core competencies of an APN. References Wetherell B, Swainston K. Women's Post-Natal Experiences of Pre-eclampsia/Eclampsia.: Division of Health Psychology Annual Conference 2021. 29/06/21 → 30/06/21. https://research.tees.ac.uk/en/publications/womens-post-natal-experiences-of-pre-eclampsiaeclampsia Bijl RC, Bangert SE, Shree R, Brewer AN, Abrenica-Keffer N, Tsigas EZ, Koster MPH, Seely EW. Patient journey during and after a pre-eclampsia-complicated pregnancy: a cross-sectional patient registry study. BMJ Open 2022;12(3):e057795.
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- 5. und 26.9.24: Klinisch pharmazeutische Seminare

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Arzneimittelverzeichnis der SAPP für Schwangere und Stillende:
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https://amiko.oddb.org/de/fulltext?keyword=SAPP&key=sapp

SAPP: Schwangere

ATC-Code: N02BE01, N02AJ13

Wirkstoff: Paracetamol

Hauptindikation: Schmerzen

sappinfo Monographie

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intravenös, peroral, rektal	4000mg	4000mg	<4000mg	<4000mg

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