Experiences in Pharmaceutical Care for Newborns with Klippel-Trenaunay Syndrome

2024.11

Clinical Pharmacist :Yun-chia Chang
China Medical University Hospital/China Medical University Children's Hospital

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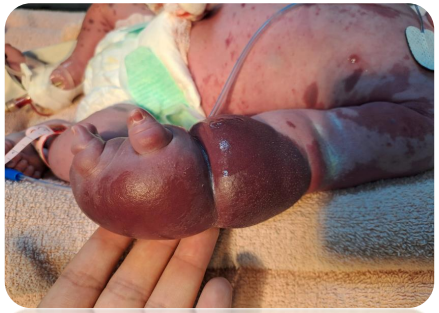
Case



Preterm infant born at 35+1 weeks
Ideal birth weight of 2800 grams
Swelling and redness left upper limb was noted with diffused purple patches over trunk

G3P3A0, C/S,GA：35＋1/7weeks, ideal birth weight：2800g

- **Maternal history**:

35y/o, had received regular antenatal examination:

1. Fetal right chest lymphangioma,left arm swelling and edema suspect due to lymphatic return obstruction
2. Heart shifts to right side, suspect right lung hypoplasia

Oligohydramnios initially, AFI increased one month before delivery and became border polyhydramnios with anemia(Hb:7.9g/dL)
Bilateral lower limb edema 3+ one week before delivery
PROM(-), maternal fever(-), GBS(-)

- **Birth history**:

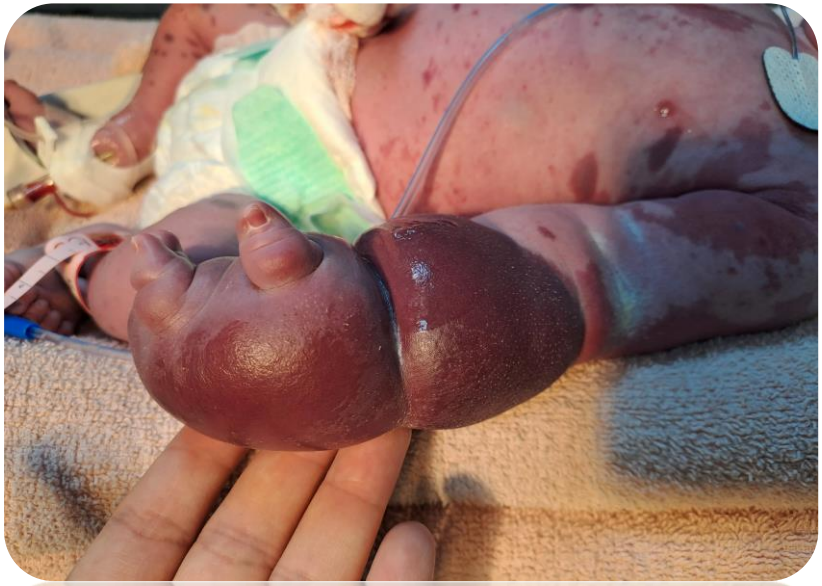
Born on 1/25 and the Apgar score was 7 at 1 minute and 9 at 5 minutes.
>Swelling and redness left upper limb was noted with diffused purple patches over trunk.
>Diffused hemangioma and patechia were also found.

- **Active problem**:

1. Diffused hemangioma and lymphangioma suspected Klippel-Trenaunay syndrome
2. Respiratory failure, suspect transient tachypnea of the newborn

- **Physical Examination:**

Vital sign： T:36.5 'C, HR:133bpm, RR:42bpm, BP：63/45 mmHg
Body length： 40.5 cm (< 3th percentile)
Body weight：3075 g(90-97th percentile)
HC： 33cm (50-90th percentile)
HEENT： nasal flaring
CHEST： symmetric expansion, **chest retraction,right chest bulge**
EXTREMITIES：**left upper limb deformity, enlargement and redness**
Skin：**diffused hemangioma and petechia**



Swelling and edema in the left arm

Purple patches scattered across the trunk

No emergent surgery indication.
Medical treatment first.
The patient will need multiple future surgery due to his extensive form of KT syndrome.
Arrange OPD f/u to our service if the patient is discharged.

Plastic surgery

Hematologic-Oncology

KTS(Klippel-Trenaunay syndrome) without Kasabach-Merritt phenomenom should be highly suspected, however complete image study and genetic diagnosis are required.

<u>Suggestion</u> :

- Please check stool OB, UA, and DIC profile(plt, D-dimer, PT/APTT/fibrinogen) 3 times weekly, till stable
- Try IV methylprednisolone 2mg/kg/day (plus famotidine) for 2 weeks, then taper.
- PO propranolol, slowly titrate to 2mg/kg BID PC(1mg BID --> 2mg BID --> 2.5mg BID)

INTRODUCTION

Klippel-Trenaunay Syndrome?

International Society for the Study of Vascular Anomalies (ISSVA) classification for vascular anomalies

- Klippel-Trenaunay syndrome (KTS) is rare.
- Klippel-Trenaunay syndrome (KTS) as a syndrome with capillary and venous malformations as well as limb overgrowth, with or without lymphatic malformation

Back to overview

ISSVA classification for vascular anomalies

Type Alt ← for previous view

Vascular malformations associated with other anomalies		
Klippel-Trenaunay syndrome: *	CM + VM +/- LM + limb overgrowth	PIK3CA

- KTS is part of the PIK3CA-related overgrowth spectrum (PROS), a group of disorders in which a somatic pathogenic variant in the PIK3CA gene causes segmental or focal overgrowth.

Diagnosis

- A clinical diagnosis may be sufficient in persons with **≥ 2 of the following** 3 features of classic KTS:
  - Capillary malformations
  - Venous malformations
  - Limb hypertrophy
- Consider genetic testing to confirm the diagnosis of a PIK3CA-related overgrowth spectrum disorder.

>>>Bioinformatics software (GeneYX) did not identify any gene mutations that are clinically significant or associated with clinical conditions.

Treatment &Discussion

The management of Klippel-Trenaunay syndrome (KTS) is largely supportive and primarily aimed at improving symptoms and treating and preventing complications in order to optimize quality of life.

Clotting disorders & thromboembolism	• Enoxaparin/Heparin • Aspirin/Rivaroxaban
Infantile Hemangiomas	• Propranolol/timolol • Steroids
Vascular/Lymphatic malformation	• Sirolimus • Alpelisib
Cellulitis	• Empiric treatment • MRSA
Pain control	• Opiates • Sirolimus/Alpelisib

Clotting disorders and thromboembolism

Patients with KTS have ongoing clotting, most often a localized intravascular coagulopathy in areas of venous malformation, and an increased risk of superficial thrombophlebitis and, less commonly, of deep venous thrombosis(DVT) and pulmonary thromboembolism(PE).

Special Interest Group in Vascular Anomalies within the American Society of Pediatric Hematology/Oncology(ASPHO)

- **Peri-procedural anticoagulation in vascular malformations:**

KTS patients are “high-risk” and can be stratified into a higher-risk subgroup if they have

- Low fibrinogen levels
- Venous ectasia (ie, PEVs)
- **D-Dimer levels x 5 normal,**
- Thrombocytopenia (without other explanation)
- Positive personal/family history of thrombosis

- They recommend that all such higher-risk subgroup of KTS patients, if undergoing invasive radiological or surgical procedures should **receive 2 weeks of LMWH** pre-procedure, rechecking the **D-Dimer** and **fibrinogen levels** and to continue **LMWH post-procedure** for a further 2 weeks or until baseline ambulation is achieved, whichever is the longer.

	D-DIMER ng/mL (250-2810)	Fibrinogen mg/Dl (200-400)	Enoxaparin
2024/1/25	4327.3	480.5	3mgQ12H SC(1/30-1/31AM) 3mgQ12H IVD(1/31PM-2/2AM)
2024/2/26	39626.6		1.5mg Q12H IVD
2024/3/3	31733.3		
2024/3/11	18187.2		
2024/3/18	13842.8		3mgQ12H IVD
2024/3/25	11286.8		
2024/4/1	4142.5	402.6	

Enoxaparin

- Low-molecular-weight heparins have a small effect on the activated partial thromboplastin time and strongly **inhibit factor Xa**.
- Many prefer enoxaparin as the initial option due to better predictability of the anticoagulant effect, reduced monitoring need, and reduced risk of heparin-induced thrombocytopenia
- **For SUBQ ;禁止 IM**
- Enoxaparin administered as a bolus IV results in more rapid peak levels and faster clearance leading to significantly shortened half-life.

Discussion

Premature neonates that possess little SC fat

- Present an interesting **challenge with SC administration** of medications.
- **Dosing requirements** and anticoagulation quality measurements in infants (≤ 3 mo) who received IV or SC therapeutic enoxaparin were **not significantly different.**
- There was only one identifiable anticoagulation failure which occurred in the SC enoxaparin group, and there was **no significant difference in the rates of major bleeding or clinically relevant nonmajor bleeding between IV and SC enoxaparin** (5% vs 10%, $p = 1.00$)
- Enoxaparin-administered IV or SC led to consistent anticoagulation as measured by time in the target range with low rates of thrombus nonresolution, anticoagulation failure, or bleeding complications indicating that enoxaparin-administered IV or SC was an effective anticoagulant with acceptable safety profile in this high-risk patient population.

Pediatr Crit Care Med. 2017 May;18(5):e207-e214.

Management of Infantile Hemangiomas

- Clinicians should use **oral propranolol** as the first-line agent for IHs requiring systemic treatment (Grade A, strong recommendation).
- Clinicians should dose propranolol between 2 - 3 mg/kg/day unless there are comorbidities (eg, PHACE syndrome) or adverse effects (eg, sleep disturbance) that necessitate a lower dose (Grade A, moderate recommendation).
- Starting dose : 1 mg/kg/day

Caution (but not exclusion) in infants <5 wk of age, PCA <48 wks

Exclusion cardiogenic shock or heart failure; sinus bradycardia; heart block greater than first degree/ suspected PHACE syndrome; **asthma and/or reactive airway disease**

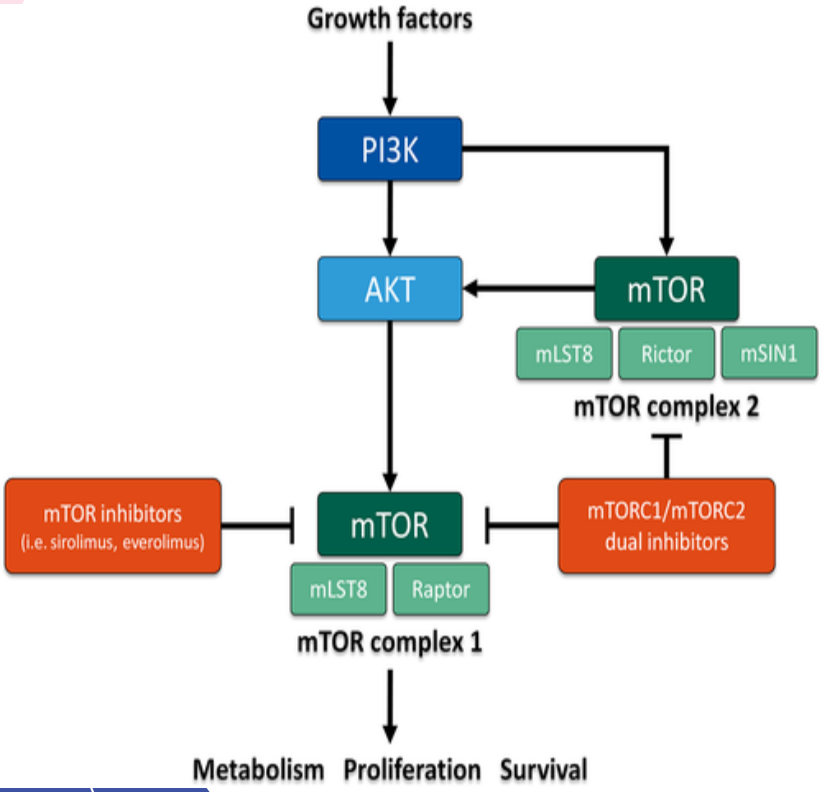
American Academy of Pediatrics (AAP): Clinical practice guideline for the management of infantile hemangiomas (2019)

Steroids

- Clinicians may prescribe **oral prednisolone or prednisone** to treat IHs if there are contraindications or an inadequate response to oral propranolol (Grade B, moderate recommendation).
- Dose ranges of prednisone or prednisolone reported most frequently in the literature are between 2 and 5 mg/kg/day, and most consider optimal dosing to be **2 - 3 mg/kg /day**. **Typical protocols include treating at full dose for 4 - 12 weeks** followed by a gradual taper and completion of therapy by 9 to 12 months of age.

American Academy of Pediatrics (AAP): Clinical practice guideline for the management of infantile hemangiomas (2019)

Vascular/Lymphatic malformation



- Inhibition of mTOR, which acts downstream of the PI3K/AKT pathway to promote cell proliferation and angiogenesis.

- ☐ mTOR inhibitor-Sirolimus(Rapamycin)
- ☐ PIK3CA inhibitors -Alpelisib

https://www.medchemexpress.com/literature/blog/apitolisib-is-an-orally-active-class-i-pi3k-and-mtorc1-2-inhibitor.html

Discussion

Sirolimus(Rapamycin)

European Archives of Oto-Rhino-Laryngology (2022) 279:3801–3810
https://doi.org/10.1007/s00405-022-07378-8

REVIEW ARTICLE

Check for updates

Efficacy of sirolimus in children with lymphatic malformations of the head and neck

S. Wiegand[1] · A. Dietz[1] · G. Wichmann[1]

Received: 29 January 2022 / Accepted: 25 March 2022 / Published online: 8 May 2022

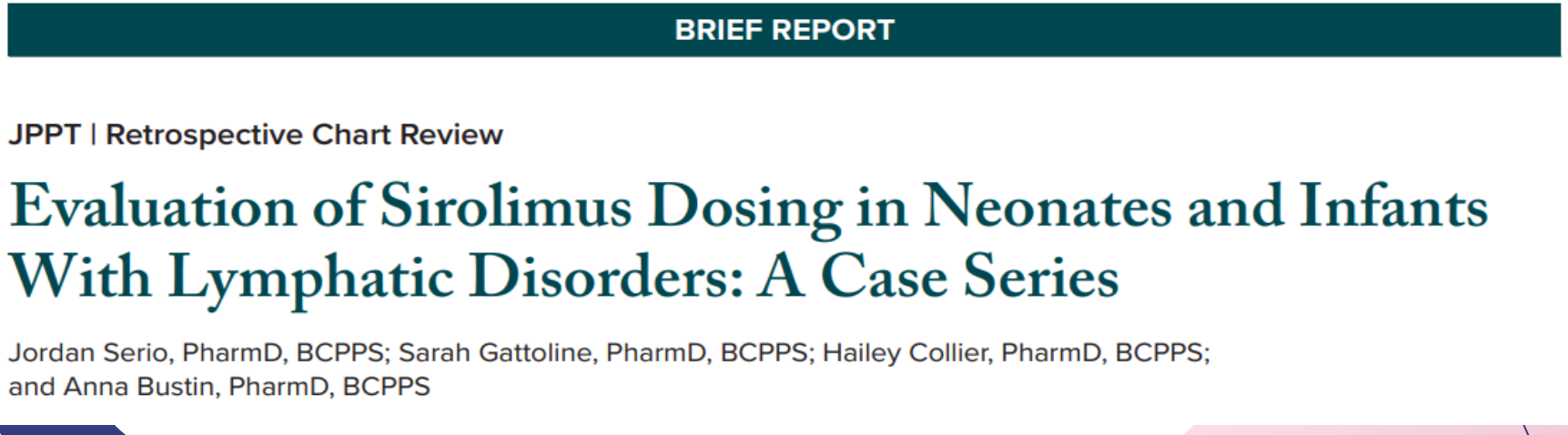
- In all, 28 studies including 105 children from **newborn** to 17 years treated with sirolimus for lymphatic malformations of the head and neck were analyzed
- The most frequent **initial dose was 0.8 mg/m^2/dose, twice daily at 12-h interval.**
- The target blood level difered between studies, 10–15 ng/mL and **5–15 ng/mL** were most often used

1.1mg/m^2/day(1/31-2/7)

Discussion

Therapeutic Drug Monitoring

- The median time to first therapeutic trough was **15.5 days**.(J Pediatr Pharmacol Ther 2022 Vol. 27 No. 5)
- Zimmerman and Kahan showed that there is an **excellent linear correlation** between the trough steady-state blood concentration and AUC(Pharmaceutics. 2021 Mar 30;13(4):470. doi: 10.3390/pharmaceutics13040470.)


BRIEF REPORT

JPPT | Retrospective Chart Review

Evaluation of Sirolimus Dosing in Neonates and Infants With Lymphatic Disorders: A Case Series

Jordan Serio, PharmD, BCPPS; Sarah Gattoline, PharmD, BCPPS; Hailey Collier, PharmD, BCPPS; and Anna Bustin, PharmD, BCPPS

	Time	BSA	Sirolimus dose(mg/m²/day)	Blood drawing time	Sirolimus Trough Concentration(ng/ml)
Stage I	1130202-1130207	0.18m²	1.1mg/m²/day	1130207 (I Day 8,PMA:37wk)	25.5
	Hold 24hr				
	1130208-1130214	0.18m²	0.55 mg/m²/day	1130214 (I Day 15,PMA:38wk)	>30
	Hold				
	Recheck			1130219 (I Day20,PMA:38+5wk)	20.9
Hold (2/15-3/17) toxic shock syndrome from MRSA, neutropenia (WBC:0.7 x10^3 /ul, ANC:335 /uL) and thrombocytopenia					
Stage II	1130318-1130325	0.22 m²	0.25 mg/m²/day	1130325 (II Day8,PMA:44+5wk)	4.32
	1130326-1130412	0.22 m²	0.27 mg/m²/day	1130403 (II Day17,PMA:46wk)	5.84

Target range :5-15 ng/mL Normal range Below concentration Above concentration

Received: 30 September 2016 | Revised: 23 November 2016 | Accepted: 28 December 2016
DOI: 10.1002/pbc.26470

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

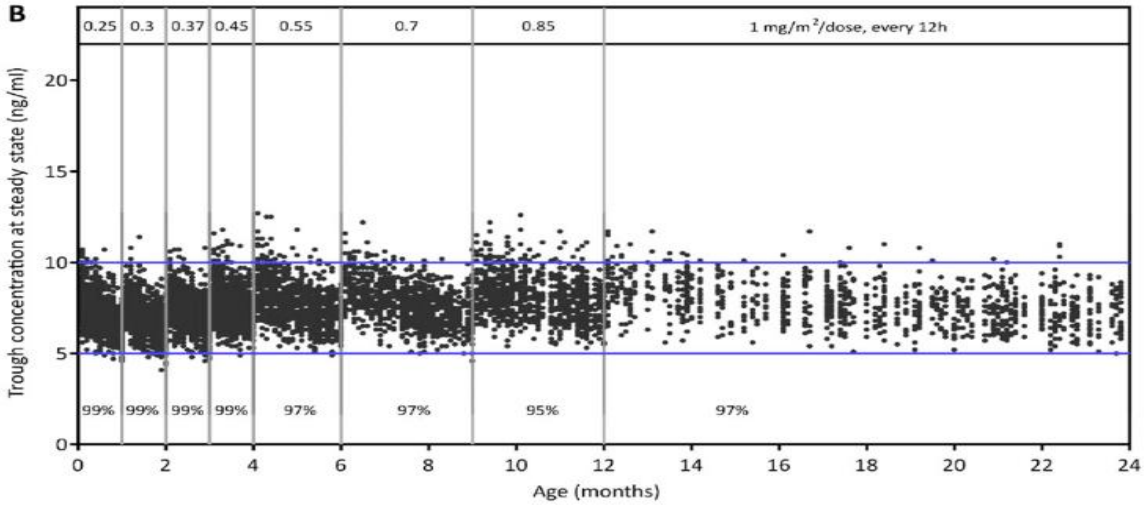
Developmental pharmacokinetics of sirolimus: Implications for precision dosing in neonates and infants with complicated vascular anomalies

Tomoyuki Mizuno[1] | Tsuyoshi Fukuda[1,4] | Chie Emoto[1,4] | Paula S. Mobberley-Schuman[2] | Adrienne M. Hammill[2,4] | Denise M. Adams[3] | Alexander A. Vinks[1,4]

TABLE 1 Estimated sirolimus starting doses for the indicated target concentration ranges

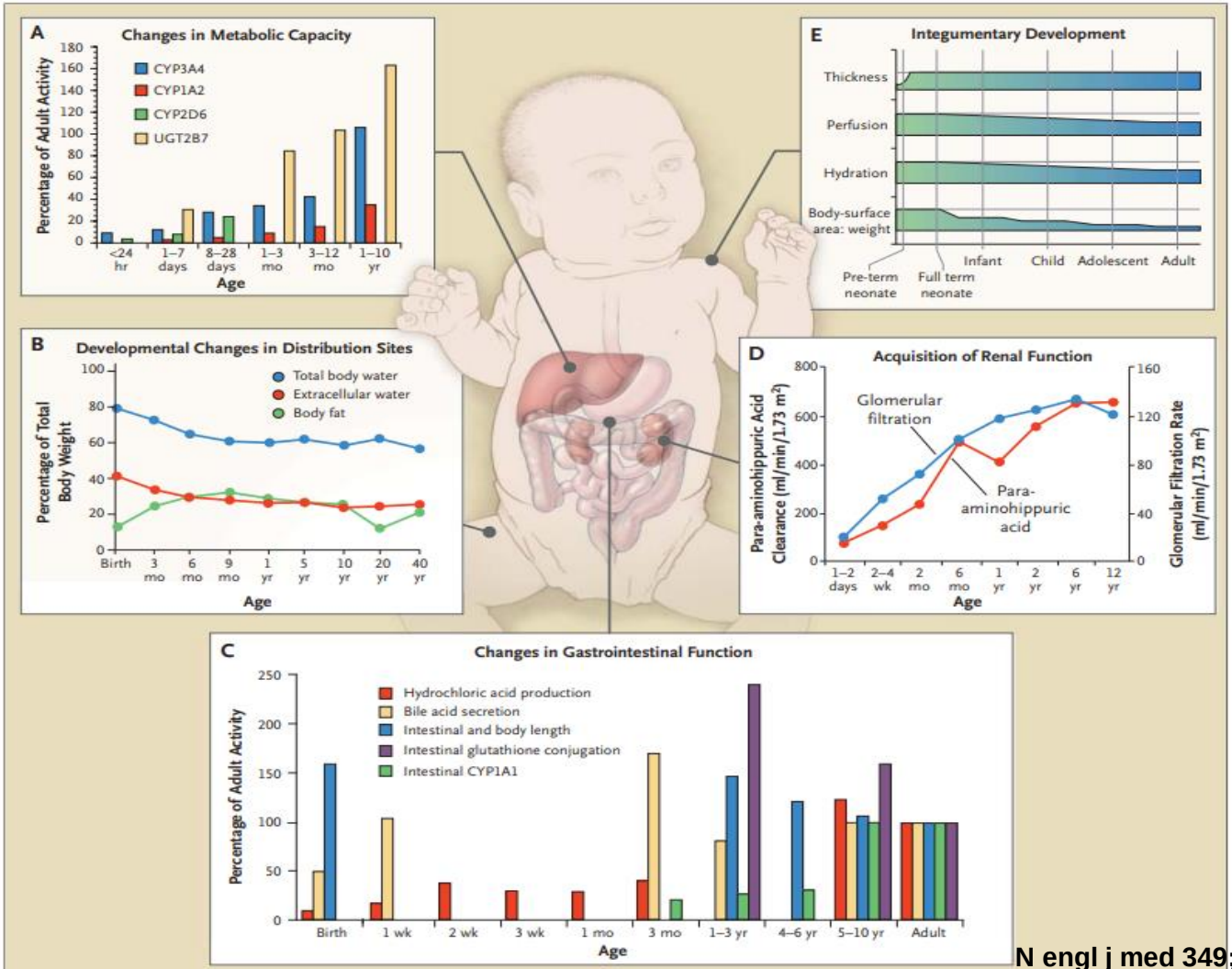
	Target concentration range	
	10–15 ng/ml	5–10 ng/ml
Age group (months)	Dose*	Dose*
0–1	0.4	0.25
1–2	0.5	0.30
2–3	0.6	0.37
3–4	0.7	0.45
4–6	0.9	0.55
6–9	1.1	0.70
9–12	1.3	0.85
12-24	1.6	1.0

*mg/m^2/dose, administered twice daily



Patient monitoring

What can we do?



N engl j med 349;12 september 18, 2003

Therapeutic Drug Monitoring in Neonates

- Larger variability in PK, and non-PK related factors in neonates compared to adults result in a less clear relation between the administered dose and the concentration measured.
- Blood sampling opportunities in neonates are limited by the small blood volume and the need to minimize painful procedures.

Curr Pharm Des . 2017;23(38):5790-5800.

THANKS

Do you have any questions?

039087@tool.caaumed.org.tw