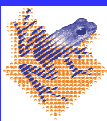


Help dokter, mijn baby ziet geel!

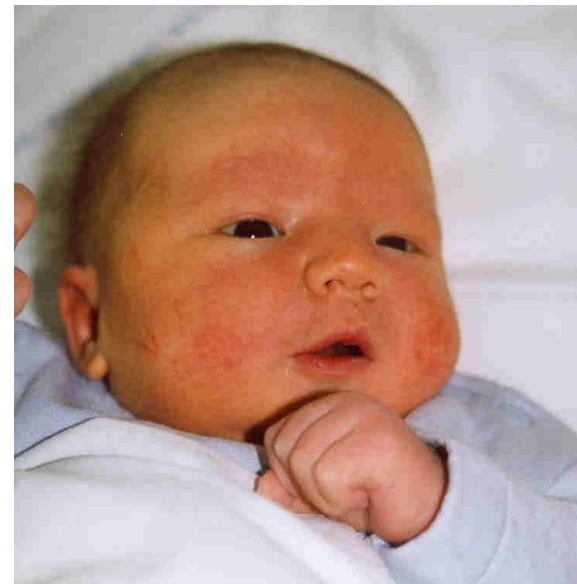
Over de klinische relevantie van accurate en precieze bilirubine metingen

Christian Hulzebos, kinderarts-neonatoloog



Beatrix Kinderziekenhuis UMC Groningen

Tenminste 6 redenen waarom juiste bilirubine bepalingen relevant zijn



1. Hoge incidentie van ongeconjugeerde hyperbilirubinemie bij neonaten

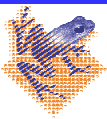
- 60 - 80 % van de a terme en preterme neonaten ontwikkelen hyperbilirubinemie
- 1 - 2 % van de kinderen met een gestatieduur > 35 weken: ernstige hyperbilirubinemie (USA data)¹
- 1500 - 2000 a terme and ~1400 preterme neonaten per jaar hebben intensieve behandeling nodig²

¹Maisels NEJM 2008; ²www.nvk.pedinet.nl/pdfs 2008



2. Hyperbilirubinemie is neurotoxisch

- Kernicterus
- Bilirubine geïnduceerde neurotoxiciteit



2. Hyperbilirubinemie is neurotoxisch

Total bilirubin (B_T)

99.9% is bound to albumin



0.1% is unbound or free
bilirubin (B_f)

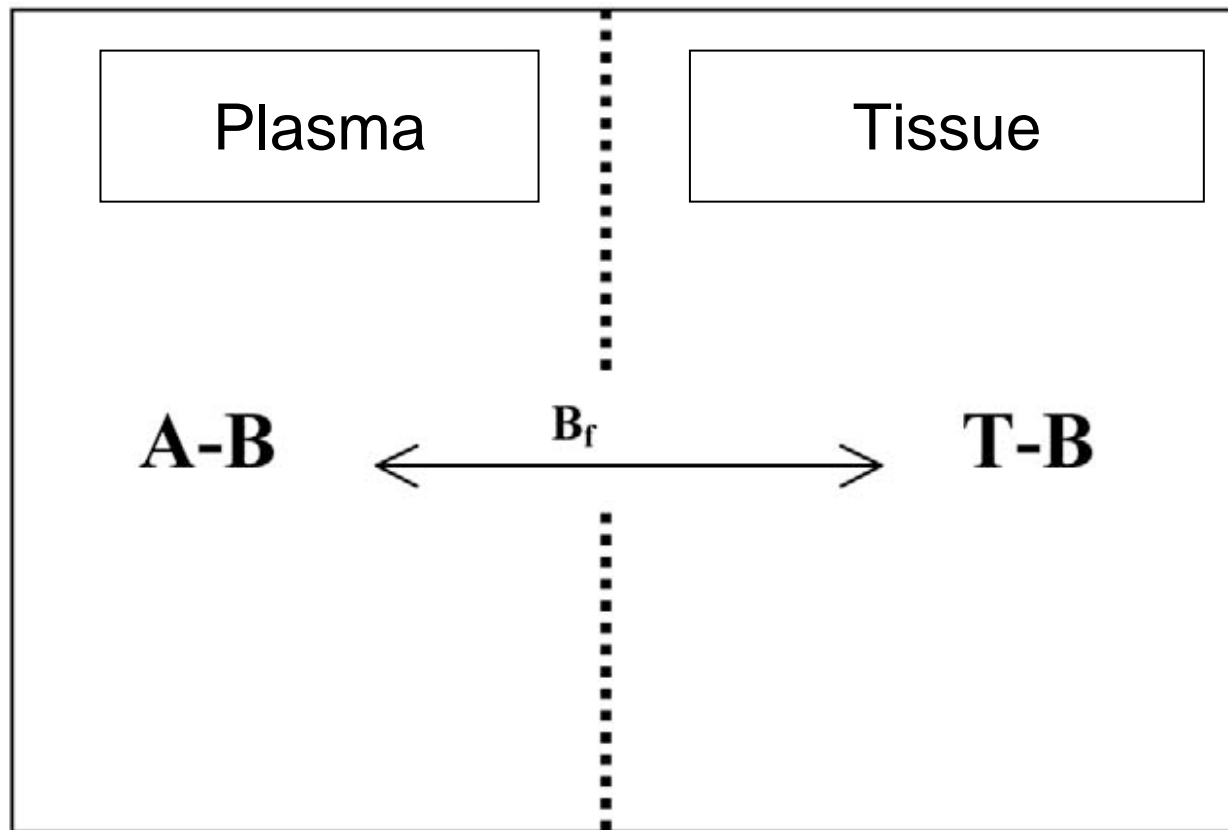


Only B_f can enter tissue

Ahlfors and Wennberg Semin Perinatol 2004



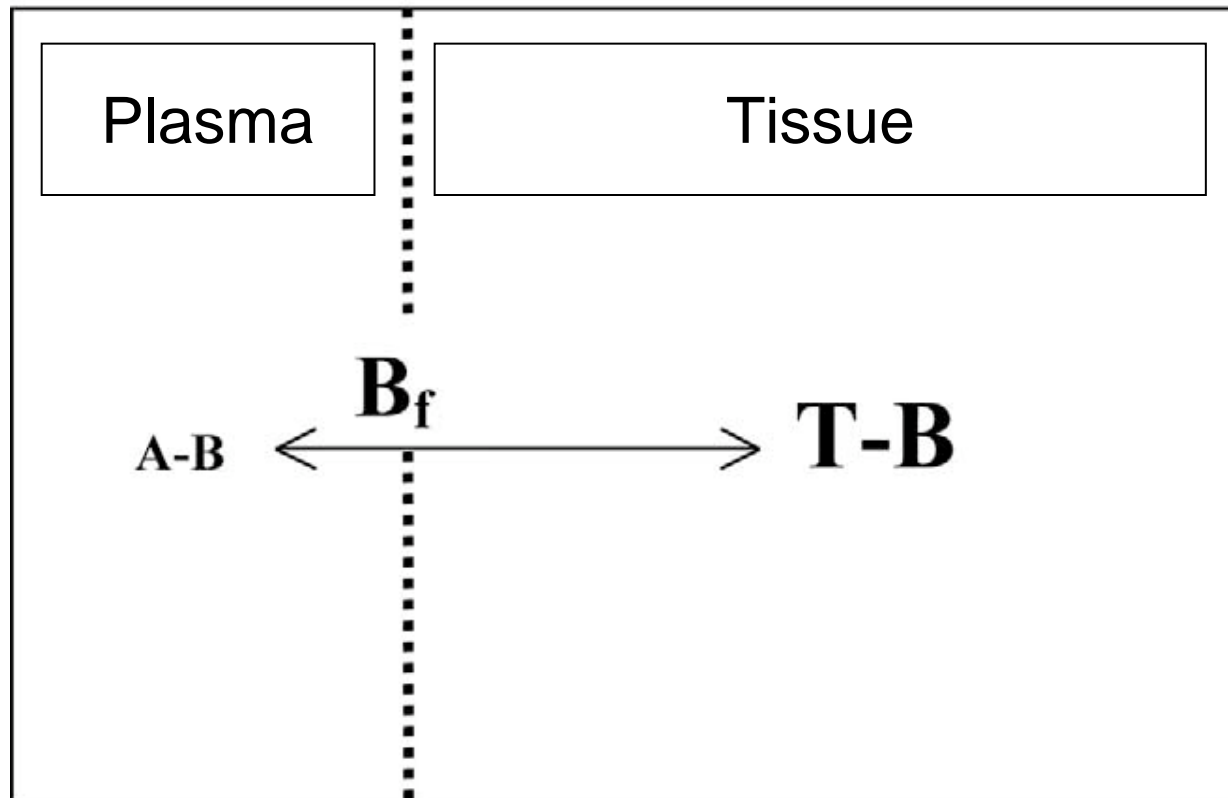
Vrije bilirubine (B_f) naar weefsels



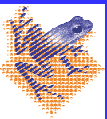
Ahlfors and Wennberg Semin Perinatol 2004



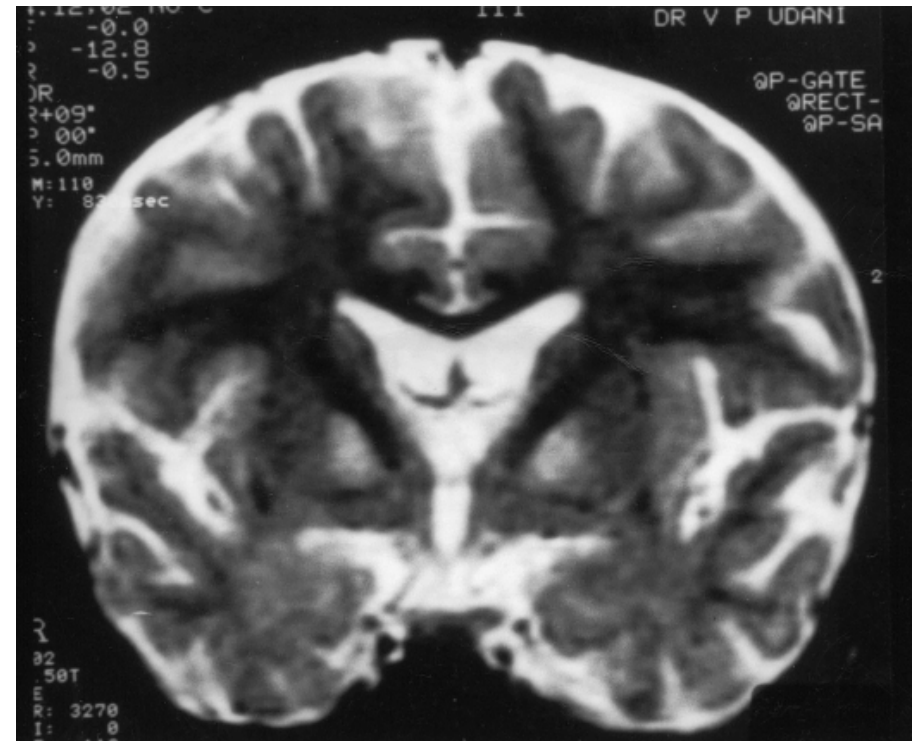
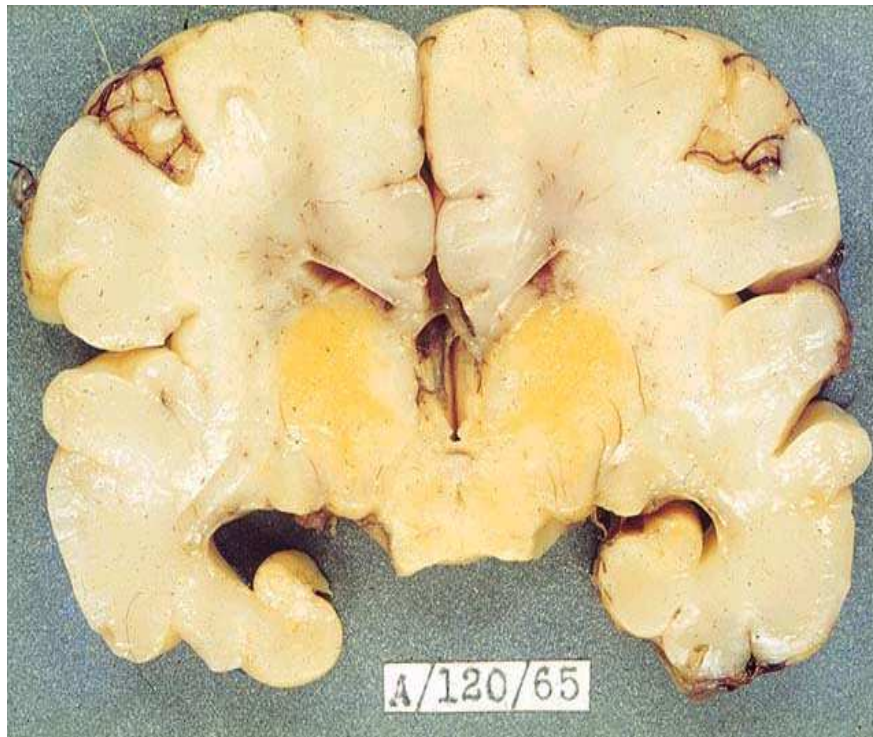
Minder albumine: meer B_f naar weefsels



Ahlfors and Wennberg Semin Perinatol 2004



Kernicterus



¹Schmorl G Vehr Dtsch Ges Pathol 1904; ²Shah et al Australasian Rad 2003



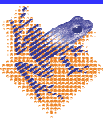
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Kernicterus - acute symptomen



Hypotonie, lethargie en slecht drinken

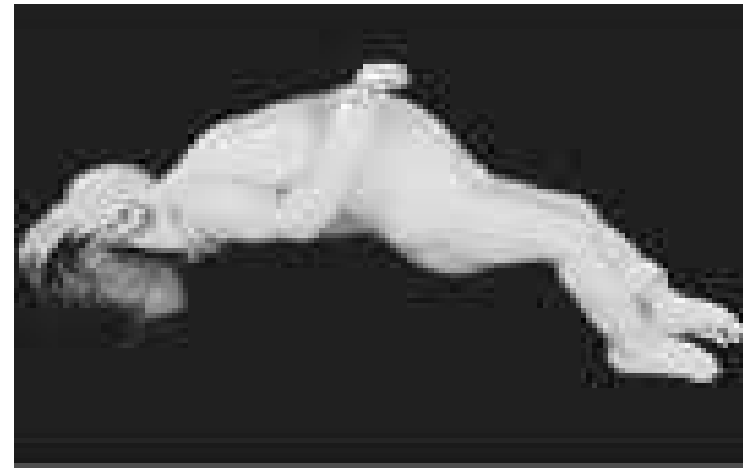
¹Maisels NEJM 2008; ²www.nvk.pedinet.nl/pdfs 2008



Kernicterus - acute symptomen



Hypertonie, discomfort, overprikkelbaar, koorts, huilen, convulsies



Retrocollis-opisthotonus, huilen, apnoe, koorts, convulsies, coma, dood



Kernicterus - permanente symptomen

Choreoathetosis

Vertikale blik parese

Auditoire dysfunctie

Glazuurafwijkingen

Motorische achterstand

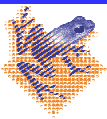
NB Intelligentie is meestal normaal



Bilirubine geïnduceerde neurotoxiciteit

- Auditoire disfunctie
- Milde neurologische afwijkingen

Shapiro Pediatr Neurol 2003



3. Toename bilirubine neurotoxiciteit

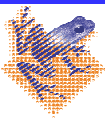
- 1994 American Academy of Pediatrics: verhogen behandelgrenzen
- Toename bilirubine toxiciteit^{1,2}

TABLE 2 Readmission TSB Associated With Chronic or Autopsy-Confirmed Kernicterus in 111 Cases Reported to the Pilot Kernicterus Registry: 1991–2002

Cause for Hyperbilirubinemia	N	Range, mg/dL ($\mu\text{mol/L}$)	Mean TSB, mg/dL ($\mu\text{mol/L}$)
Idiopathic hyperbilirubinemia	39	20.7–52.0 (354–889)	36.7 (628)
Sepsis/infection	5	21.5–48.0 (368–821)	30.1 (515)
G6PD deficiency	24	25.6–54.0 (438–924)	39.7 (679)
Hemolysis (other)	22	25.0–59.9 (428–1024)	38.9 (665)
Birth trauma	18	23.8–53.9 (407–922)	34.6 (592)
Other ^a	3	40.3–49.0 (689–838)	43.1 (737)
Total cases	111	20.7–59.9 (354–1024)	38.1 (652)
Acute-phase kernicterus with no sequelae	7	25.6–36.0 (438–615)	29.3 (501)

^a Crigler-Najjar syndrome ($n = 2$) and galactosemia ($n = 1$).

¹Shapiro Pediatr Neurol 2003; ²Wennberg et al Ped 2006



3. Toename bilirubine neurotoxiciteit

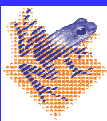
Population-based studies of kernicterus incidence in infants ≥ 35 weeks' gestation in the Western world.

Country	Years of infants' birth	Incidence/live births	
		Acute bilirubin encephalopathy ^a	Kernicterus – chronic bilirubin encephalopathy ^b
Denmark [4]	1994–1998	1/53,000	1/64,000
Denmark [7]	1994–2003		1/79,000
United Kingdom [3]	2003–2005	1/100,000	1/150,000
Canada [5]	2007–2008	1/49,000	1/43,000

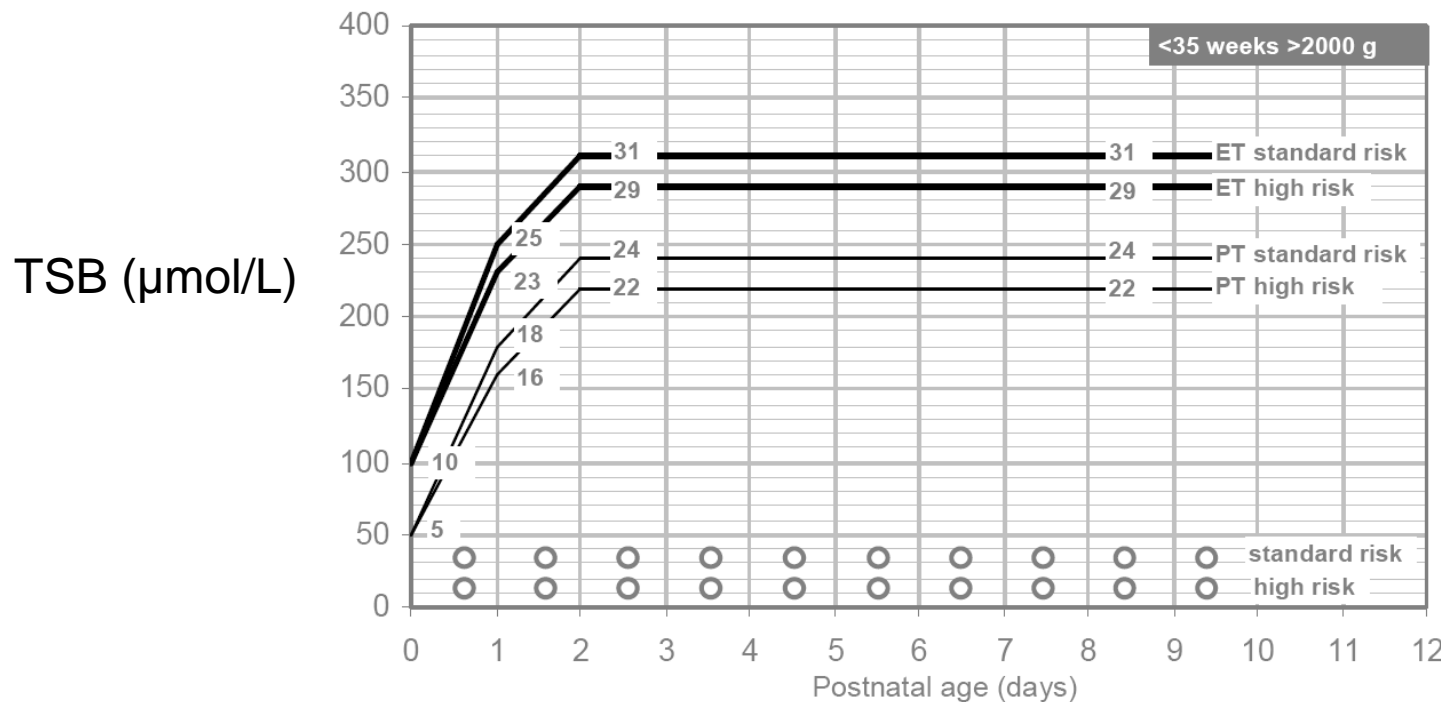
^a Lethargy, poor suck, abnormal tone, opisthotonos, and seizures.

^b Athetosis, dystonia, sensorineural hearing loss, gaze abnormalities, and dental dysplasia.

Maisels Early Hum Develop 2009



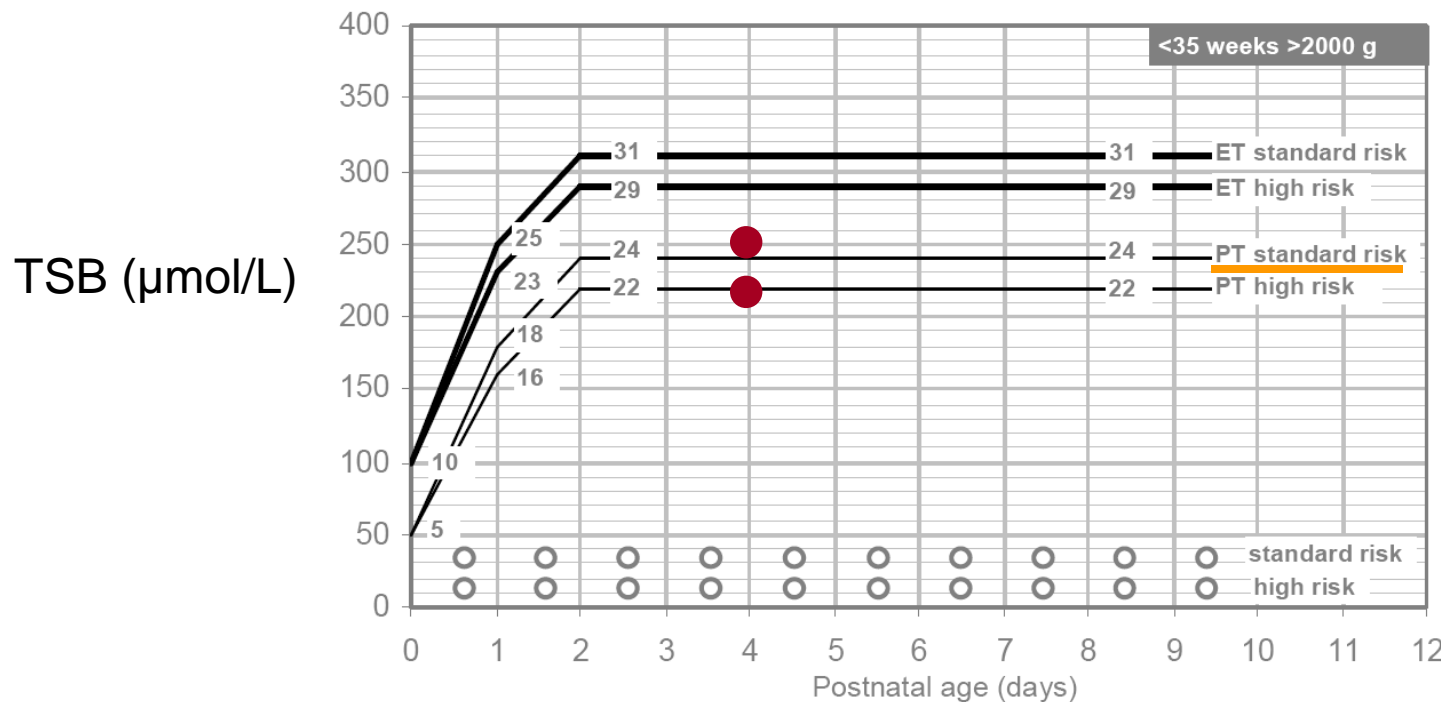
4. Behandeling is gebaseerd op Totale Serum Bilirubin (TSB)



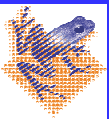
Adapted from Dijk et al NTvG 2009 and Van Imhoff et al 2009



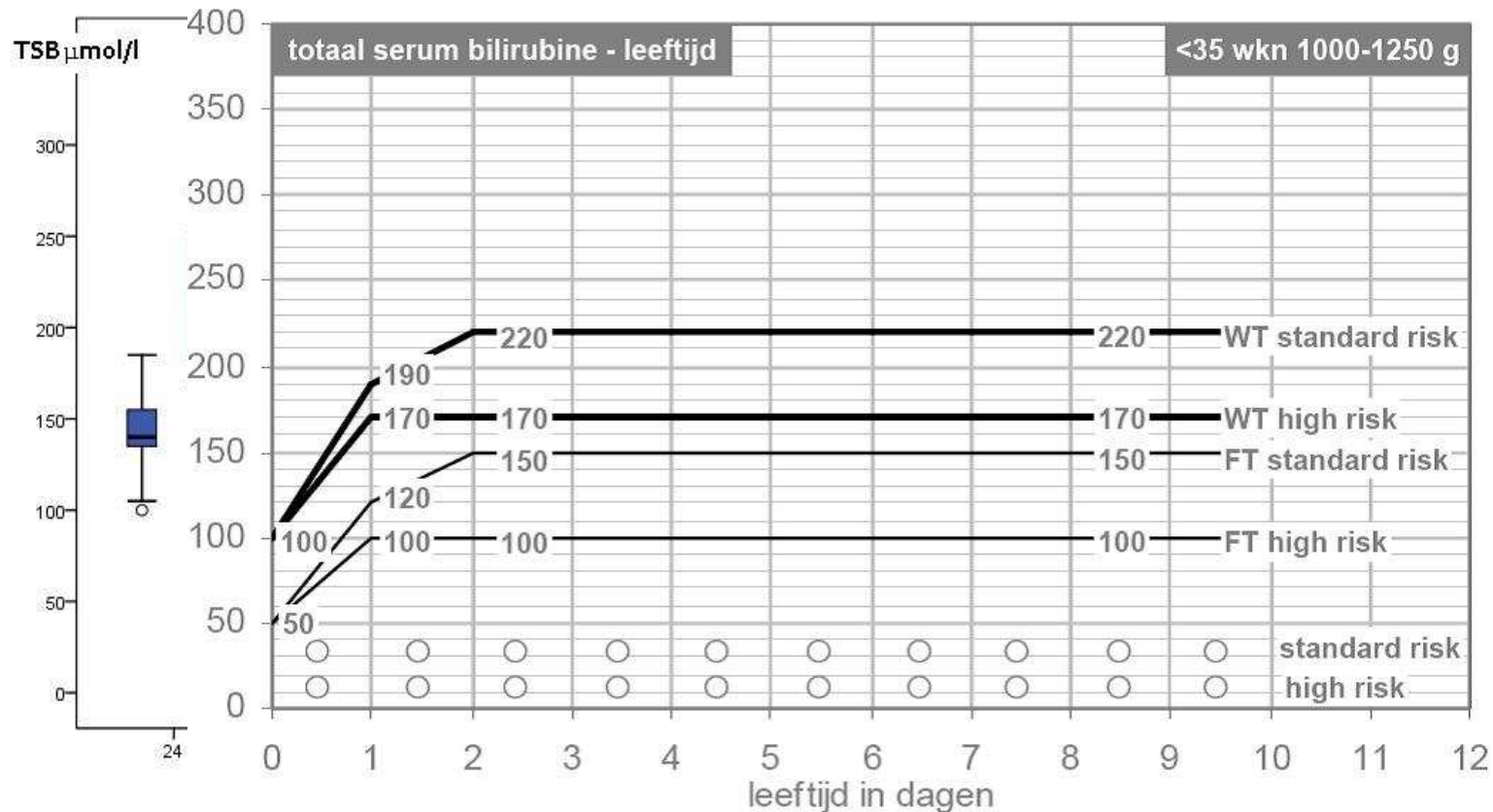
4. Behandeling is gebaseerd op Totale Serum Bilirubin (TSB)



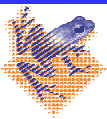
Adapted from Dijk et al NTvG 2009 and Van Imhoff et al 2009



Grote variatie van behandelgrenzen



²www.nvk.pedinet.nl/pdfs 2008



5. Bijwerkingen van huidige behandelingen - foterapie

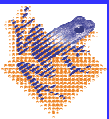
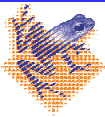




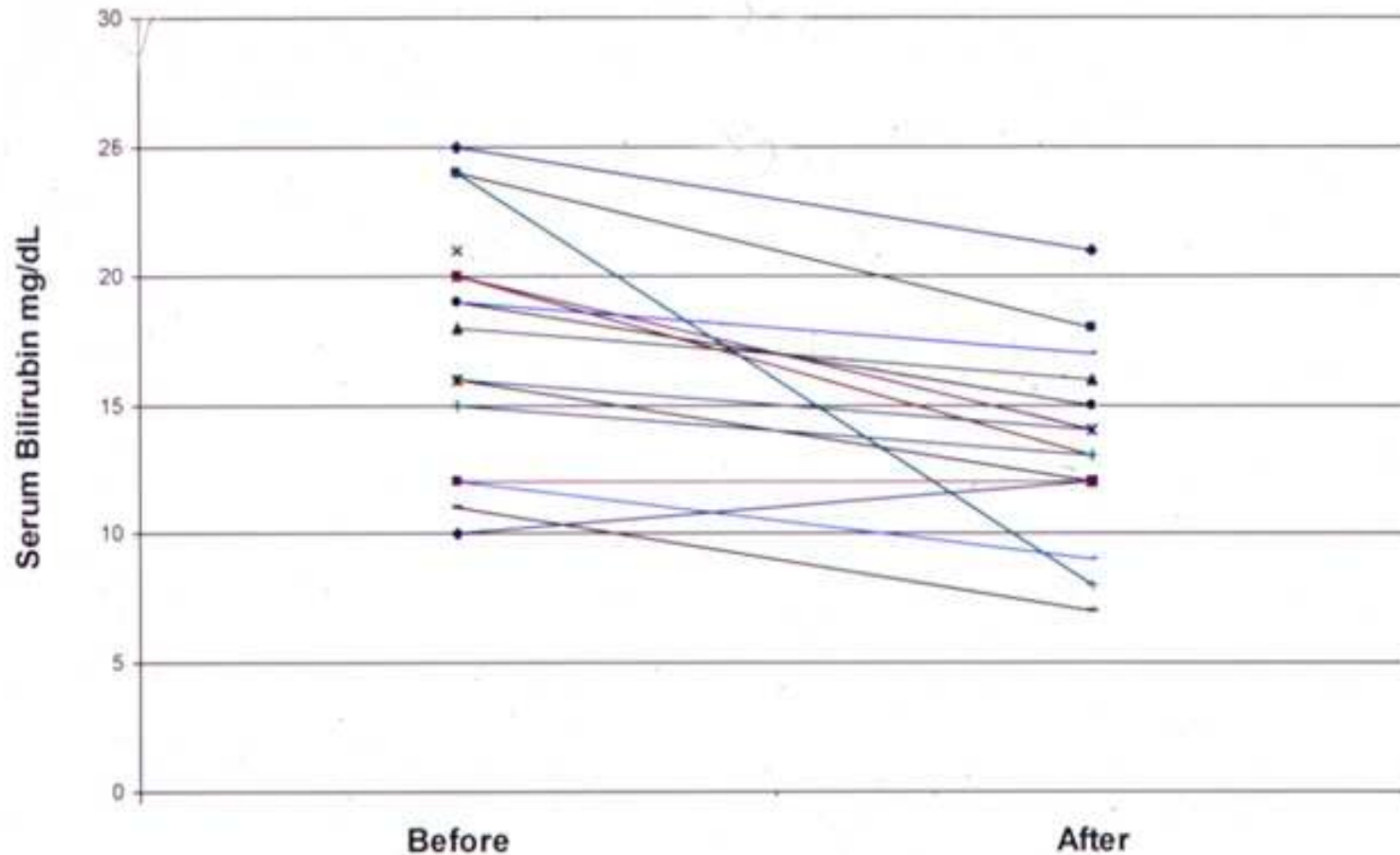
FIG.—Miss J. Ward, S.R.N., in 1956, with one of the earliest of the infants given phototherapy at Rochford General Hospital.



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Effect of Sunlight on Jaundiced Preterm Infants

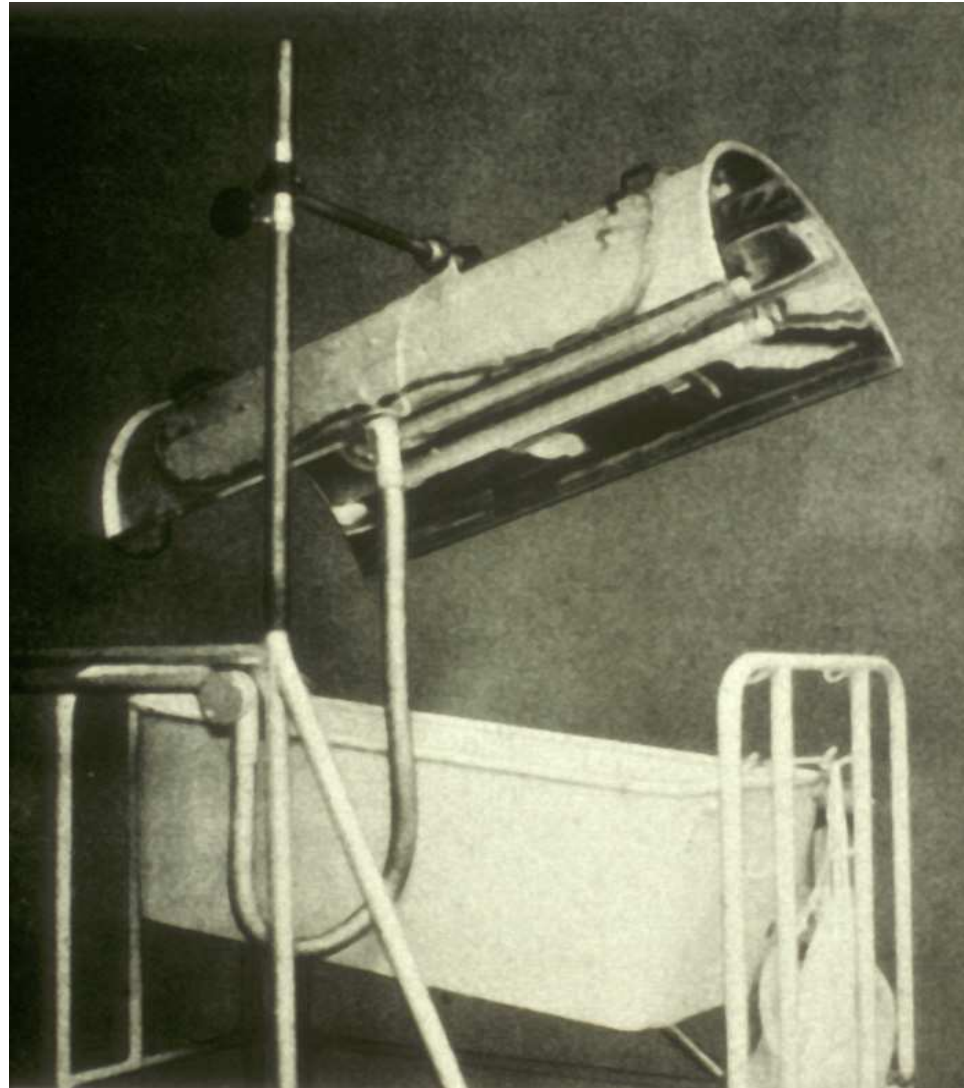
Cremer et al Lancet 1958;1:1094



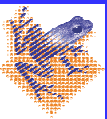
13 neonaten: 2 – 4 uren in de zon



De eerste foterapie lamp



Cremer et al Lancet 1958

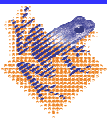


Beatrix Kinderziekenhuis UMC Groningen

De nieuwste foterapie lamp



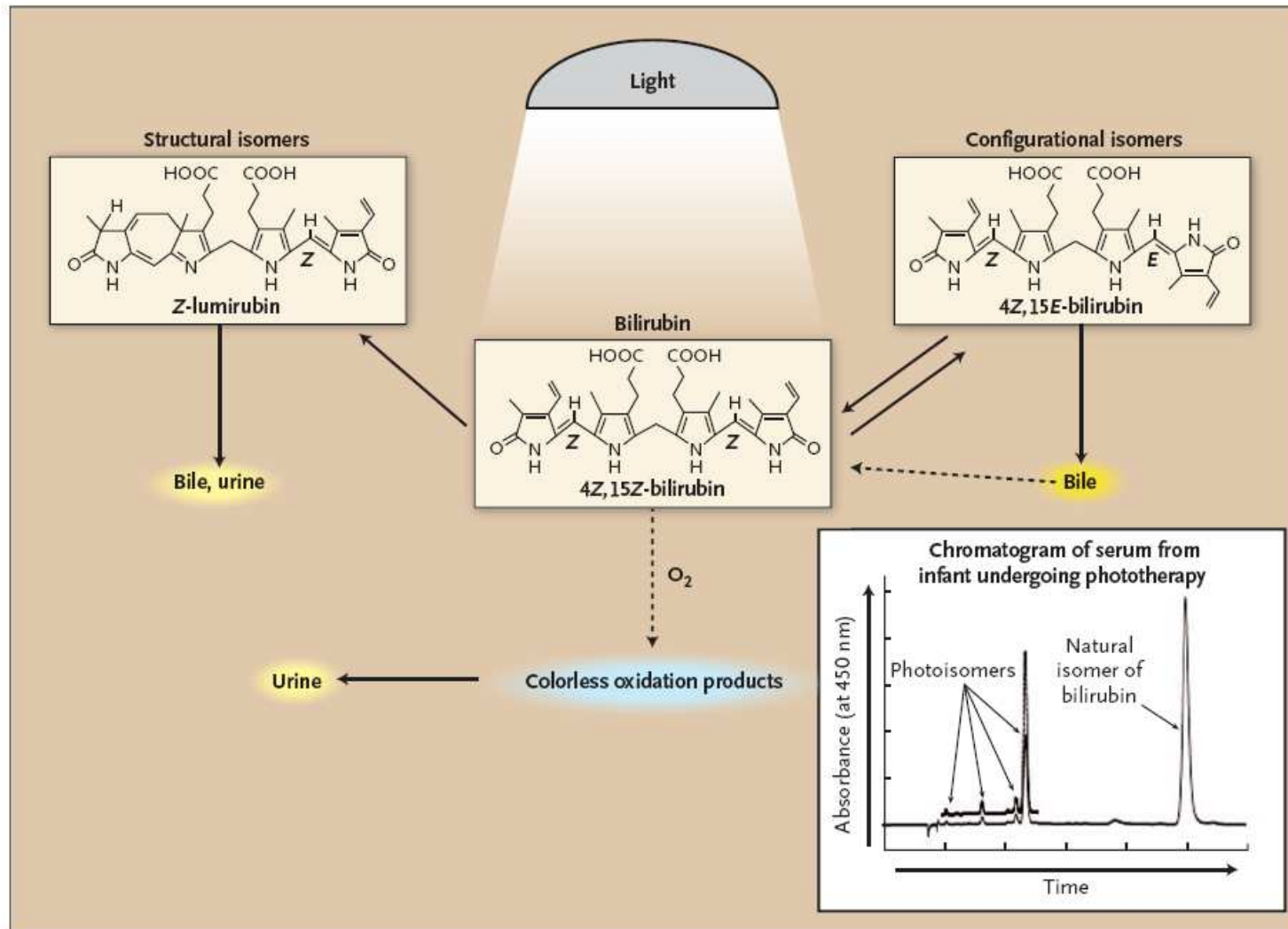
Bloo (Mediprema)





Bloo (Mediprema)

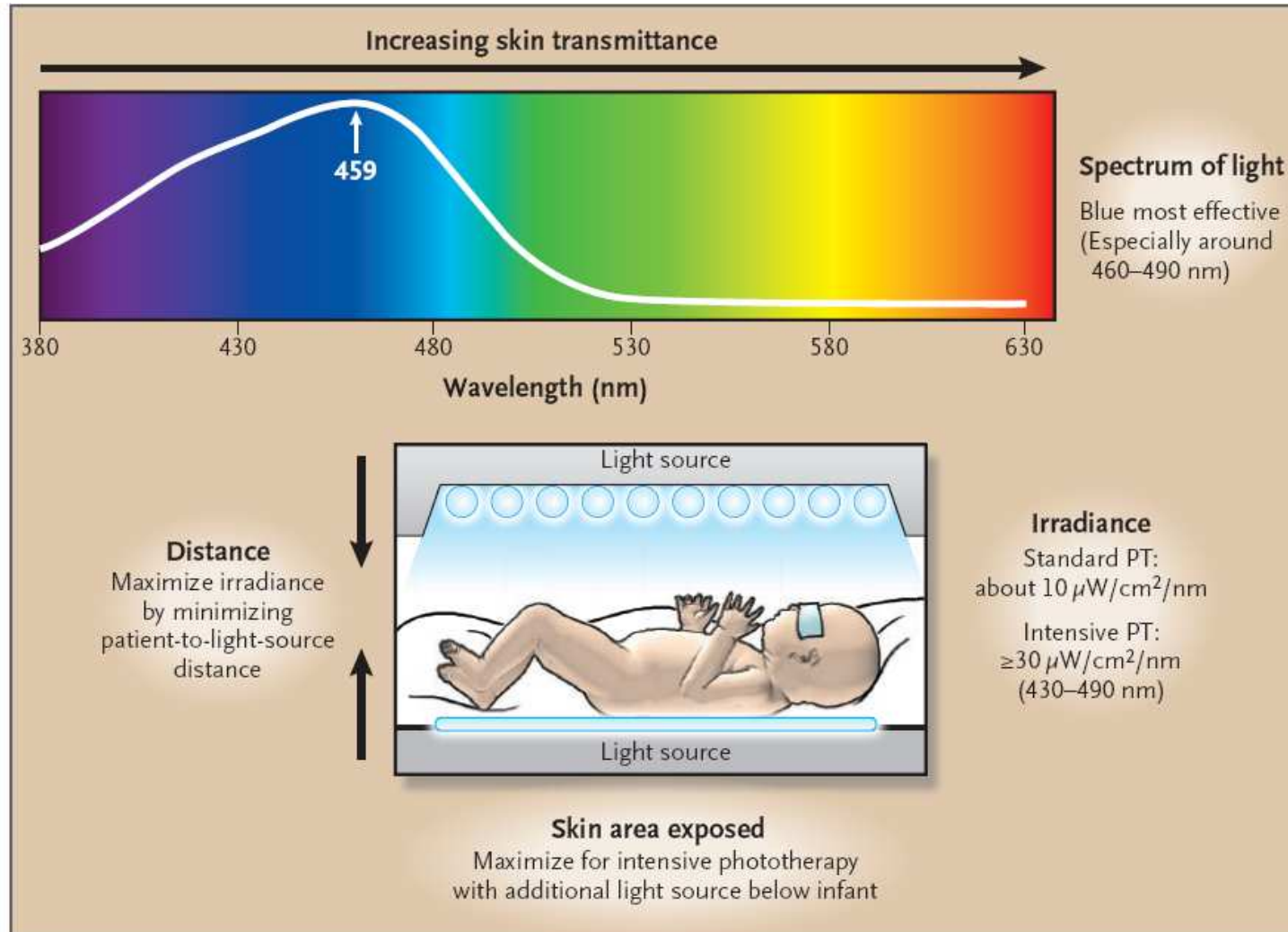
Mechanisme van foterapie



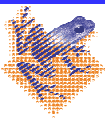
Maisels NEJM 2008



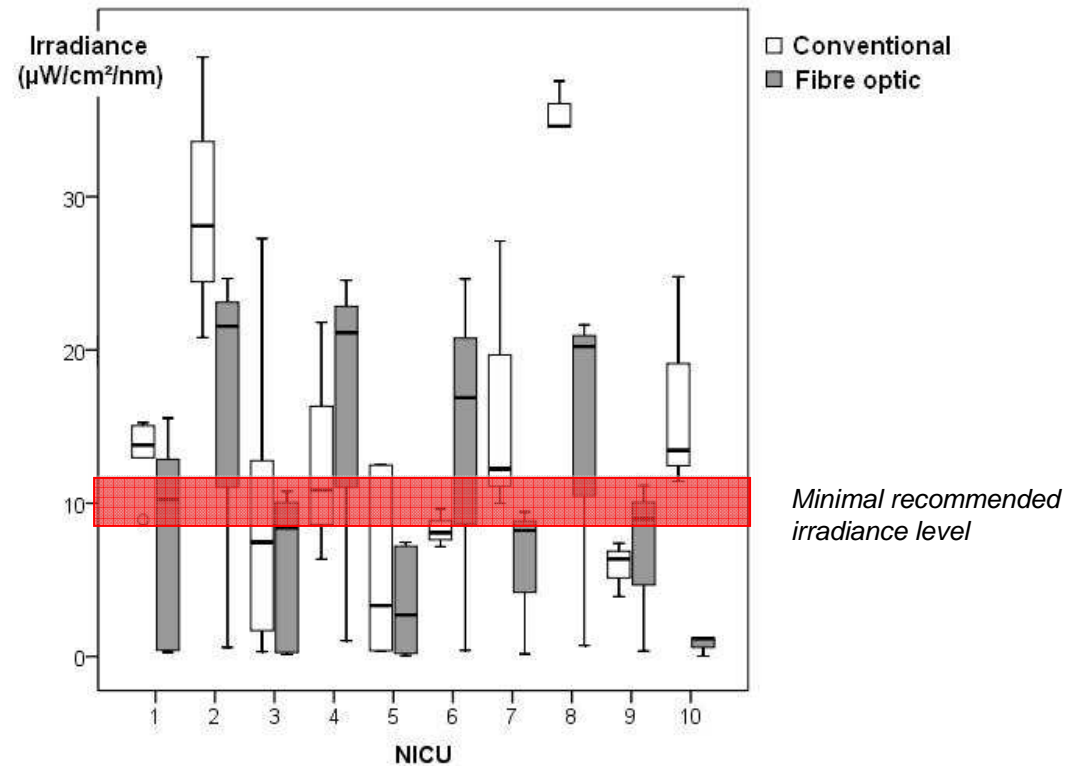
Effectiviteit van fotherapie



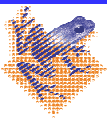
Maisels NEJM 2008



Grote variatie in lichtintensiteit



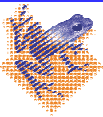
Van Imhoff 2009



5. Bijwerkingen van huidige behandelingen - foterapie

Side effects and associated risks of Phototherapy
Side effects Retinal damage (when eyes are unprotected) Skin pathology: Bronze baby syndrome or purpuric eruptions of the skin in cholestatic conditions
Erythematous rash if simultaneous treatment with Sn-mesoporphyrins
Increased insensible water loss Intervention with social and psychological interactions
Associations <u>Short term</u> Haemodynamic changes, increase of cerebral blood flow, reduction of renal blood flow and reopening of ductus arteriosus
<u>Longterm</u> Atypical melanocytic nevi Asthma Diabetes type 1

Adapted from Maisels 2008

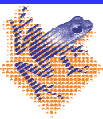


5. Bijwerkingen van huidige behandelingen - wisseltransfusie



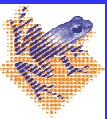
- Morbiditeit (tot 5%): arritmie, trombose, trombocytopenie, enterocolitis, infectie¹
- Mortaliteit: 3/ 1000²

¹Watchko 2000; ²Jackson Pediatr 1997

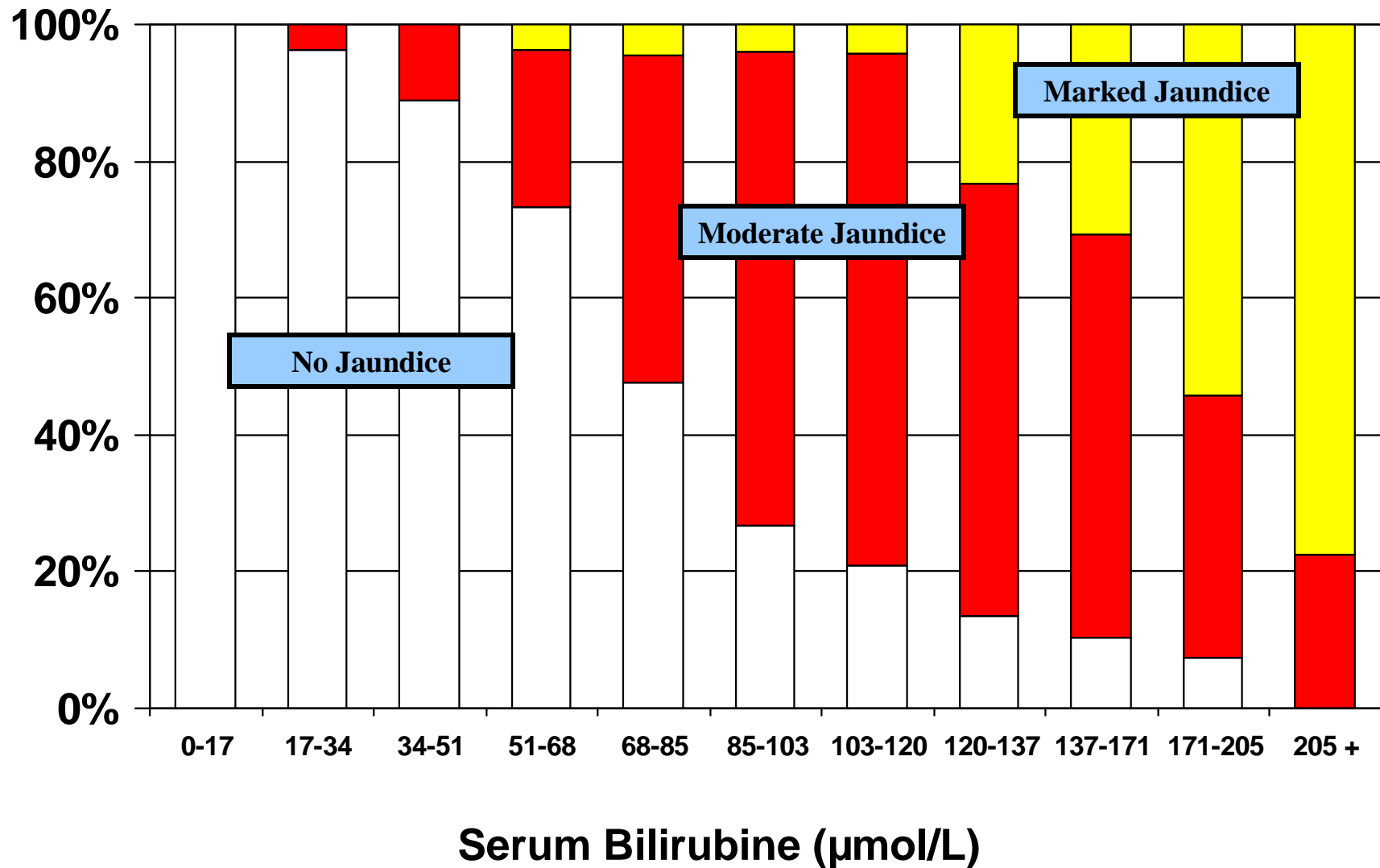


6. Ontbreken van goed alternatief

- Visuele inspectie
- Vrije bilirubine metingen
- Transcutane bilirubine metingen



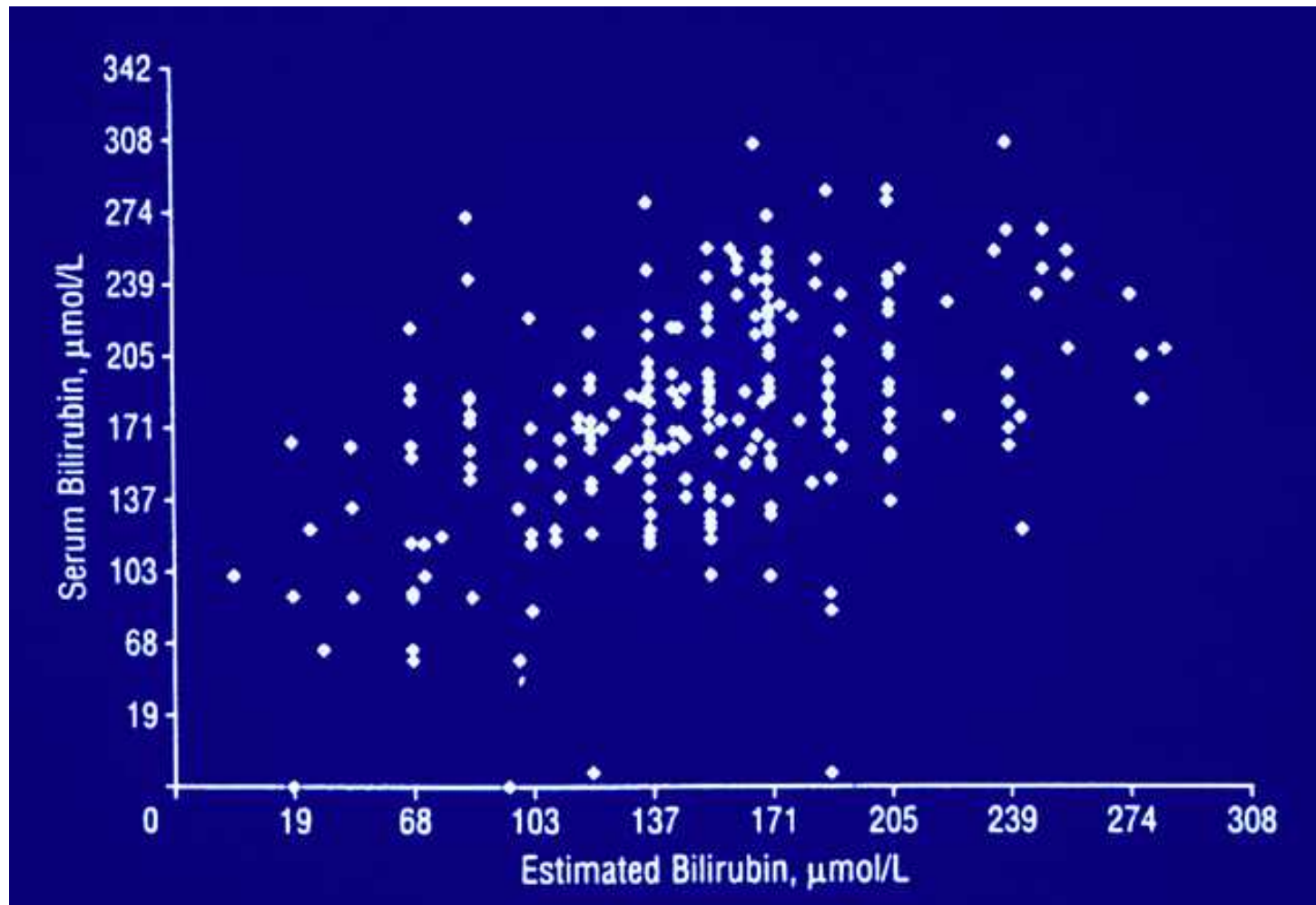
Visuele schattingen van TSB concentraties



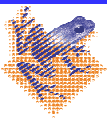
Davidson et al. Am J Dis Child 1941



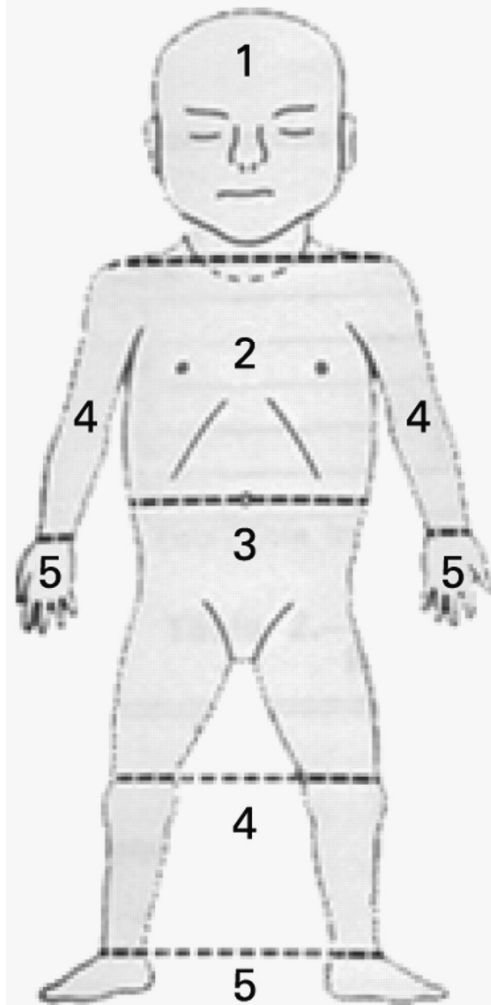
Visuele schattingen van TSB concentraties



Moyer VA, et al. Arch Pediatr Adolesc Med 2000



Cephalocaudale progressie



Grade	Extent of jaundice
0	None
1	Face and neck only
2	Chest and back
3	Abdomen below umbilicus to knees
4	Arms and legs below knees
5	Hands and feet

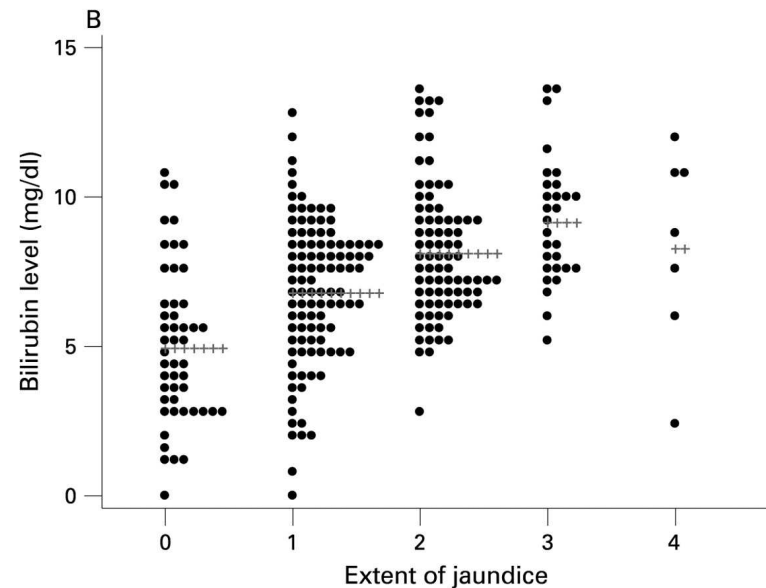
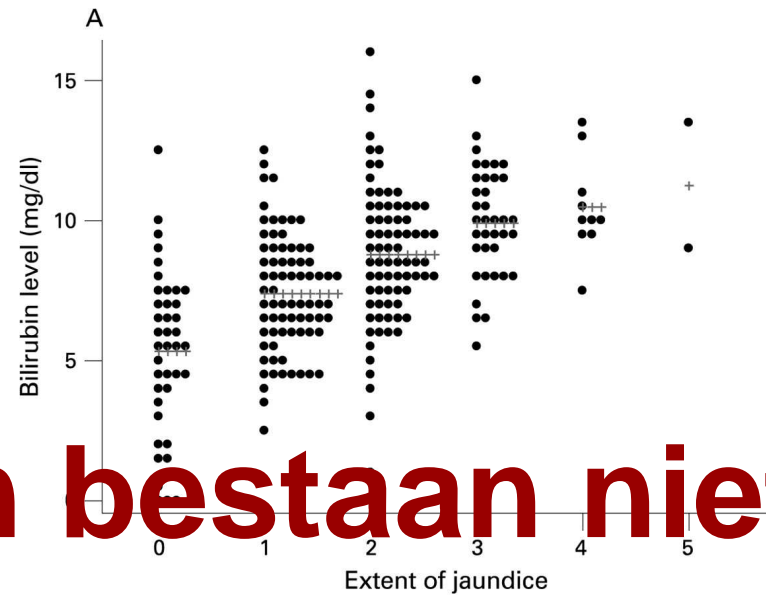
Keren R et al. Arch Dis Child Fetal Neonatal Ed 2009



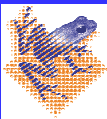


Bili ogen bestaan niet!

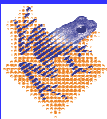
Grade	Extent of jaundice
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Keren R et al. Arch Dis Child Fetal Neonatal Ed 2009

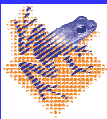
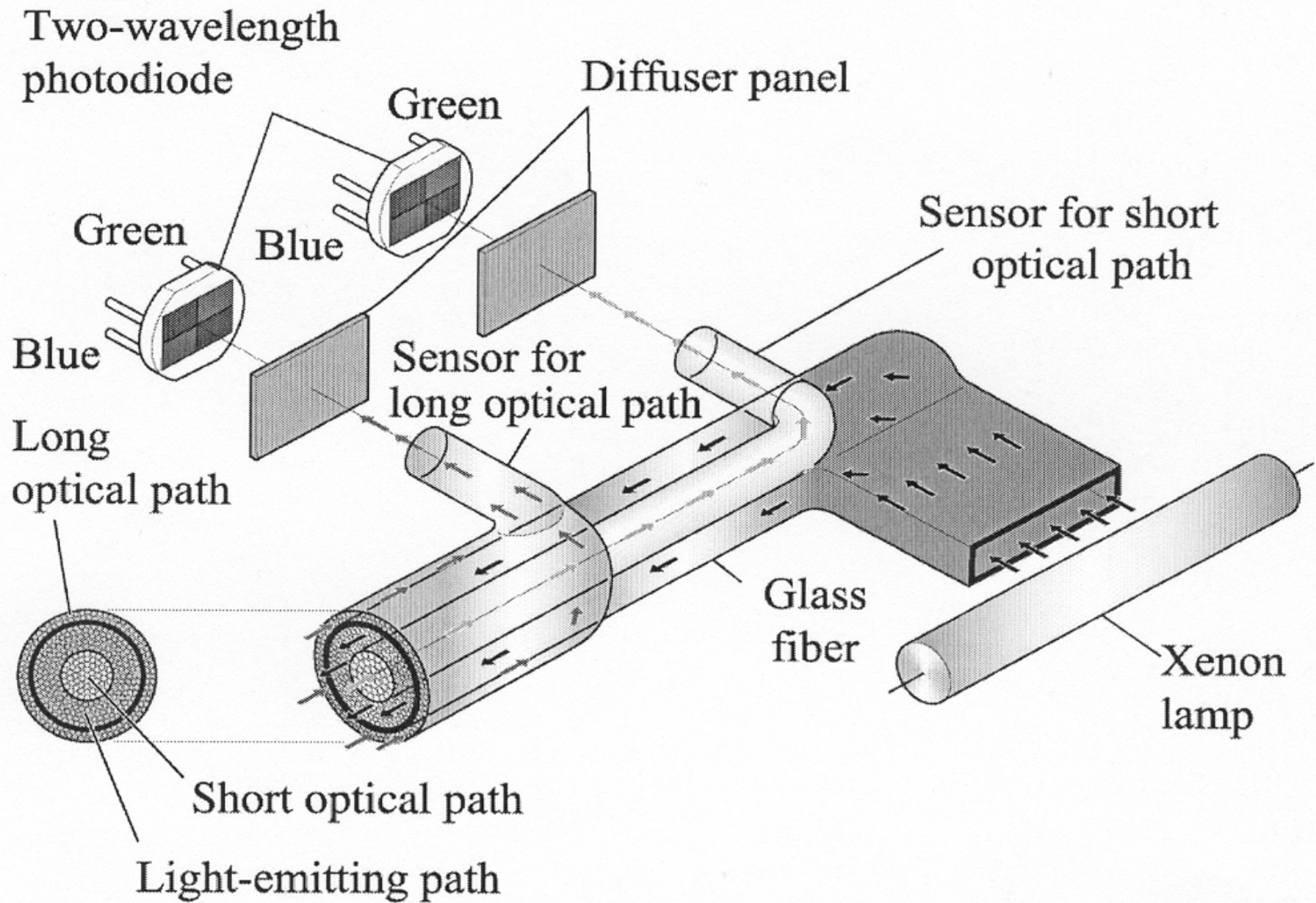


Vrije bilirubine - geen routine

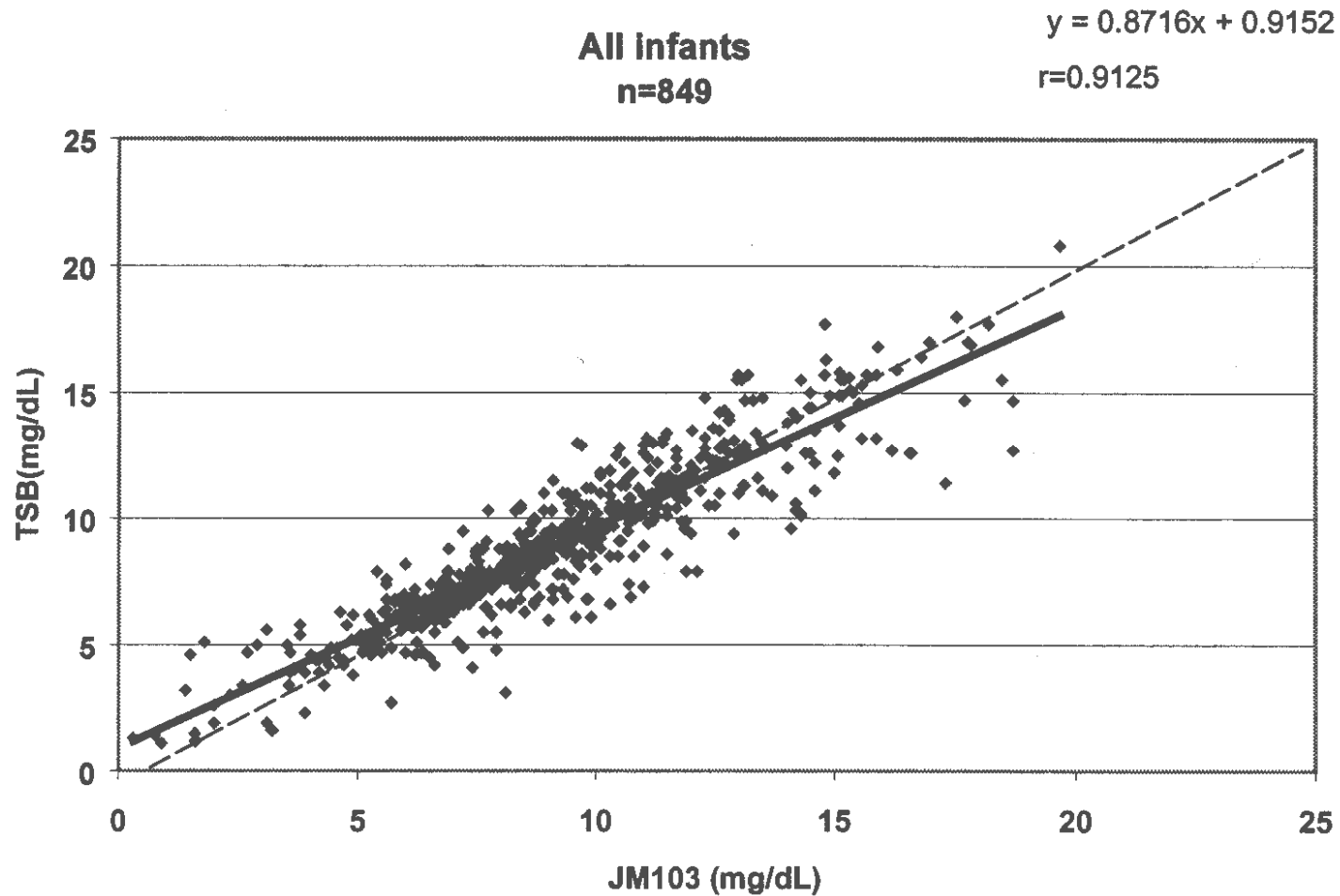


Transcutane bilirubine (TcB)

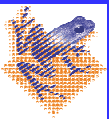




Transcutane bilirubine (TcB)



Maisels et al Pediatrics 2004

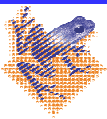


Transcutane bilirubine (TcB)

Can tell you:

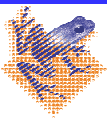
- **“Should I worry about this infant?”**
- **“Should I obtain a TSB in this infant?”**

Maisels et al Jonxis Lecture 2010

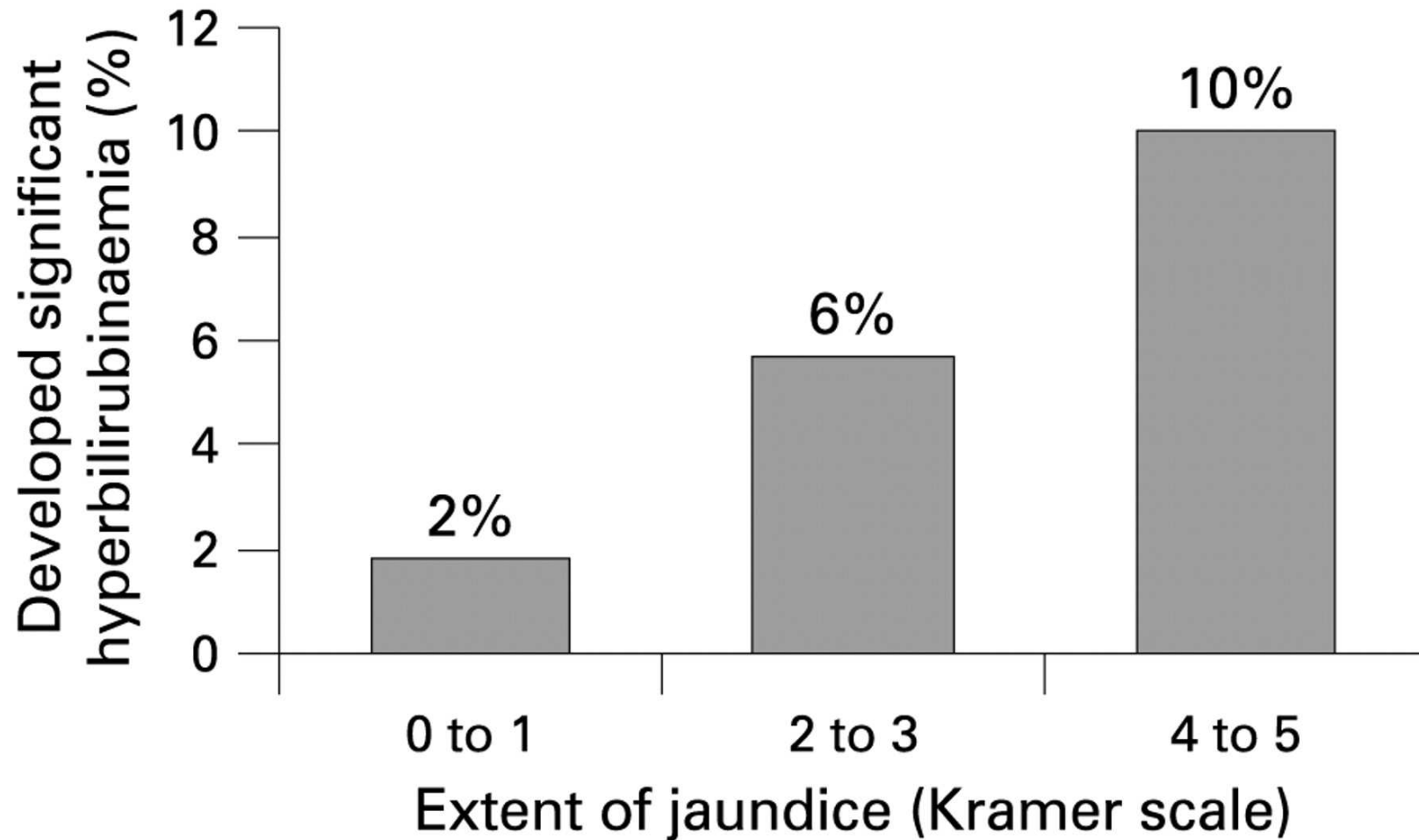


TSB juist meten is klinisch relevant

- Ongeconjugeerde hyperbili komt vaak voor
- Hoge bili's zijn neurotoxisch
- Kernicterus komt nog steeds voor
- Behandeling "TSB-based"
- Bijwerkingen behandelingen
- Geen goed alternatief



Extent of jaundice and development of significant hyperbilirubinaemia.



Keren R et al. Arch Dis Child Fetal Neonatal Ed
2009;94:F317-F322

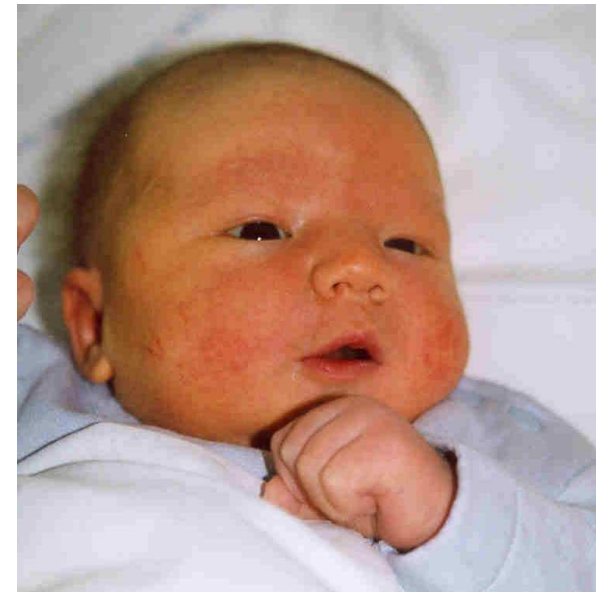


Introduction

Neonatal hyperbilirubinemia is caused by high bilirubin production in relation to limited conjugation capacity.

Casus

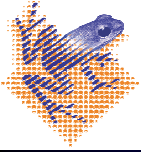
- jongetje, GA 39 wk /gewicht 3870 g
- klinische partus, vacuümextractie ivm hoogstand hoofd
- 2^e levensdag naar huis, borstvoeding
- 3^e levensdag “ietsje geel”



Casus

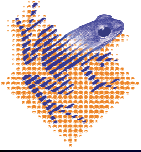
- 5^e levensdag matig drinken, sloom



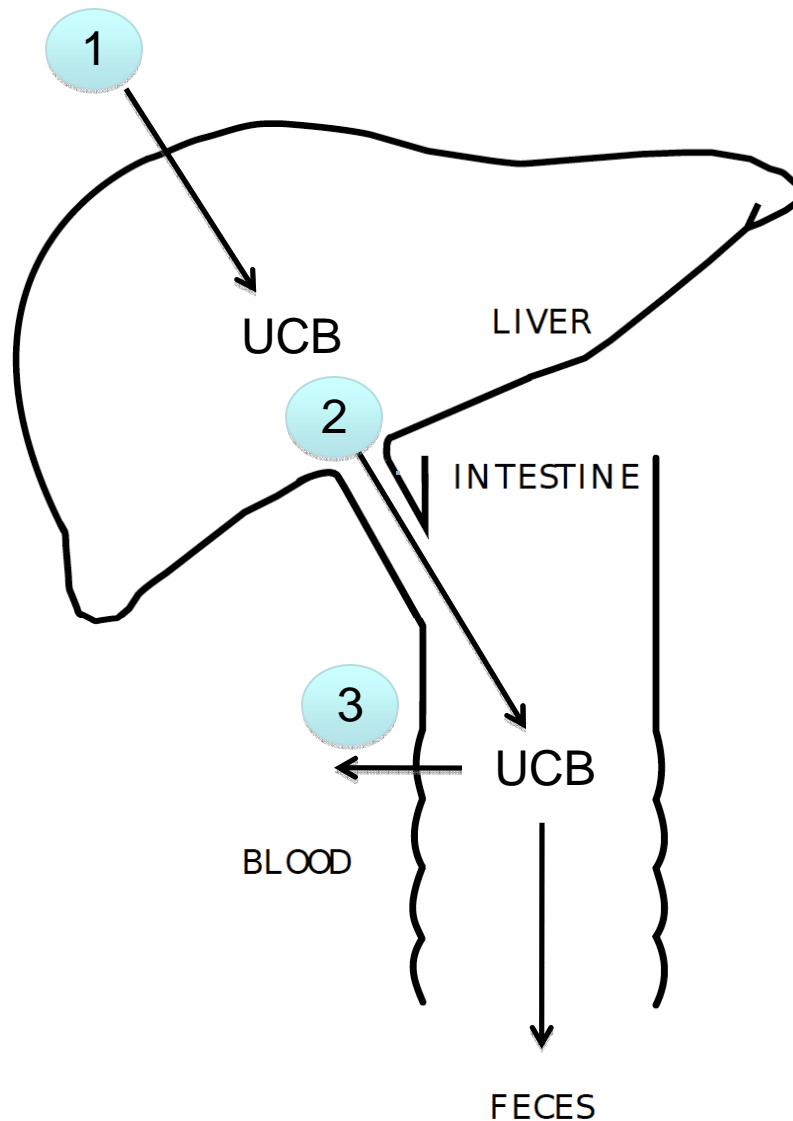


Icterus neonatorum

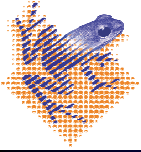
- gele verkleuring huid en slijmvliezen
- ongeconjungeerd bilirubine in de huid en slijmvliezen
- zichtbaar geel vanaf ca 100 $\mu\text{mol/l}$



Wat is de oorzaak van icterus neonatorum?

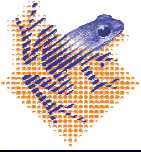


- 1 versnelde bloedafbraak
- 2 onrijpheid lever-enzymen (glucuronyl-transferase)
- 3 versterkte enterohepatische kringloop



Fysiologische icterus

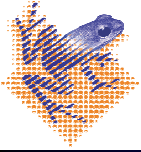
- aanvang icterus > 24 uur
- maximum op 3^e-4^e levensdag (170-200 $\mu\text{mol/L}$)
- duur maximaal 10 dagen



Differentiaal diagnose

- Versterkte bloedafbraak
- Lever conjugeert niet goed (=nog slechter)
- Gal uitscheiding gestoord (geconjugeerde bili verhoogd)





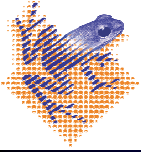
Risico's icterus neonatorum

- slecht drinken
- gevaar voor dehydratie
- sufheid

- Stapeling in hersenen,
in basale ganglia

- Kernicterus
- BIND (bilirubin induced
neurological damage)

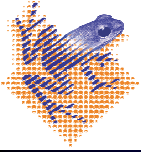




Kernicterus, vroege symptomen

- lethargie, coma
- hypo- hypertonie
- prikkelbaarheid
- "high-pitched cry"
- convulsies
- koorts
- bomberende fontanel
- opisthotonus

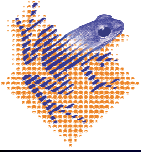




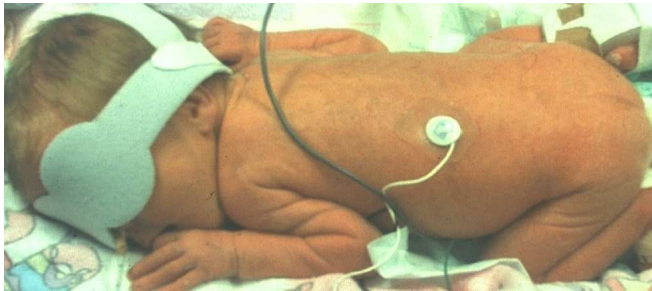
Kernicterus: lange termijn gevolgen



\$5 Million recovery for family of brain-damaged child for failure of physicians to diagnose jaundice/hyperbilirubinemia
December, 1998

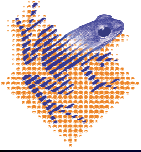


Icterus neonatorum - Behandeling - Fotherapie



- afbraak tot wateroplosbare producten o.i.v. licht
- fotherapie lamp

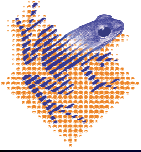




Icterus neonatorum – Behandeling - Wisseltransfusie



- O-negatieve RBC en AB-negatief plasma
- isovolumetrisch wisselen (20 ml uit; 20 ml in)
- risico's
 - cathetercomplicaties
 - cardiocirculatoire complicaties
 - transfusiegerelateerde complicaties



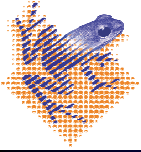
Icterus neonatorum - Behandeling

1. Fotherapiepie

- Photodynamische reacties *in vitro*
- DNA veranderingen *in vitro*
- Kans op retina beschadiging *in vivo*
- “Bronze Baby Syndrome” *in vivo*
- Interferentie met ouder kind contact

2. Wisseltransfusie

- Aanzienlijke morbiditeit
- Mortaliteit (vnl bij zieke prematuren)



Opbouw

- Wat is hyperbilirubinemie?
 - Fysiologie
 - Wat is het gevaar?
- } Klinisch probleem
Deel I
-
- Experimentele therapieën
 - Proefdier onderzoek
 - Therapeutische consequenties?
- } Basaal onderzoek
Deel II