



MAASTRICHT

17th-21st September 2019

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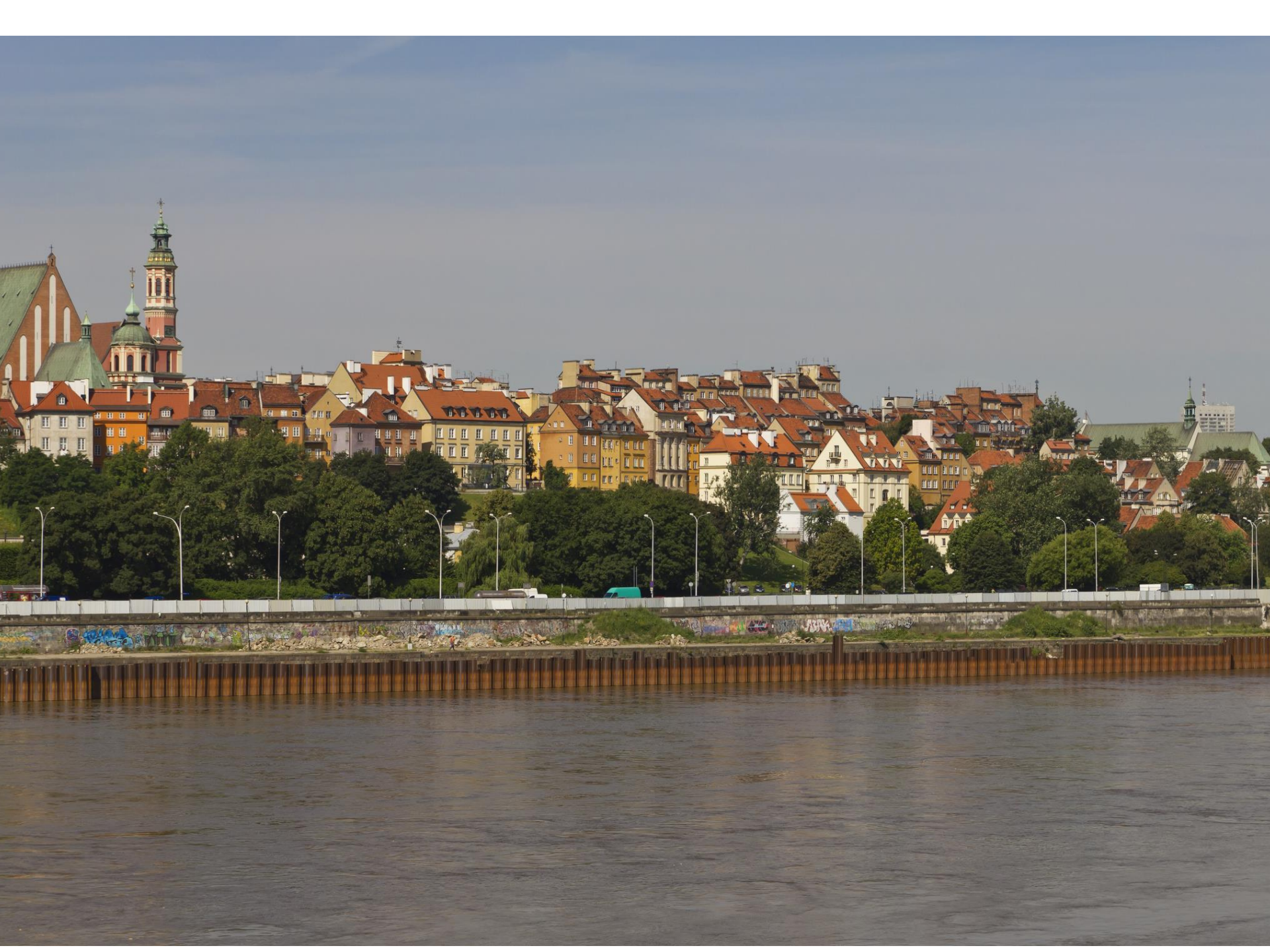
«Сучасні ТОП-теми неонатологічних європейських конгресів»



Międzynarodowa Konferencja
Naukowo-Szkoleniowa
10-11 października 2019

Airport Hotel Okęcie****, Warszawa
www.neonatus.org





Antibiotic stewardship in the NICU

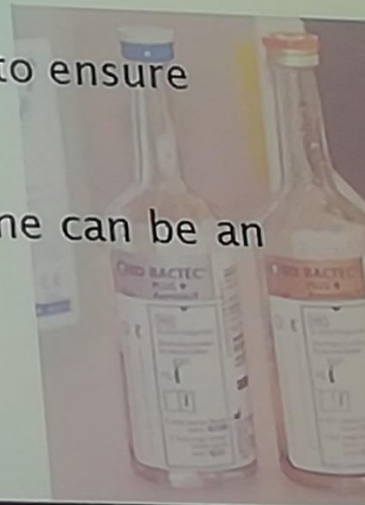


Angelika Berger

Div. of Neonatology, Pediatric Intensive Care and Neuropediatrics
MedUniWien

Diagnosis of neonatal sepsis

- Blood culture gold standard
- **Use minimum of 1ml of blood when ever possible**
- Sensitivity drops by 10-40% when 0,5ml instead of 1ml is used
- Connell et al.: blood cultures in neonates - in 35% volume less than 0,5ml
- Education and quality improvement initiatives to ensure adequate volume being collected
- A blood culture from a newly placed arterial line can be an alternative to peripheral venipuncture

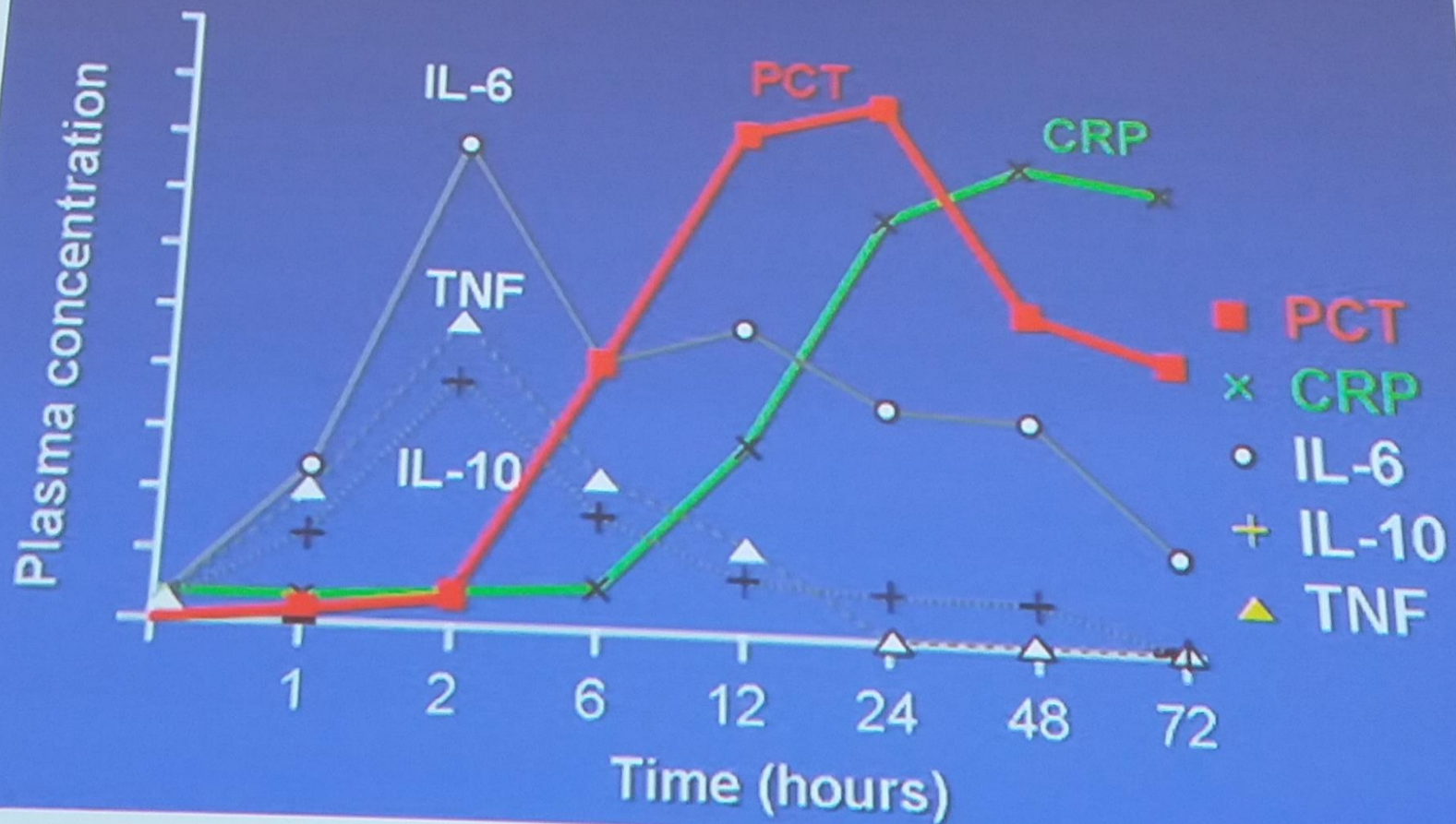


Biomarkers for ruling out neonatal infections

- Normal I:T ratio or 2 negative CRP values 24hrs apart can rule out EOS with high accuracy
- Frantz et al.: IL-8 plus CRP vs CRP alone reduces antibiotic use by 73% in preterm infants with suspected LOS without increasing missed infections
- PCT - higher sensitivity compared to CRP for neonatal sepsis
- **Interpret biomarkers always in combination with clinical picture**



Kinetics of biomarkers in sepsis



Prokalcytonina - wzrost

- Wykrywana w osoczu w 2 godz po wstrzyknięciu endotoksyny, po 6–8 godz osiąga plateau
- Dla porównania CRP jest wykrywane po 12 h godz i osiąga plateau po 20–72 h
- Do normy obniżają się odpowiednio -

PCT po 2–3 dniach , **CRP po 3–7 dniach.**

Assicot M i wsp. , Lancet, Vol 341, No. 8844, p515–18, 1993

Cord blood procalcitonin and Interleukin-6 are highly sensitive and specific in the prediction of early-onset sepsis in preterm infants

Eva Steinberger, Nora Hofer & Bernhard Resch 

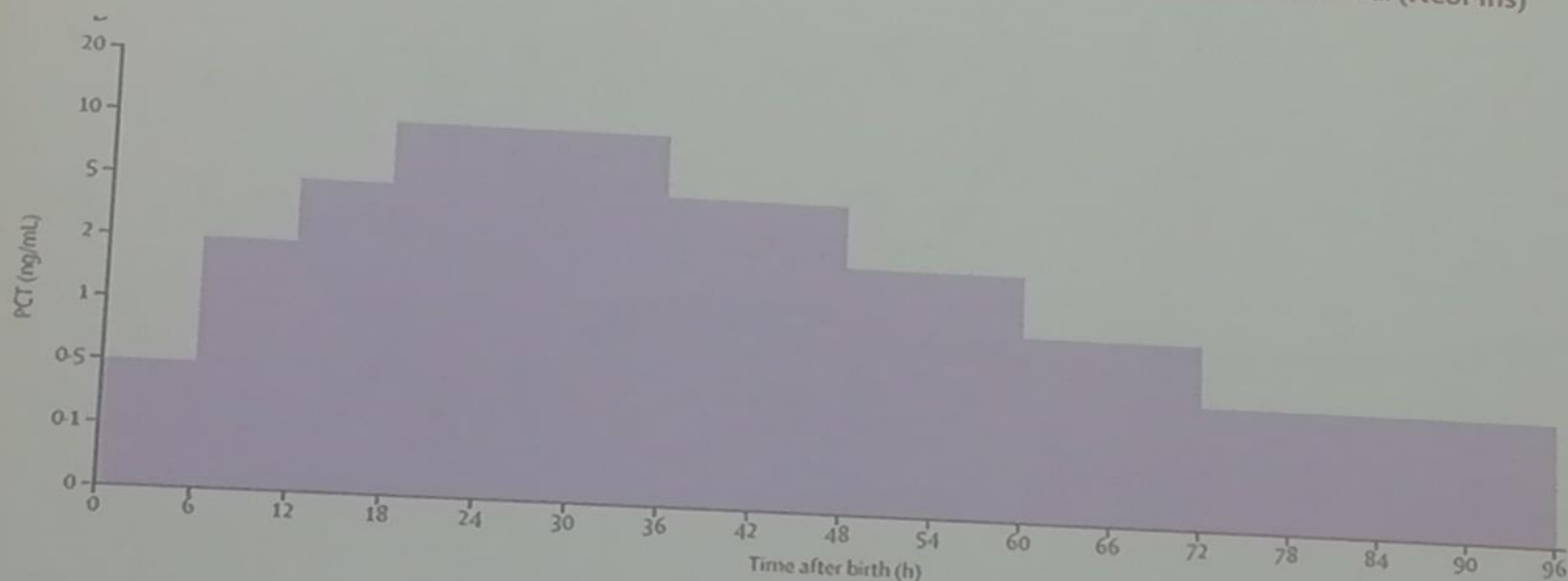
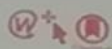


- ✓ Wartość odcinająca dla PCT to 0.235 $\mu\text{g/L}$ (czułość 78.6%, swoistość 86.3%),
- ✓ IL-6 wartość odc. 15.85 ng/L (czułość 73.7%, swoistość 84.2%),
- ✓ PCT plus IL-6 dało czułość 77.1% swoistość **91.7%**.

ANTIBIOTICS IN NEWBORNS AFTER BIRTH

HOW TO STOP?

Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPlns)



Badanie NeoPinS



Annemarie van Rossum

Erasmus MC University Medical Center
Rotterdam - Sophia Children's Hospital
Netherlands

Study design:

Neonates suspected of EOS $\geq$
34 weeks

Exclusion criteria:

- surgery first week of life
- congenital malformation

Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial: **NeoPinS**

THE LANCET

Volume 390, Issue 10297, 26 August–1 September 2017, Pages 671–681

Aim: reduce antibiotic treatment in suspicion of EOS by PCT guided treatment with unchanged outcome (re-infection, mortality)

Procalcitonin intervention study: NeoPInS



May 2009 – February 2015
18 centers



2440 Neonates suspected of EOS assessed for eligibility

499 No consent for participation, reason:

- 283 Reason unknown
- 108 Logistical reasons
- 68 Language barrier
- 48 Ineligibility
- 11 Refused, resistance against earlier stop antibiotics
- 10 Refused, resistance against additional blood draw
- 0 Social reason

1941 Screened neonates

231 Ineligible, due to

- 132 No parental consent form
- 25 No parental consent for data storage
- 14 Parental consent withdrawn before randomization
- 45 Ineligibility, of which:
 - 22 congenital malformation
 - 20 other reasons
 - 3 surgery in the first week of life
- 14 No 100% data monitoring/ retrieval feasible
- 1 Protocol claim: max. surrogates not possible

1710 Randomized neonates for 'Intention-to-treat analysis' (ITT)

n = 866 PCT group (ITT)

PCT-guided decision making for antibiotic treatment

- 121 Protocol violations
- 68 Missing key variables
- 41 Misclassifications with effect on outcome
- 10 Lost to follow up
- 2 Lost to transfer to other hospital

n = 745 PCT group (PP)

Antibiotic treatment guided by PCT non organ

n = 844 Standard group (ITT)

Antibiotic treatment guided by local policy

- 181 Protocol violations
- 85 Misclassifications with effect on outcome
- 70 Deblinded: 22 PCT values known
- 19 Missing key variables
- 7 Lost to follow up

n = 663 Standard group (PP)

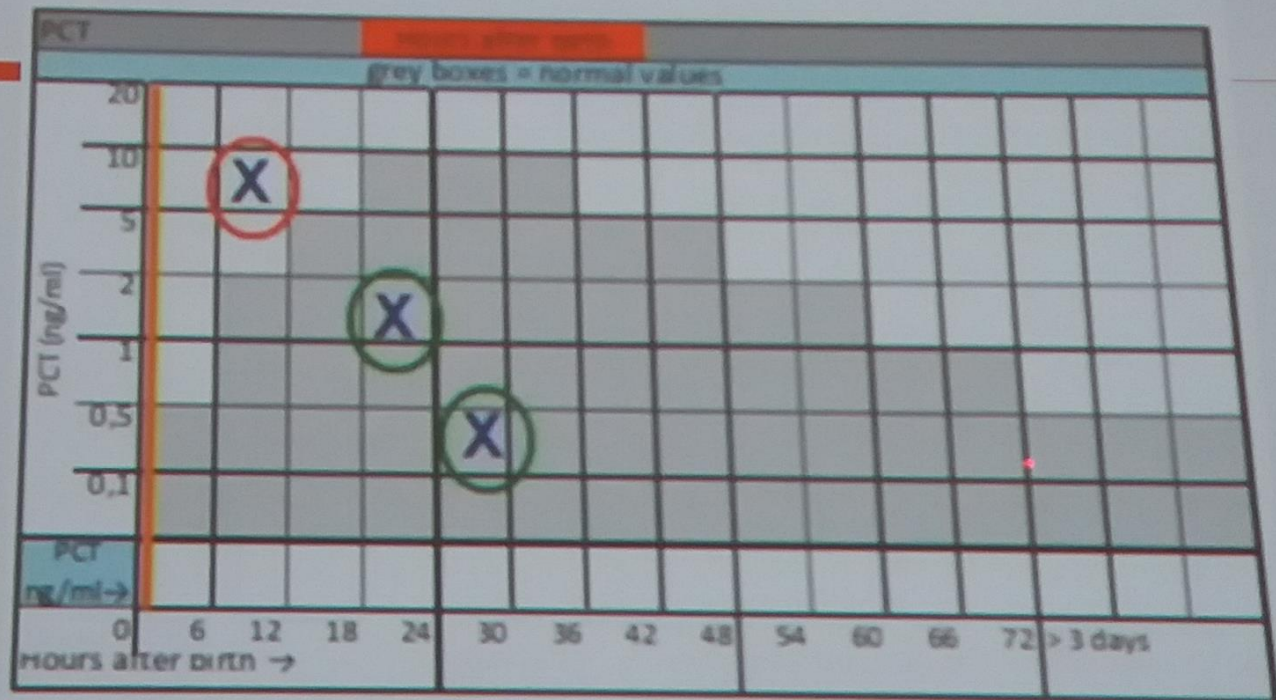
Antibiotic treatment guided by local policy

1408 Randomized neonates for 'Per protocol analysis' (PP)

Erasmus MC

Erasmus

PCT guided treatment



Minimum
24 hours therapy

If clinical condition allows:

→ **STOP** therapy

High amount of antibiotic use in NICUs

- Point prevalence study of 29 US NICUs - 47% of 827 infants on antibiotics on day of survey (Grohskopf et al. PIDJ 2005)
- 72% of infants in level III US NICUs received at least 1 antibiotic course, only 5% prescribed for culture-proven infection (Scout study, Cantey et al. PIDJ 2015)
- Survey of 127 NICUs across California: 40-fold variation from 2,4% - 97,1% (mean 24,5%) of patient days - „Antibiotic usage in NICUs often is excessive and considerable proportion of antibiotic use lacks clear indication“ (Schulman et al. Pediatrics 2015)

An antibiotic policy to prevent emergence of resistant bacilli

P de Man, B A N Verhoeven, H A Verbrugh, M C Vos, J N van den Anker

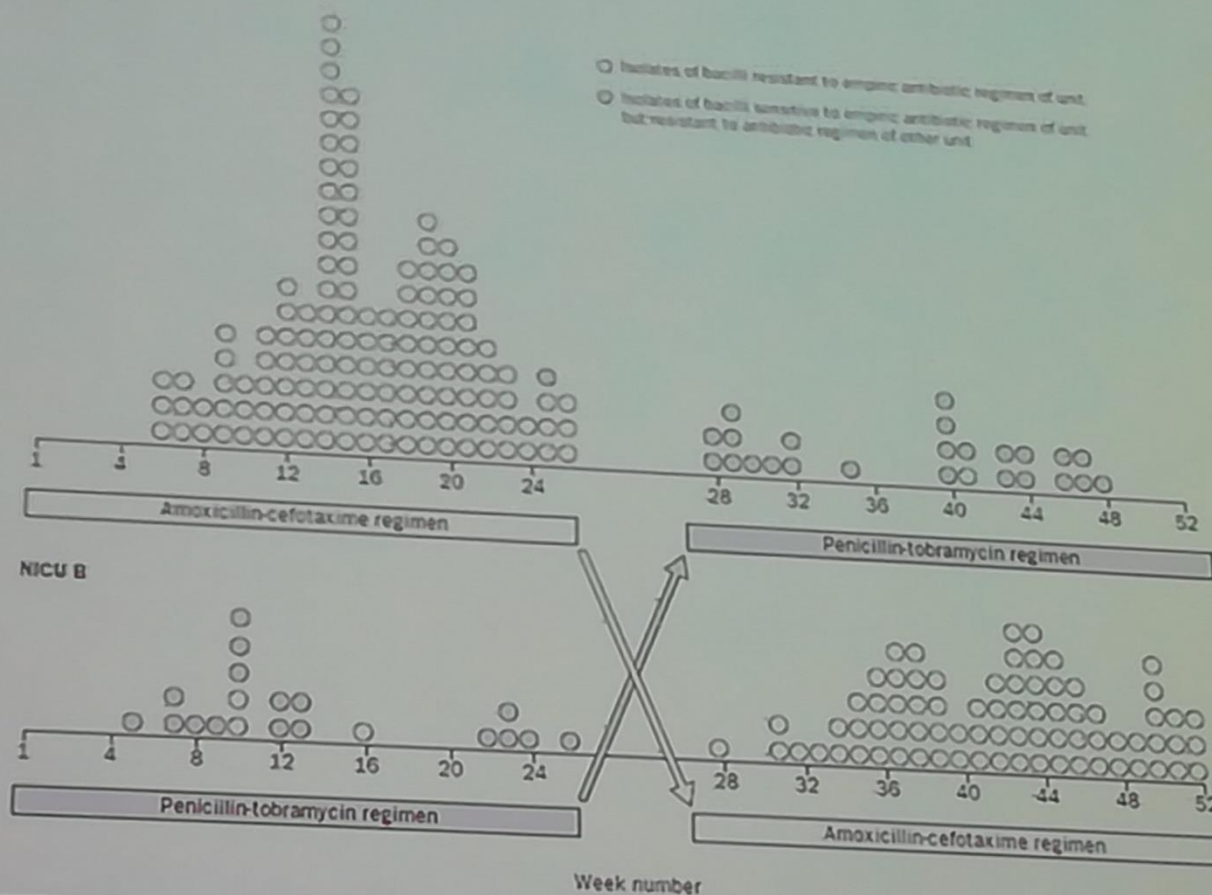
- 2 identical NICUs, different empirical antibiotic regimens
- NICU B: PenG/Tobramycin EOS
Flucloxacillin/Tobra LOS
- NICU A: Ampicillin/Cefotaxim EOS
Flucloxacillin/Cefotaxim LOS
- After 6 months regimen change
- Weekly surveillance cultures (rectal and pharyngeal swabs)



An antibiotic policy to prevent emergence of resistant bacilli

P de Man, B A N Verhoeven, H A Verbrugg, M C Vos, J N van den Anker

NICU A



Не тільки високий ризик
антибіотико-резистентності,
але високий *індивідуальний*
ризик для несприятливих
наслідків тривалого
використання антибіотиків у
передчасно народжених

Association between 3rd gen cephalosporins and invasive candidiasis in ELBWI

3701 ELBWI 12 centers, 284
(7,7%) invasive candidiasis

Center candidiasis
incidence: 2.4% - 24%

Correlation with average
use of 3rd gen
cephalosporins

TABLE 2 Logistic Regression Analysis of Risk Factors for Invasive Candidiasis Among Infants in 12 NICUs, 1998-2001

Variable	Odds Ratio, Point Estimate	95% Confidence Interval
Center (same as Table 1)		
1	Reference*	Reference*
2	1.873	0.642-5.465
3	2.187	0.752-6.365
4	2.382	0.983-5.770
5	2.041	0.767-5.432
6	1.877	0.691-5.104
7	2.81	1.206-6.549
8	3.211	1.383-7.455
9	3.532	1.439-8.670
10	3.792	1.383-10.396
11	4.924	2.072-11.703
12	6.542	2.865-14.941
Non-center variables with P < .15		
Exposure to BSA	2.157	1.422-3.271
Gestational age	0.752	0.672-0.841
Maternal hypertension	0.532	0.323-0.877
Gravida status	1.073	0.999-1.153
ROM > 24 h	1.530	1.077-2.174
Age at first enteral feed	1.032	1.015-1.049
≥ 2 doses surfactant	1.438	1.007-2.052
PDA no surgery vs no PDA	1.935	1.340-2.793
PDA surgery vs no PDA	1.586	1.003-2.507
SGA status	1.666	0.925-2.999



Association between prolonged duration of initial empirical antibiotics and NEC

5639 ELBWI 19 centers NICHD, sterile cultures

Prolonged duration of initial empirical antibiotic treatment (≥ 5 d) associated with 30% increased rates of NEC and death

Each empirical treatment day associated with 4% increased odds of NEC/death after adjustment for GA, APGAR and race

TABLE 5 Multivariate Logistic Regression Analysis of Antibiotic Duration and NEC or Death

Outcome	Duration of Initial Empirical Antibiotic Treatment (Odds per Day)		Prolonged Initial Empirical Antibiotic Treatment	
	OR (95% CI)	P	OR (95% CI)	P
NEC or death (total, $N = 3883$; with outcome, $n = 884$)	1.04 (1.02–1.06)	<.01	1.30 (1.10–1.54)	<.01
NEC (total, $N = 3899$; with outcome, $n = 427$)	1.07 (1.04–1.10)	<.001	1.21 (0.98–1.51)	.08
Death (total, $N = 3882$; with outcome, $n = 631$)	1.16 (1.08–1.24)	<.001	1.46 (1.19–1.78)	<.001

ORs were adjusted for study center, gestational age, small-for-gestational age status, gender, black race, 5-minute Apgar score of <5, rupture of membranes for >24 hours, outborn, prenatal steroid treatment, intrapartum antibiotic treatment, maternal hypertension, maternal hemorrhage, and multiple birth. The total numbers of infants shown represent the numbers of infants with nonmissing outcome and covariate data who were included in each model.



Association between prolonged duration of initial empirical antibiotics and BPD

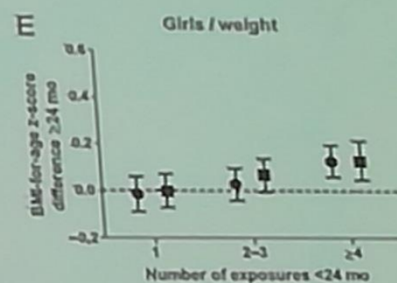
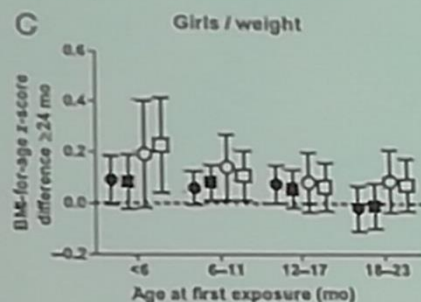
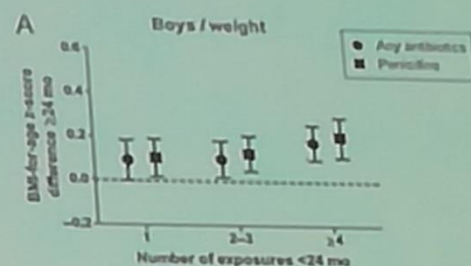
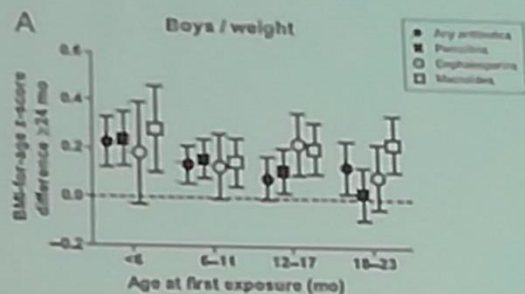
After controlling for severity of illness, each additional day of antibiotic therapy in first 14 DOL was associated with increased risk for and severity of bronchopulmonary dysplasia (patients with sepsis and NEC excluded)

Table II. Multivariable analysis of factors associated with risk for death or BPD and severity of BPD in VLBW Infants

Risk factors	OR (95% CI)		
	All infants	Infants ≤ 28 weeks gestation	Infants ≥ 29 weeks gestation
Primary outcomes			
Death or BPD			
CRIB-II score	1.8 (1.65-1.96)	1.73 (1.51-1.98)	1.30 (1.17-1.64)
Days of antibiotic therapy	1.13 (1.09-1.16)	1.13 (1.09-1.18)	1.11 (1.06-1.17)
Postnatal steroids	10.17 (3.17-32.62)		20 (4.13-96.75)
Secondary outcomes			
Mild BPD			
CRIB-II score	1.71 (1.32-2.34)	1.93 (1.45-2.87)	1.36 (1.04-1.91)
Days of antibiotic therapy	1.02 (0.96-1.11)	1.08 (0.99-1.22)	1.00 (0.87-1.16)
Moderate BPD			
CRIB-II score	1.77 (1.58-2.03)	1.8 (1.34-2.26)	1.30 (0.93-2.04)
Days of antibiotic therapy	1.14 (0.86-1.68)	1.14 (0.62-1.81)	1.1 (0.58-2.10)
Severe BPD			
CRIB-II score	1.91 (1.54-2.31)	2.11 (1.45-2.89)	1.76 (1.32-2.18)
Days of antibiotic therapy	1.16 (1.04-1.33)	1.15 (1.08-1.27)	1.19 (1.03-1.54)
Sepsis	1.76 (1.08-3.14)	1.65 (0.87-2.63)	1.88 (0.92-4.51)
Increased severity of BPD			
CRIB-II score	1.44 (1.36-1.52)	1.36 (1.27-1.46)	1.44 (1.22-1.71)
Days of antibiotic therapy	1.06 (1.04-1.08)	1.07 (1.05-1.10)	1.11 (1.05-1.16)
Sepsis	1.39 (1.22-1.57)	1.56 (1.08-2.32)	
Surfactant doses	2.34 (1.85-2.96)		



Antibiotics in early infancy and adverse long-term outcome



Statistical adjustments:
Maternal smoking after first trimester, parental relationships, mode of delivery, birth weight and birth length

>12.000 healthy infants, antibiotic exposure before 6 months of age or repeatedly during infancy was associated with increased body mass in healthy children.



Antibiotics in early infancy and Asthma

- Prospective birth cohort study Tokyo
- 1550 newborns 2003-2005
- 48% of children received antibiotics within first 2 years of life

⇒ Antibiotic exposure in first 2 years of life associated with asthma, atopic dermatitis and allergic rhinitis at 5 years of age

Associations of Antibiotic Use in Children Younger Than 3 Years With Wheeze and Allergy Outcomes in Children at 5 Years Old

	Crude OR	95% CI		P value	Adjusted OR ^a	95% CI		P value	Power ^b
		Lower	Upper			Lower	Upper		
Current wheeze									
All antibiotics	1.36	0.95	1.94	.089	1.24	0.86	1.78	.255	
Penicillin	1.11	0.60	2.09	.736	1.16	0.61	2.18	.653	
Cephem	1.44	0.96	2.16	.075	1.39	0.92	2.09	.122	
Macrolide	1.20	0.78	1.85	.410	1.04	0.66	1.64	.856	
Current asthma									
All antibiotics	1.78	1.15	2.75	.009	1.72	1.10	2.70	.017	0.75
Penicillin	1.88	0.58	2.53	.602	1.21	0.58	2.56	.612	
Cephem	2.02	1.28	3.20	.003	1.97	1.23	3.16	.005	
Macrolide	2.59	0.97	2.60	.064	1.46	0.88	2.44	.145	0.84
Current atopic eczema									
All antibiotics	1.42	1.03	1.95	.032	1.40	1.01	1.94	.044	0.55
Penicillin	1.42	0.93	2.44	.203	1.41	0.82	2.43	.219	
Cephem	1.41	0.98	2.04	.068	1.37	0.94	1.99	.103	
Macrolide	1.59	1.09	2.32	.016	1.58	1.07	2.33	.022	0.64
Current rhinitis									
All antibiotics	1.82	1.18	2.80	.007	1.65	1.05	2.58	.030	0.68
Penicillin	1.29	0.23	1.52	.278	0.58	0.22	1.51	.264	
Cephem	1.88	1.19	2.98	.007	1.82	1.12	2.93	.015	0.73
Macrolide	1.77	1.10	1.52	.020	1.50	0.90	2.49	.121	

^aAdjusted for maternal history of allergy (asthma, atopic dermatitis, or allergic rhinitis), maternal education level, maternal age at pregnancy, maternal body mass index, maternal smoking during pregnancy, mode of delivery, gestational age at delivery, previous live births, daycare, bronchitis, and sex of the child.

Selecting Empiric Therapy

- Prompt treatment reduces mortality of early neonatal sepsis ⇒ start early already at sepsis suspicion (e.g. ampicillin or PenG plus gentamicin), stop after 48hrs if cultures and laboratory parameters remain negative
- Know blood-culture isolates of your ward in order to establish an empirical regimen for nosocomial sepsis (e.g. vancomycin or oxacillin plus gentamicin)
- Avoid agents with overlapping spectrum of activity (no evidence of increased efficacy, potential of increased toxicity)
- Avoid using 3rd generation cephalosporins in the NICU
- Do not use carbapenems empirically

Re-evaluating Antibiotic Regimen

- Evaluate daily whether antibiotics are still necessary (>97% of blood cultures with clinically meaningful bacterial growth are positive within 48hrs)
- Stop antibiotics in case of negative cultures and stable patient by 48hrs
- Limit perioperative prophylaxis to maximum of 48hrs after surgery (max 72hrs after cardiac surgery)
- Switch to antibiotic with narrower spectrum if possible
- Do not treat positive cultures from non-sterile body sites (e.g. tracheal aspirates) when clinical course is not suggestive of infection

Examples of how to translate these principles into specific action

Utilize local epidemiology data

Avoid using meropenem for suspected LOS if rates of MDR gram-negative organisms is low

Avoid therapy with overlapping activity

Do not simultaneously use pip/taz or meropenem with metronidazole to treat NEC

Give the right dose and interval of drug

Target vancomycin trough levels at 15-20mg/L to treat MRSA pneumonia

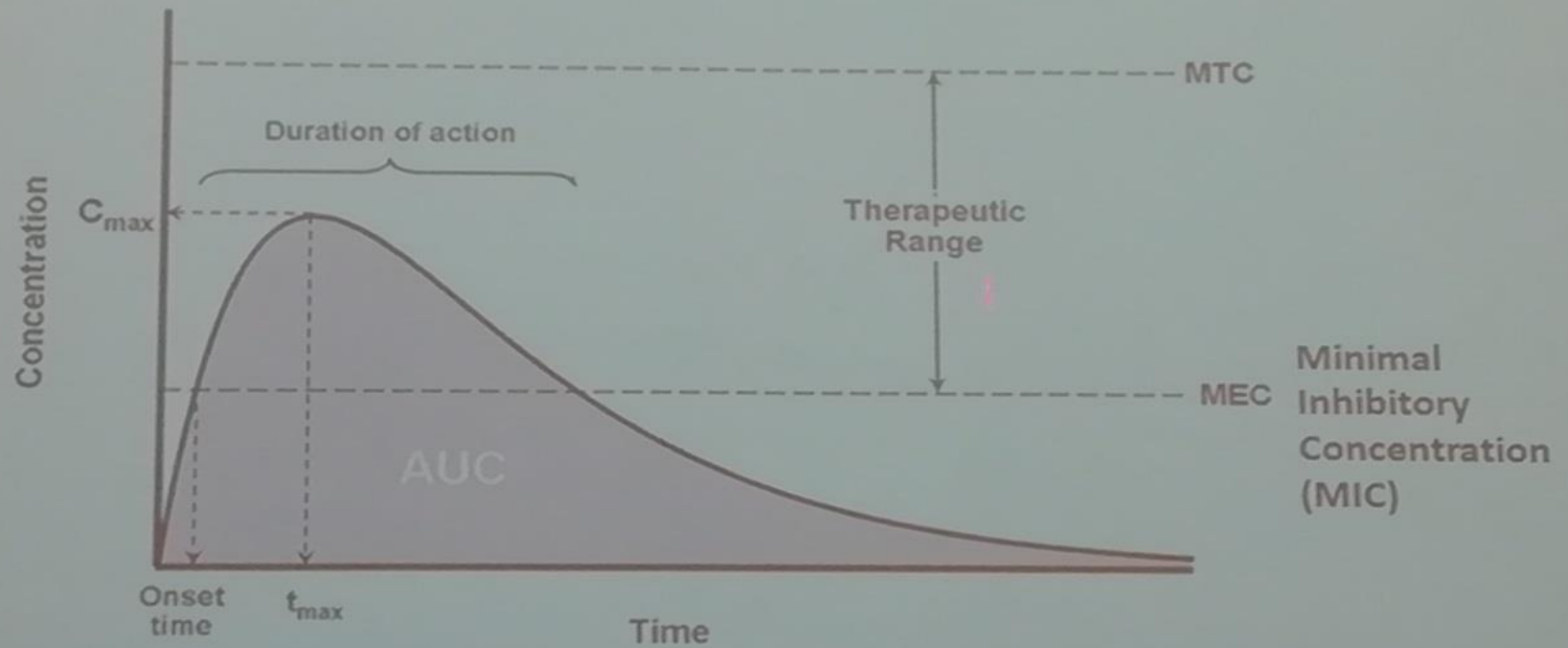
Review culture results and adjust antibiotics - narrow antibiotic coverage promptly

MSSA - switch from vancomycin to flucloxacillin or oxacillin
Discontinue vancomycin when gram-neg bacilli are isolated

Stop therapy if indicated by culture results

Discontinue antibiotics after 48hrs if blood culture is negative and ongoing infection is not suspected

PK/PD



Aminoglycosides:

aim for a high peak and wait for a low trough level

Aminoglycosides exhibit concentration dependent killing

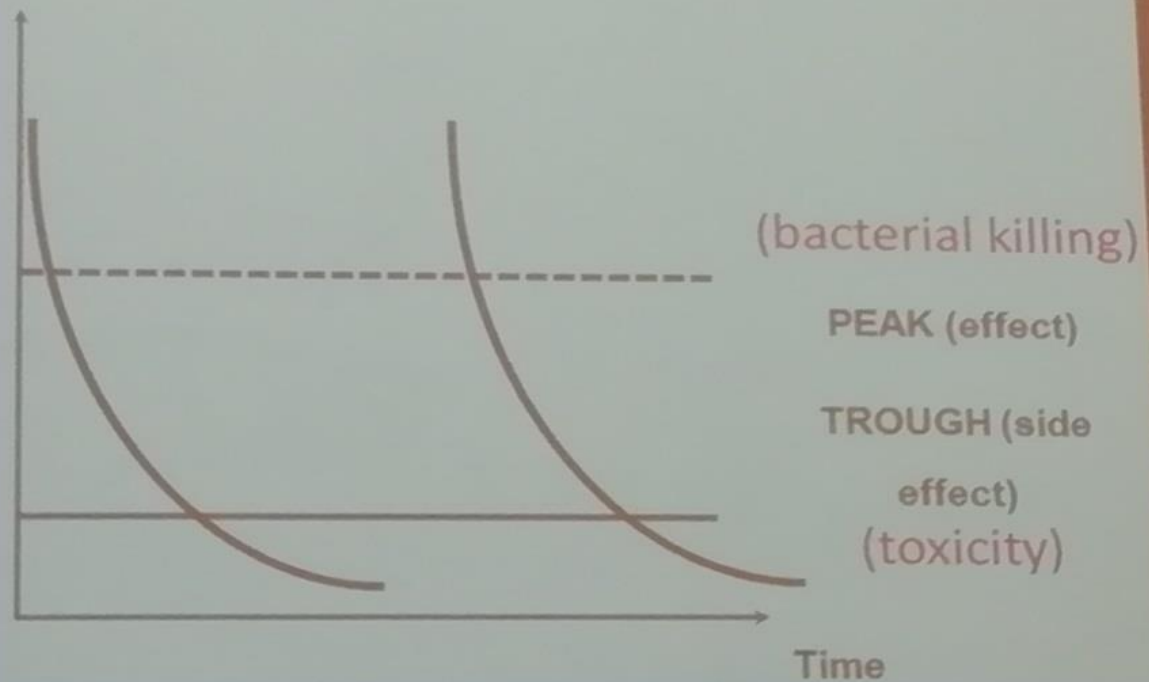
Single daily (extended time interval) is more effective and less toxic

Aminoglycosides:

aim for a high peak and wait for a low trough level

Peak/MIC > 8

ratio of the peak
Concentration to MIC
(aminoglycosides)



Aminoglycosides:

One characteristic of pharmacodynamics is the **post-antibiotic effect (PAE)**:

→ the delayed regrowth of bacteria following exposure to an antibiotic.

Take home messages.....

- Days on antibiotics are associated with increased risk of NEC, BPD, death and potential adverse long-term outcomes of preterm infants
- Antibiotic stewardship interventions are particularly important for NICU patients
- Always take blood-cultures (ideally min 1ml) before starting antibiotics
- Use local epidemiology to guide the selection of empiric therapy
- Develop local antibiotic policies to guide rational empirical treatment and to restrict broad-spectrum antibiotics
- Do not use empiric 3rd gen cephalosporin or penem - use aminoglycoside-based empirical regimens



Take home messages.....

- Do not treat colonisation
- Do not use prophylactic antibiotics in case of ventilation, chest tube, i.v. line, ...
- Limit perioperative prophylaxis to maximum of 48hrs after surgery (max 72hrs after cardiac surgery)
- Trust your microbiology - rely on blood culture results and adapt the empirical regimen when appropriate
- Stop antibiotics if cultures remain negative and child is clinically well after 48hrs
- Try your best to prevent infections by reinforcing infection control - HAND HYGIENE HAND HYGIENE HAND HYGIENE









Why Worry about Healthcare-Associated Infections? *(Money/Mortality/Mental deficiency)*

- * HAIs are costly; 100,000 deaths and \$6.5 billion dollars in excess expenditure annually (U.S.)
- * The Center for Medicare and Medicaid Services no longer reimburses hospital for expenses associated catheter related blood stream infections
- * They are responsible for up to 45% of deaths after two weeks of age
- * HAIs are associated with poorer neurodevelopmental outcomes.
- * HAIs are common events in the NICU

Adverse Neurodevelopmental Outcome in ELBW Infants with Infections

MDI < 70	1.3 (CI 1.1,1.5)	1.3 (CI 1.1,1.6)	1.6 (CI 1.2,2.2)
PDI < 70	1.5 (CI 1.3,2.0)	1.5 (CI 1.2,1.9)	2.4 (CI 1.7,3.4)
CP	1.3 (CI 1.0,1.6)	1.4 (CI 1.1,1.8)	1.7 (CI 1.2,2.5)
Microcephaly	1.3 (CI 1.1,1.6)	1.5 (CI 1.2,1.7)	2.0 (CI 1.5, 2.6)

Stoll et al JAMA 292: 2357, 2004 (n=6093, 18 month follow-up)

Pathogens Causing Central Line Infections (Yale 1989-2013)

	1989-2003	2004-2009	2010-2013
Staphylococcus-coagulase negative	29%	21%	3%
Staphylococcus aureus	8%	13%	21%
Enterococcus/Group D Streptococcus	9%	13%	5%
Gram negative enterics	26%	23%	51%
Fungi	8%	6%	3%

Risk Factors for Catheter Line-Associated Blood Stream Infections in VLBW Infants

- ★ Strongest correlation with birth weight & gestation
- ★ Use of parenteral alimentation and central lines
- ★ Steroids for BPD
- ★ Histamine blockers
- ★ Low serum IgG levels at birth

Risk Factors for Catheter-Associated Blood Stream Infections in VLBW Infants

- ★ Prolonged duration of mechanical ventilation
- ★ Overcrowding & heavy workloads
- ★ Staffing problems (inexperienced nurses)

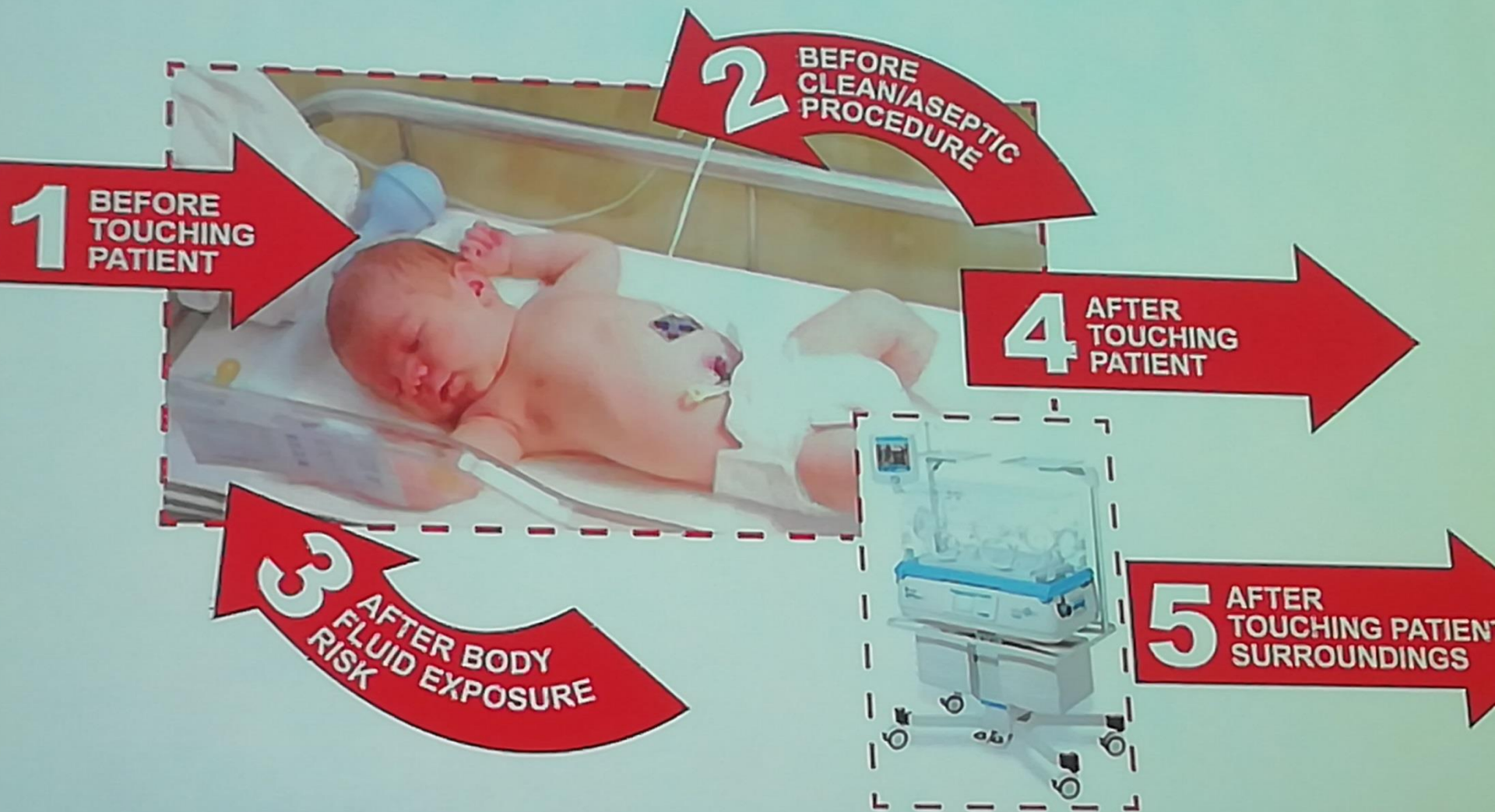
Strength of Evidence & Indications for Handwashing and Hand Antisepsis

- ★ Brushes are no longer recommended (1B)
- ★ Do not use artificial nails or extenders (1A)
- ★ Keep natural nails short (no dark nail polishes); clear nail polish is acceptable



World Health
Organization

Guidelines for Hand Hygiene in Health Care

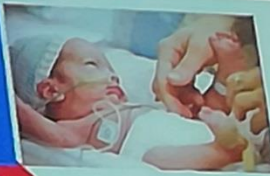




Orłowska, Katarzyna Starzec, Przemko Kwińska
Jagiellonian University Collegium Medicum



Preterm diet



Mothers own
milk (MOM)

Donor breast
milk (DBM)

“biological”

CM based
“products”:
- formulas
- fortifiers

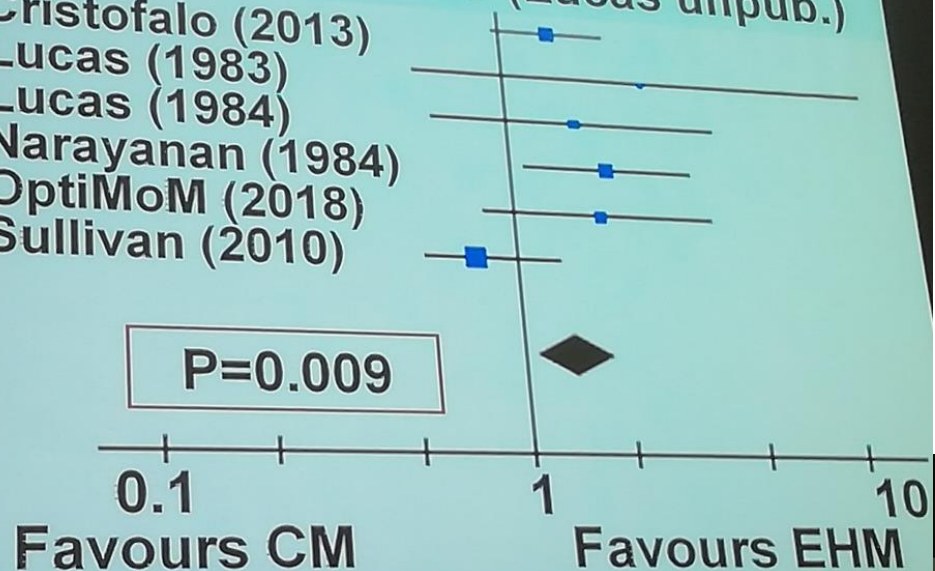
manufactured

Meta-analysis of global evidence from RCTs of NEC in those exposed to CM

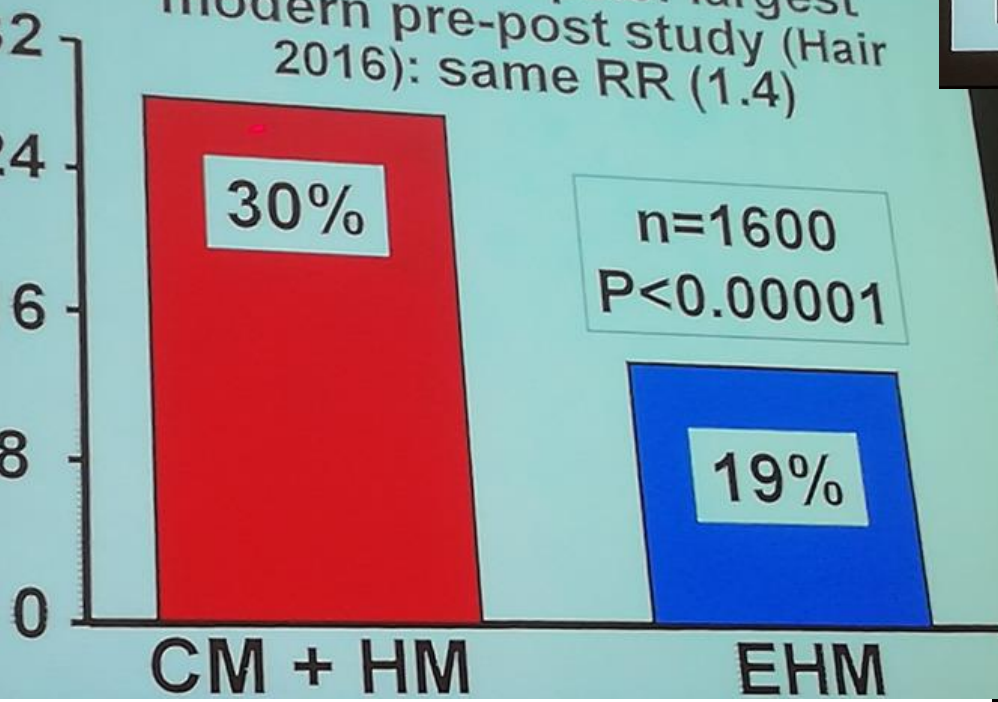


Proven sepsis – risk ratio 1.4
6 RCTs; n = 1113 (Lucas unpub.)

Cristofalo (2013)
Lucas (1983)
Lucas (1984)
Narayanan (1984)
OptiMoM (2018)
Sullivan (2010)

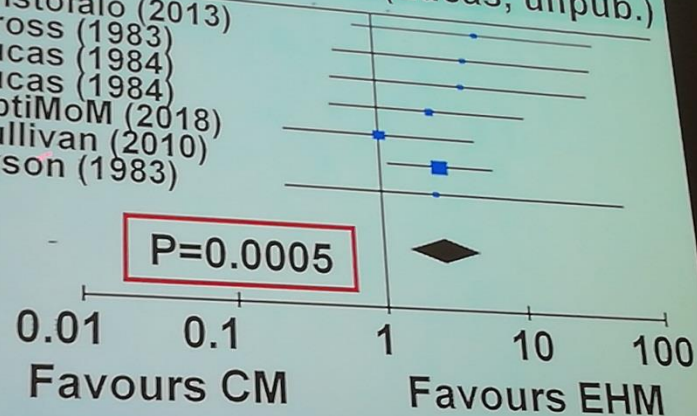


Late onset sepsis: largest modern pre-post study (Hair 2016): same RR (1.4)



NEC – risk ratio 2.8
7 RCTs; n = 1035 (Lucas, unpub.)

Cristofalo (2013)
Gross (1983)
Lucas (1984)
Lucas (1984)
OptiMoM (2018)
Sullivan (2010)
Tyson (1983)



lower NEC incidence

	baseline	EHM
Christiana	6%	0.8%
Indiana	3.4%	1%

Even in low NEC units major fall
in NEC with CM exclusion

8 quasi-experimental studies
(n= 4000; <1250g) examine NEC
before & after excluding CM:



3x NEC rate
with CM in
diet

Baseline NEC rate: 3.4% - 20%

Mortality



Earlier RCTs
seldom
record
death – the
few data
show no
clear effect

How much cows milk
in the diet is safe ?



Dose-response
effects in US trials

Abrams et al



Sepsis,
NEC and
surgery
for NEC

0%

Cow's milk

100%

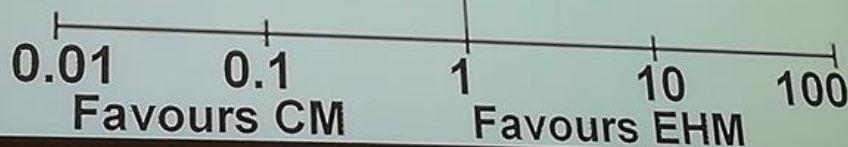
Meta-analysis of global evidence from RCTs of NEC in those exposed to C



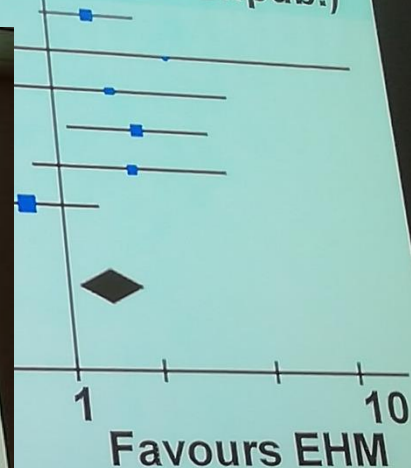
All ROP (n = 2779)
risk ratio 2.3 (random effect model)

Assad 2014
Colacci 2017
Hair 2016
Manzoni 2013
OptiMoM 2018
Sullivan 2010

P=0.009



Proven sepsis – risk ratio 1.4
6 RCTs; n = 1113 (Lucas unpub.)
Cristofalo (2013)



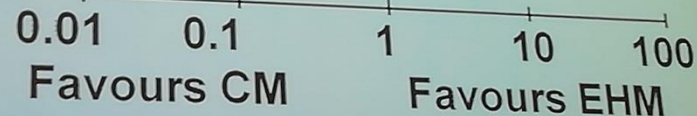
Mortality



Earlier RCTs
seldom
record
death – the
few data
show no
clear effect

NEC – risk ratio 2.8
7 RCTs; n = 1035 (Lucas, unpub.)
Cristofalo (2013)
Gross (1983)
Lucas (1984)
Lucas (1984)
OptiMoM (2018)
Sullivan (2010)
Tyson (1983)

P=0.0005



Meta-analysis of global evidence from RCTs of NEC in those exposed to C



Proven sepsis – risk ratio 1.4
6 RCTs; n = 1113 (Lucas unpub.)
Cristofalo (2013)

All ROP (n = 2779)
risk ratio 2.3 (random effect model)
Assad 2014
Colacci 2017
Hair 2016
Manzoni 2013
OptiMoM 2018
Sullivan 2010

BPD/CLD n = 2,310: RR 1.3

Assad 2014
Colacci 2017
Cristofalo 2013
Hair 2016
OptiMoM 2018
Sullivan 2010

P=0.02
random effect

0.1 1 10
Favours CM Favours EHM

Mortality



clear effect

Favours CM

Favours EHM

2.8
(s, unpub.)

**Hypothesis: CM exposed
group less alveolarisation**



**increased
respiratory
disease**



**Adult lung
capacity
reduced**

**Both Hair and Lucas
independently find longer
duration of ventilation with CM**



The key medical issue
Worse feed tolerance with CM
means a higher duration of
potentially hazardous PN



Two
examples
with - long
term effects

1. PN solutions
contaminated with aluminum
? adverse affect on brain &
bones as in dialysis patients



One MDI point lost for
each day of standard PN
in the NICU



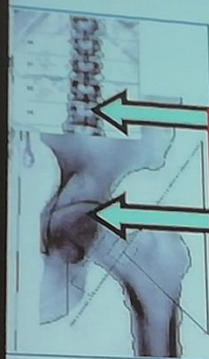
ALUMINUM TRIAL

Regular PN v
PN – with 90%
less aluminum

Published in
NEJM



13-15 yr follow-up



Standard PN: reduced
lumbar spine & hip
bone mass

Risk factors for later
osteoporosis / hip fracture

AL

Re

PN
less

Pu

2. parenteral lipid dose-related to
arterial stiffness at 25-28y follow-
up predictive of vascular events



-15 yr follow-up

Standard PN: reduced
lumbar spine & hip
bone mass

factors for later
osteoporosis / hip fracture

Possible further indirect adverse impacts of CM on neurodevelopment

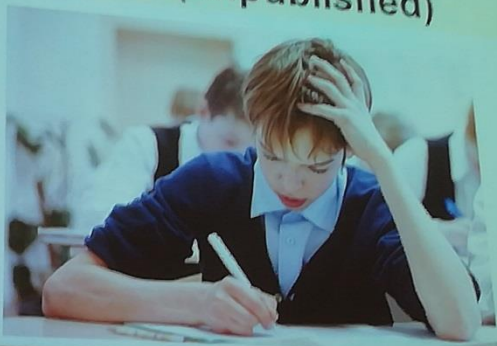


Numerous studies link NEC/ sepsis to adverse neuro-development

However few adjust for confounding factors



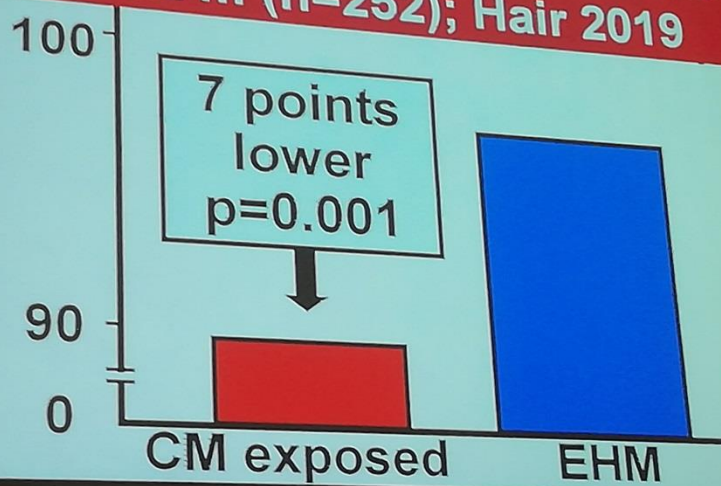
NEC associated with 7 point reduction in IQ
Lucas (unpublished)



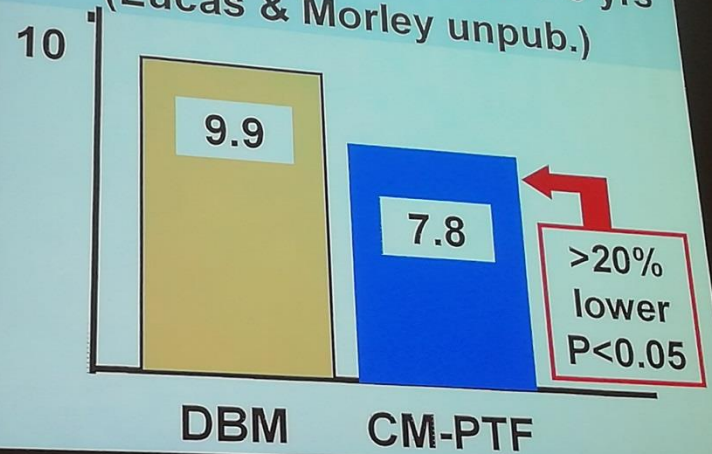
Our adjusted data show babies with NEC 3.4 times more likely to develop CP ($P=0.003$) and those with sepsis 2.2 times more likely ($p=0.04$)



Bayley III cognitive composite 18-22 m (n=252); Hair 2019



WISC arithmetic score at 7-8 yrs (Lucas & Morley unpub.)



Brain in those fed CM products

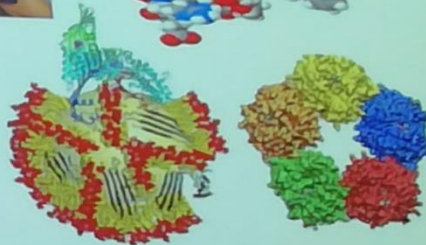
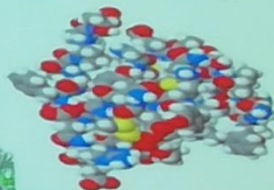
lower cognitive scores

Smaller brain (MRI)

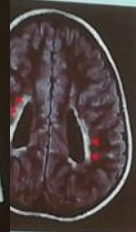
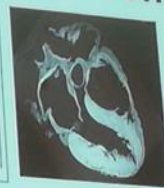
Less white matter/myelin in brain – basis of connectivity



14 Adverse effects of CM - RCTS



more outcomes from cohort data



14 Adverse effects of CM



8 more outcomes from cohort data



Summary – established and growing evidence that those exposed to CM show broad adverse outcomes



**Notably
in EP
infants**

A modern trend in preterm infant feeding



Supported by recommendations
(e.g. ESPHAN, AAP) to use DBM
if MOM insufficient

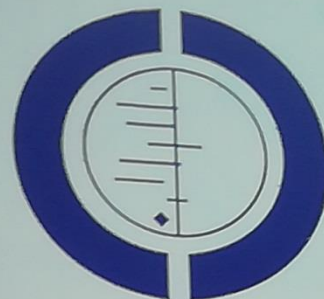
Hydrolysed fortifiers in the NICU



Need comparative RCTs with HMDF

Few data on smaller neonates

Hydrolysed protein unphysiological



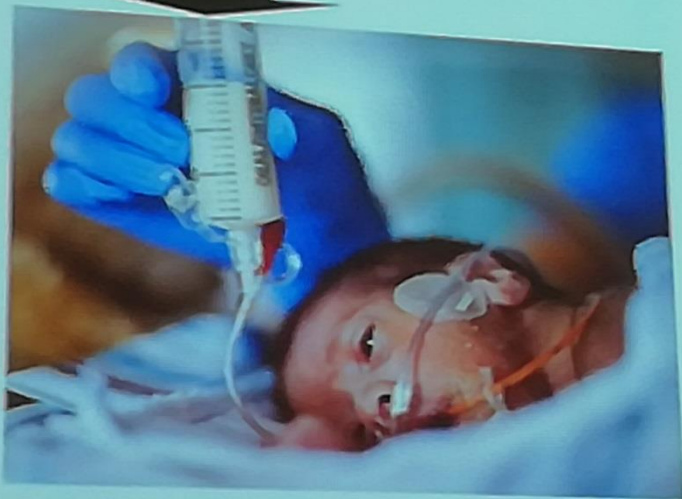
THE COCHRANE
COLLABORATION®

Recent meta-
analysis of 11
RCTs of
hydrolysed v
intact protein
formulas – no
effect on NEC

Ng, Klassen, Embleton, McGuire
2019

What can be done?

In US >300 NICUs use products manufactured from DBM along with MOM, to provide an EHM diet for EP babies without CM



40,000
babies

19:52



Zaburzenia funkcji nerek i powikłania sercowo- naczyniowe u noworodków urodzonych przedwcześnie

prof. dr hab. n. med. Przemko Kwinta

Klinika Chorób Dzieci,

Uniwersytet Jagielloński Collegium Medicum w Krakowie

Program wielospecjalistycznej oceny stanu zdrowia dzieci urodzonych z ekstremalnie małą masą ciała

Noworodki urodzone w woj. Małopolskim z masą ciała $\leq 1000\text{g}$
od 1.09.2002 do 31.08.2004 (n=191)



Dzieci żyjące w wieku 6-7 lat (n=89)



Dzieci objęte oceną w wieku 6-7 lat (n=81; **91%**)

Powikłania nefrologiczne

- Stężenie cystatyny C w surowicy
- Oznaczenie mikroalbuminurii
- Ultrasonografia nerek
- 24-goddziny pomiar ciśnienia tętniczego

Ocena w wieku 11 lat

Noworodki urodzone
przedwcześnie

Dzieci objęte oceną w wieku 7 lat
(n=81)

Dzieci objęte oceną w wieku 11 lat
(n=64; **80%**)

Grupa kontrolna

Dzieci objęte oceną w wieku 7 lat
(n=39)

Dzieci objęte oceną w wieku 11 lat
(n=36; **92%**)

11:16

Wtórne punkty końcowe

	Cases		Controls		p value
	mean	SD	mean	SD	
Cystatin C, mg/L	0.932	0.133	0.847	0.102	<0.001
eGFR, mL/min/1.73 m ²	100.62	16.53	111.89	15.26	<0.001
Mean SBP, mm Hg	111.8	9.8	107.2	9.07	<0.001
Mean DBP, mm Hg	68.6	6.8	66.3	7.7	0.03
SBP, pc	60.3	27.2	50.5	28.4	0.01
DBP, pc	74.1	21.7	64.8	27.6	0.003
Absolute left kidney length, cm	8.56	0.75	9.009	0.73	<0.001
Relative left kidney length	0.93	0.069	0.96	0.068	0.004
Absolute right kidney length, cm	8.56	0.80	9.007	0.73	<0.001
Relative right kidney length	0.95	0.076	0.97	0.069	0.005

Nefroprotekcja

- Unikanie leków potencjalnie nefrotoksycznych
 - Aminoglikozydy
 - Wankomycyna
- Unikanie diuretyków pętlowych
 - Furosemid
- Odpowiednia dieta
 - Podaż białka 4,5 g/kg/d ???
- Zmniejszenie ryzyka kamicy nerkowej
 - Odpowiednie zbilansowanie gospodarki wapniowo-fosfora

Nefroprotekcja

- Badanie ciśnienia tętniczego u noworodków urodzonych przedwcześnie w czasie każdej wizyty pediatrycznej
 - bez względu na wiek
- Ograniczenie ryzyka zakażeń układu moczowego
 - Każde cewnikowanie – 3% ryzyka ZUM





Liisa Lehtonen

29:27

The International Closeness Survey about Parent Infant Closeness and Family Centered Care in 16 NICUs in 11 European countries

Liisa Lehtonen, MD, Professor and Anna Axelin, RN, Associate Professor
Students Pilvi Hongisto, Emma Kainiemi
Statisticians Eliisa Löyttyniemi, Terhi Kolari, Tiina Hautajärvi





Liisa Lehtonen

28:01

The 1st International Closeness Survey Survey in 2013



Objectives: To describe infant-parent physical closeness and the quality of FCC from the perspectives of mothers and fathers in 11 European NICUs,

Methods: A prospective survey was conducted in Finland, Sweden, Norway, Estonia, Spain and Italy

Raiskila S, Axelin A, Toome L, Caballero S, Silness Tandberg B, Montirosso R, Normann E, Hallberg B, Ewald U & Lehtonen L, Parents' Presence and Parent-Infant Closeness in 11 NICUs in 6 European Countries. *Acta Pædiatrica* 2017;106:878-888

Raiskila S, Lehtonen L, Silnes Tandberg B, Normann E, Ewald U, Caballero S, Varendi H, Toome L, Nordhov M, Hallberg B, Montirosso R, Westrup B & Axelin A, Parent and Nurse Perceptions on the Quality of Family-Centered Care in 11 European NICUs. *Austr Critical Care* 2016;29(4):201-209

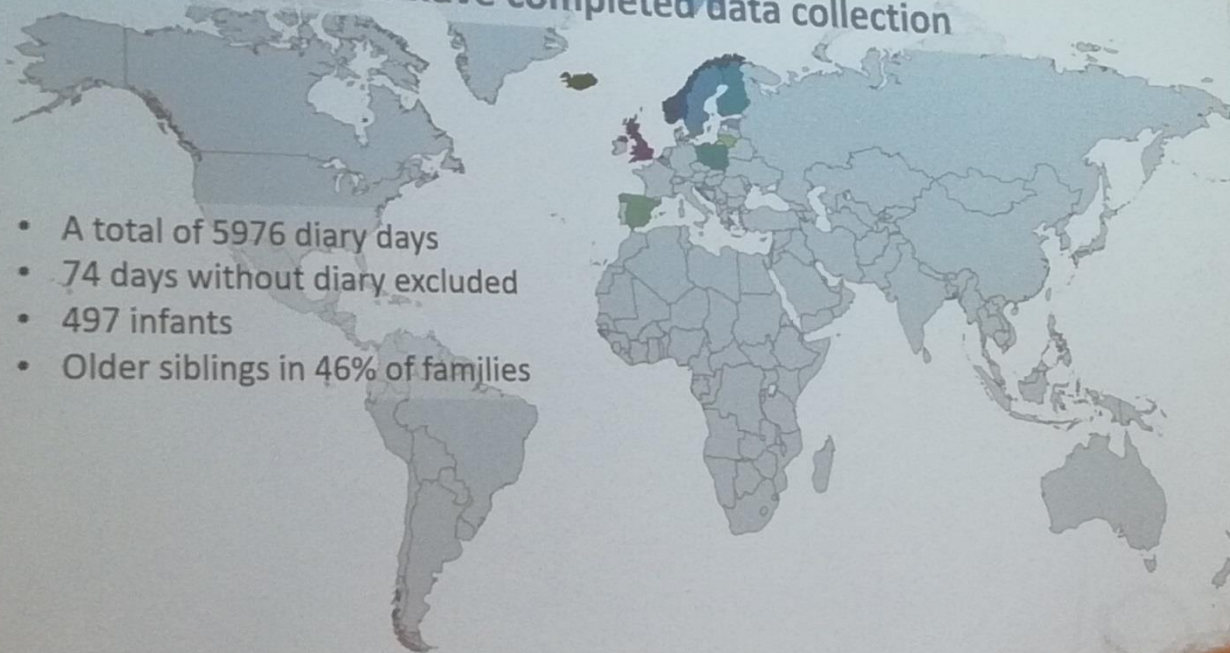


Liisa Lehtonen

21:57

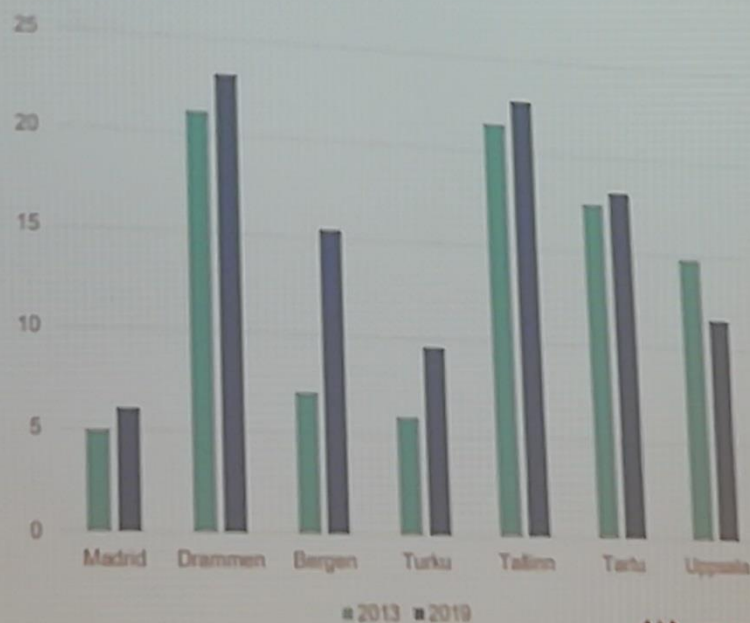
The 2nd International Closeness Survey:
16 units have completed data collection

- A total of 5976 diary days
- 74 days without diary excluded
- 497 infants
- Older siblings in 46% of families



Either parent present (hours/day) in 2013 and in 2019

City	2013	2019
 Madrid	5.0	6.1
 Drammen	21.2	23.2
 Bergen	7.1	15.4
 Turku	6.0	9.6
 Tallinn	21.5	22.8
 Tartu	17.5	18.2
 Uppsala	14.8	11.6



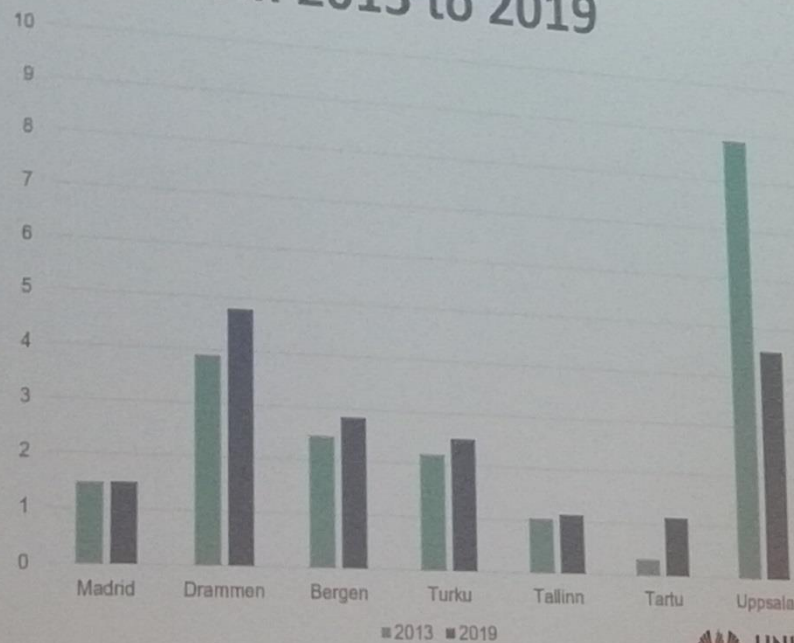


Liisa Lehtonen

12:38

Skin-to-skin contact (hours/day) : the change from 2013 to 2019

City	2013	2019
 Madrid	1.48	1.50
 Drammen	3.90	4.80
 Bergen	2.47	2.85
 Turku	2.20	2.52
 Tallinn	1.05	1.13
 Tartu	0.31	0.85
 Uppsala	8.86	4.55



Класифікація відділень залежно від ступеня сепарації батьків із дитиною

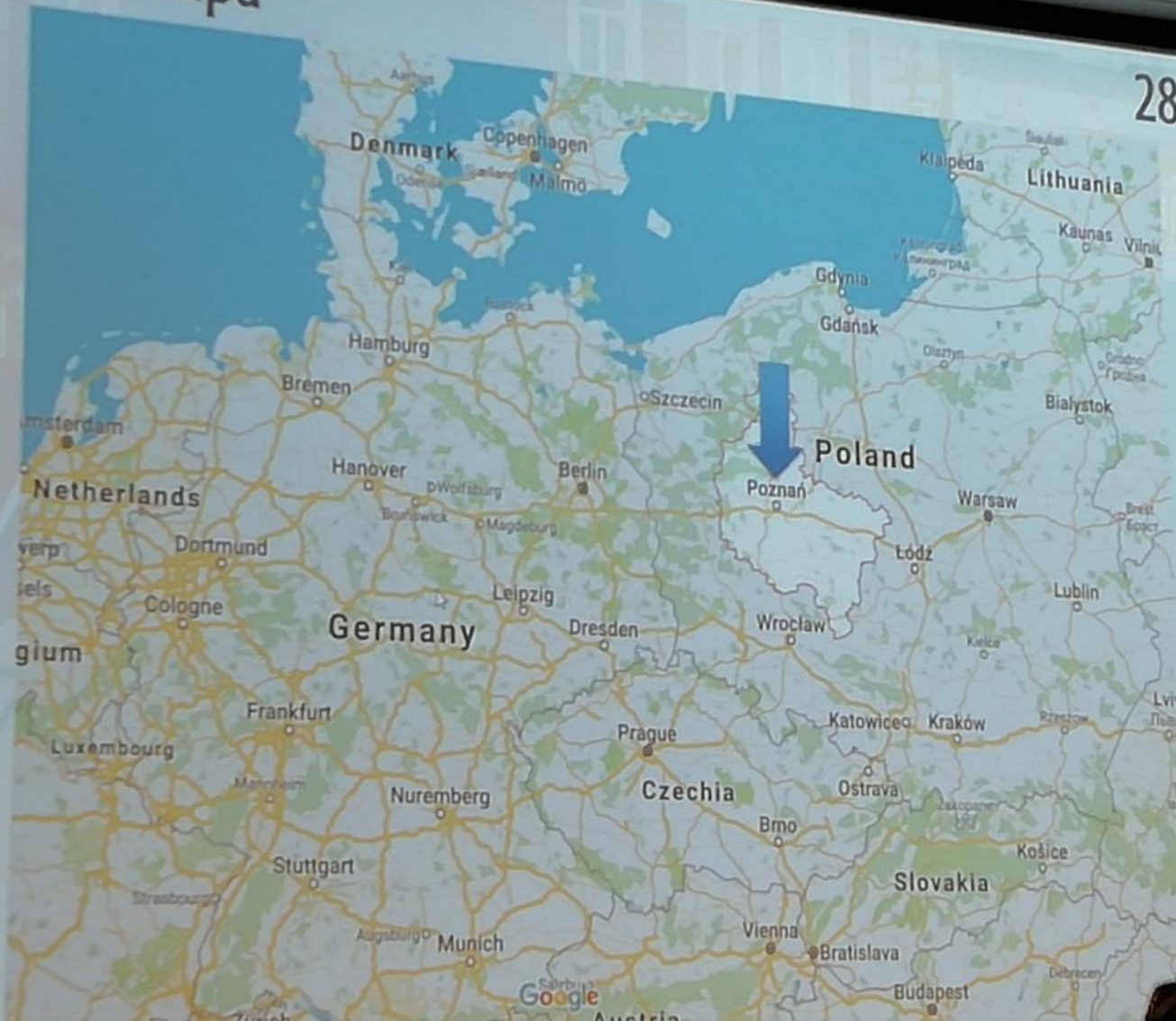
Повна сепарація	Сепарація з моменту народження, батьки відвідують дитини у ВІТН з тривалістю візитів – кілька годин на день, умови для перебування батьків у ВІТН - мінімальні	Батьки - відвідувачі
Часта сепарація	Сепарація з моменту народження, батьки можуть перебувати у відділенні – протягом дня, є певні умови для перебування батьків у ВІТН	Персонал-залежні батьки
Часткова сепарація	Сепарація з моменту народження, батьки можуть перебувати в окремій палаті із дитиною частину часу перебування дитини у ВІТН– протягом дня, є певні або хороші умови для перебування батьків	Персонал-залежні батьки
Відсутня сепарація	Батьки перебувають із дитиною від народження і до виписки, хороші умови для перебування батьків	БАТЬКИ

SFR



masz Szczapa

28:27

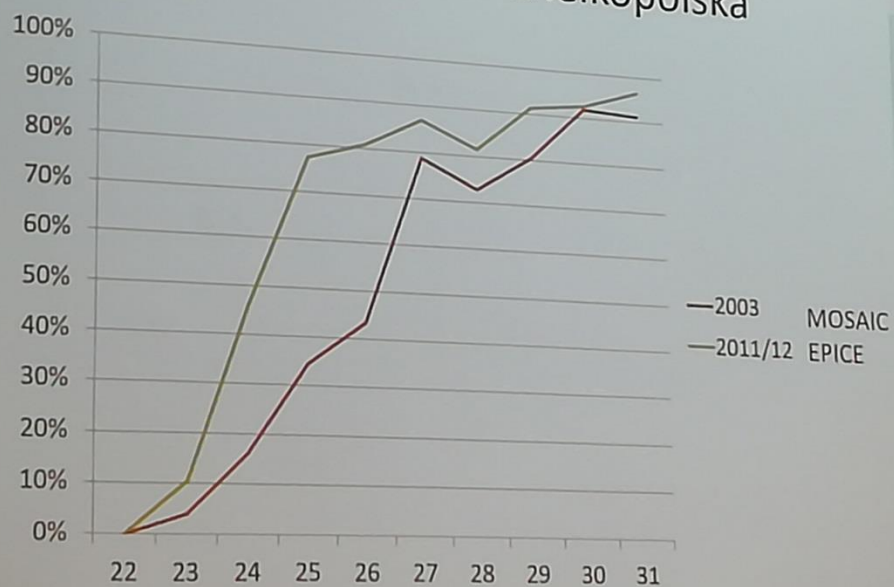




Tomasz Szczapa

25:46

Changes in survival rate trends vs gestational age in the region of Wielkopolska





19:48



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Preventative strategies and up-to date treatment of Retinopathy of Prematurity

Ann Hellström, MD, PhD

Dep of Ophthalmology, Institute of Neuroscience and
Physiology, Sahlgrenska Academy, Gothenburg University



XXXIV WYBORCZE SYMPOZJUM Polskiego Towarzystwa Neonatologicznego



Poznań, 7-9 listopada 2019 roku

17:56



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Pediatric Ophthalmology Research



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Increased incidence of severe ROP 2008-2017

Clinical science

New modifications of Swedish ROP guidelines based
on 10-year data from the SWEDROP register

Gerd Holmström ●¹, Ann Hellström,² Lotta Gränse,³ Marie Saric,⁴ Birgitta Sunnqvist,⁵
Agneta Wallin,⁶ Kristina Tornqvist,³ Eva Larsson ●¹

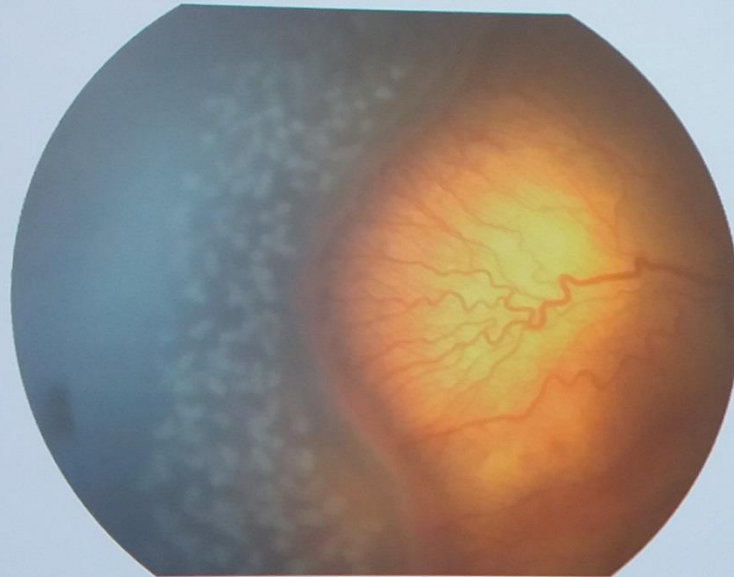
The incidence of ROP did not change during the
study period, while there was a **significant increase**
in the frequency of treatment (p=0.023)

Holmström G et al BJO Nov 2019

www.rop.gu.se

17:00

Retinopathy of prematurity a biomarker for brain development



www.rop.gu.se

16:14

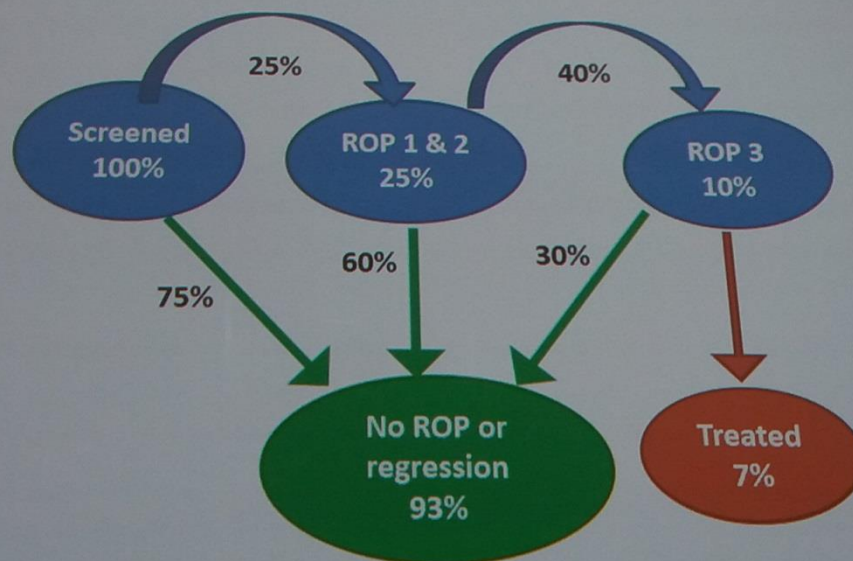


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ROP natural history - GA <31 weeks at birth



Holmström G et al BJO Nov 2019

15:07

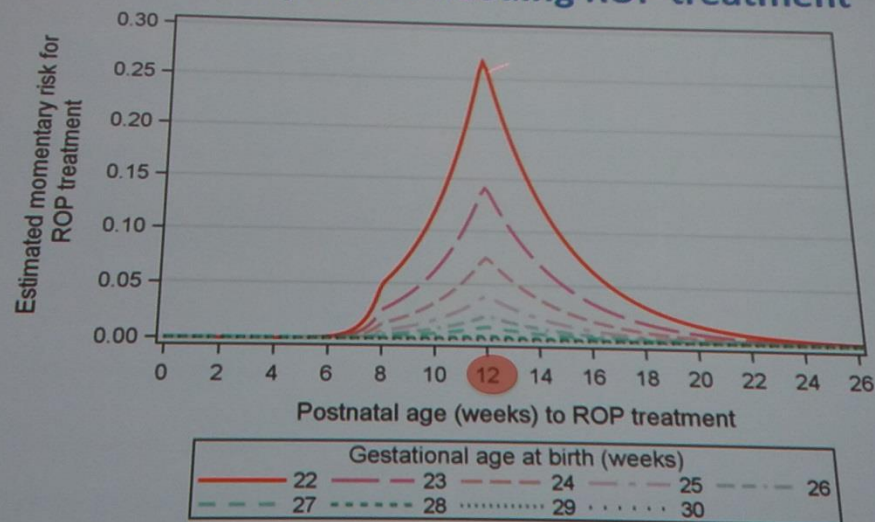


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Momentary risk of needing ROP treatment



Pivodic A et al, JAMA Ophthalmol Nov 7 2019

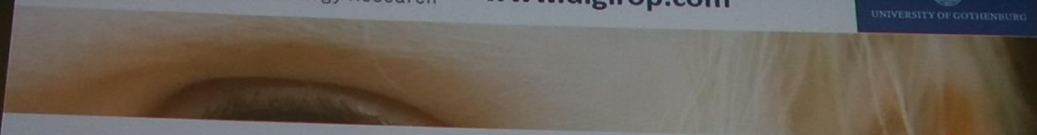
www.rop.gu.se

14:32



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www.digirop.com



GA (weeks)

25

GA (days)

2

BW (g)

780

Boy ☒ Girl ☐

Calculate

14.76%



CI: 12.32% - 17.43%

14.76% risk for ROP requiring treatment

FUNDED BY



*Knut och Alice
Wallenbergs
Stiftelse*

FÖRENINGEN DE BLINDAS VÄNNER

12:38

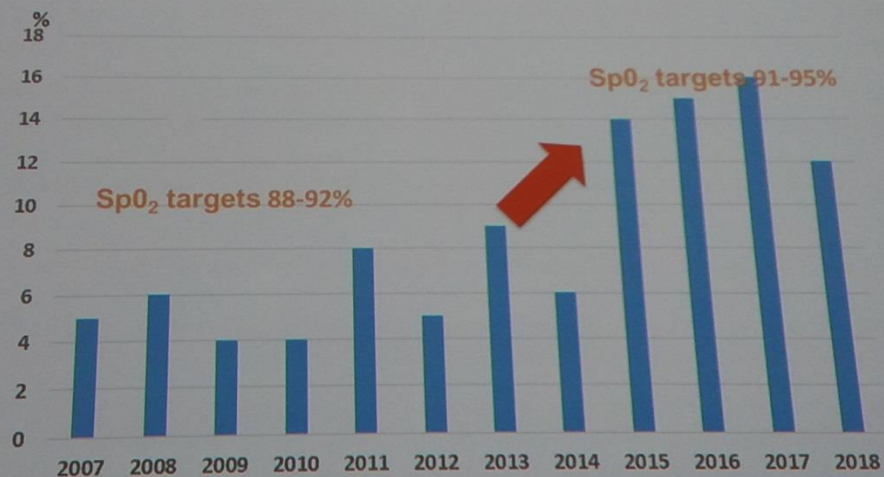


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2 fold increase of ROP treatment in western Sweden after increased SpO₂ targets (91-95%)



Lundgren P et al Acta Ped 2017 Sept

10:49



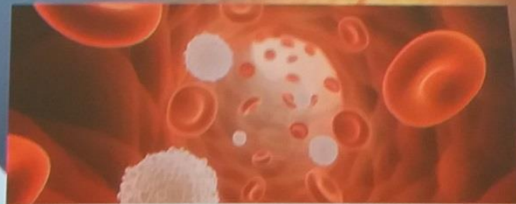
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PREVENTION

Oxygen
Blood components
Nutrition



www.top.gu.se

7:50

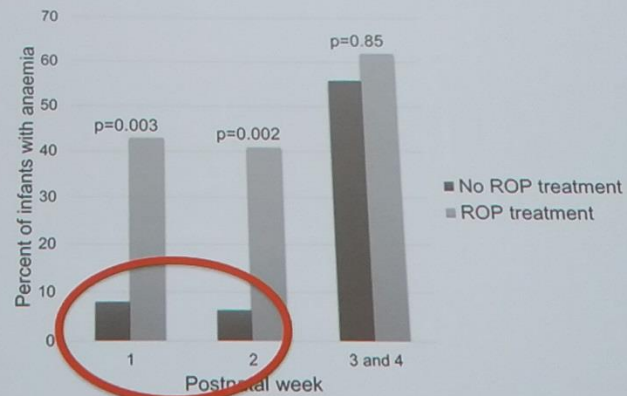


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Prevent early anemia to prevent ROP



Lundgren P et al Ped Res Sept 2018

www.rop.gu.se

7:35

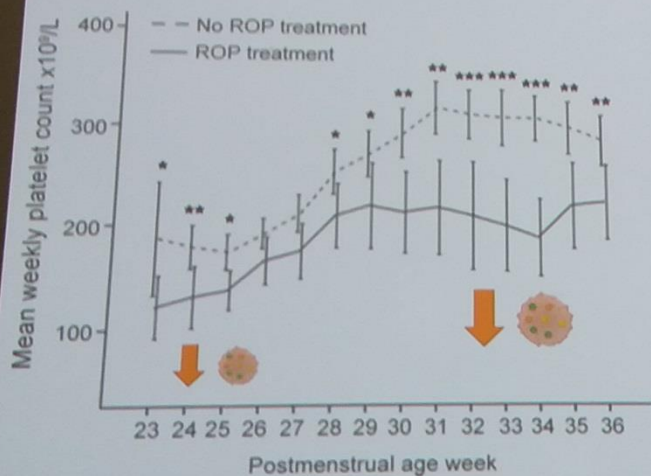


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Prevent low platelet counts to prevent ROP



Cakir B et al. JCI 2018

www.rop.gu.se

6:22

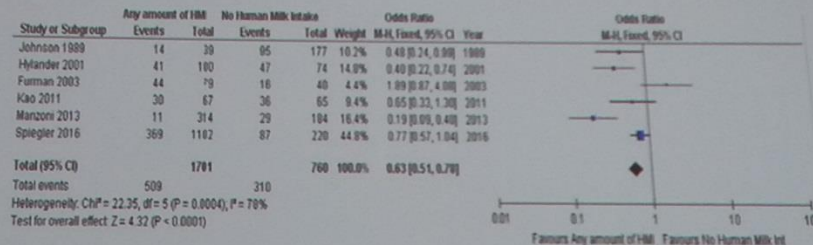


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Maternal breastmilk intake prevents severe ROP



Conclusion: Any amount of HMI is strongly associated with the protection from All ROP and Severe ROP.

State-of-the-Art

Journal of Perinatology (2016) 36, 913–920; doi:10.1038/jp.2016.98; published online 14 July 2016

Systematic review and meta-analysis of human milk intake and retinopathy of prematurity: a significant update

S K Bharwani¹, B F Green², J C Pezzullo³, S S Bharwani⁴, S S Bharwani⁴ and R Dhanireddy²

3:17



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ROP treatment – Propranolol

"Limited evidence of low-to-moderate quality suggests that prophylactic administration of oral beta-blockers might reduce progression towards stage 3 ROP....

Trials should report on long-term visual impairment. Researchers should consider dose-finding studies of systemic beta-blockers and topical administration of beta-blockers, in order to optimise drug delivery and minimise adverse events."

Kaempfen S et al, Cochrane Database Syst Rev. 2018 Mar.

2:47



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**BMJ Open Oral propranolol for prevention of
threshold retinopathy of prematurity
(ROPROP): protocol of a randomised
controlled trial**

Christoph Bührer,¹ Ömer Erdeve,² Dirk Bassler,³ Benjamin Bar-Oz⁴

Treatment with 1.6mg/kg/day propranolol, 4-10 weeks

Inclusion (n=718):

- GA <28 weeks at birth
- ROP stages 1-2

Primary aim: reducing stage 3 ROP by 50%

0:49



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Anti-VEGF treatment

Mintz-Hittner N Engl J Med 2011

Bevacizumab contains a fraction that actively transports anti-VEGF to the blood stream

that cannot penetrate the intact retina or escape the eye except in very small amounts, as shown in animal models"

0:21



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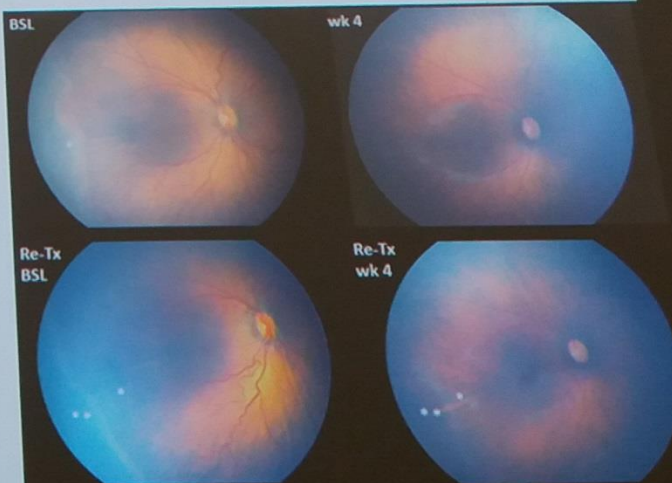


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Treatment

- Anti-VEGF (Avastin, Lucentis and Eylea?)

- Reduced visual field sensitivity (degree?)
- Myopia
- Systemic treatment (-)
- No General Anesthesia (+)
- Late recurrence 30% (-)
- Longterm outcome



Parental participation in infant care

- activities usually performed by parents:
 - feeding
 - diaper change
 - bathing
 - physiotherapeutic and logopedic exercises (after instructions from therapist)
 - for babies requiring chronic care:
 - GI tube insertion
 - tracheostomy care and suctioning, gastrostomy care
 - handling of pulseoximeters, home ventilators, oxygen concentrations etc.
 - parents of "high risk" babies receive additional training eg. CPR

Implemented practices to promote FCC

- improved personnel support (kangaroo care, BF)
- developmental care workshops
- psychologist support available 24/7
- lactation advisors – local/hospital trained, certified
- reclining chairs for kangaroo care
- special room for providing information to parents
- lockers for parents
- changes in parents' visiting regulations

NGO support



Biggest shopping yet!

First Open Tender makes the biggest shopping in the history of the Open Committee of Christmas Charity Foundation. Between 1st January and 31st March we want to buy around 2 thousand pieces of goods of the medical equipment for people. The youngest and most vulnerable patients, newborns and prematurely born babies, if all other prove to be increasing shopping effort in our history.

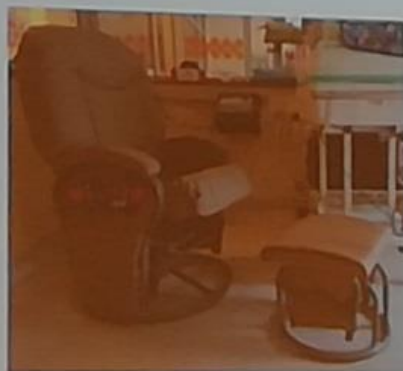
Together with a team of experts on medicine and technology, we will be looking to purchase:

- Infant incubators - 200
- Infant monitors - 200
- Infant pumps - 200
- The portable infant warmers - 100
- Infant monitors - 100
- Infant pumps - 100
- Electronic scales - 100
- Lactation pumps - 100
- Infant monitors - 100
- Infant pumps - 100
- Infant monitors - 100
- Infant pumps - 100
- Infant monitors - 100
- Infant pumps - 100

Our aim is to purchase only the best possible equipment and to ensure that each device is properly serviced and the staff is trained on how to use it. Unfortunately, after such a long time, until we reach a satisfactory price and we purchase and use it at the full capacity. Each model and piece of equipment is described by a group of experts, doctors, nurses, medical engineers and economists are drafted by a team of experts.

Result of the 27th Grand Finale:

1 7 5 9 3 8 7 1 7 PLN



SCENE

Separation and Closeness Experiences in the Neonatal Environment

Separation and Closeness Experiences in the Neonatal Environment SCENE research group

- Multi-disciplinary research group aiming to optimize parental and infant health and wellbeing in neonatal care www.utu.fi/scene
- Next meeting in November 8th-9th, 2019 in Budapest, Hungary
- Contact: anna.axelin@utu.fi