

**ТОП-теми,
які обговорюються
на європейських конгресах
з неонатології**

проф. Павлишин Г.А.

**Тернопільський державний медичний
університет ім. І.Я. Горбачевського**







2JENS

Congress of joint European
Neonatal Societies

58th ESPR Annual Meeting
7th International Congress of UENPS
3rd International Congress of EFCNI

Venice 2017

POWERED BY  MCA

October 31st
November 4th

www.jenscongress.eu

Organising Institutions:

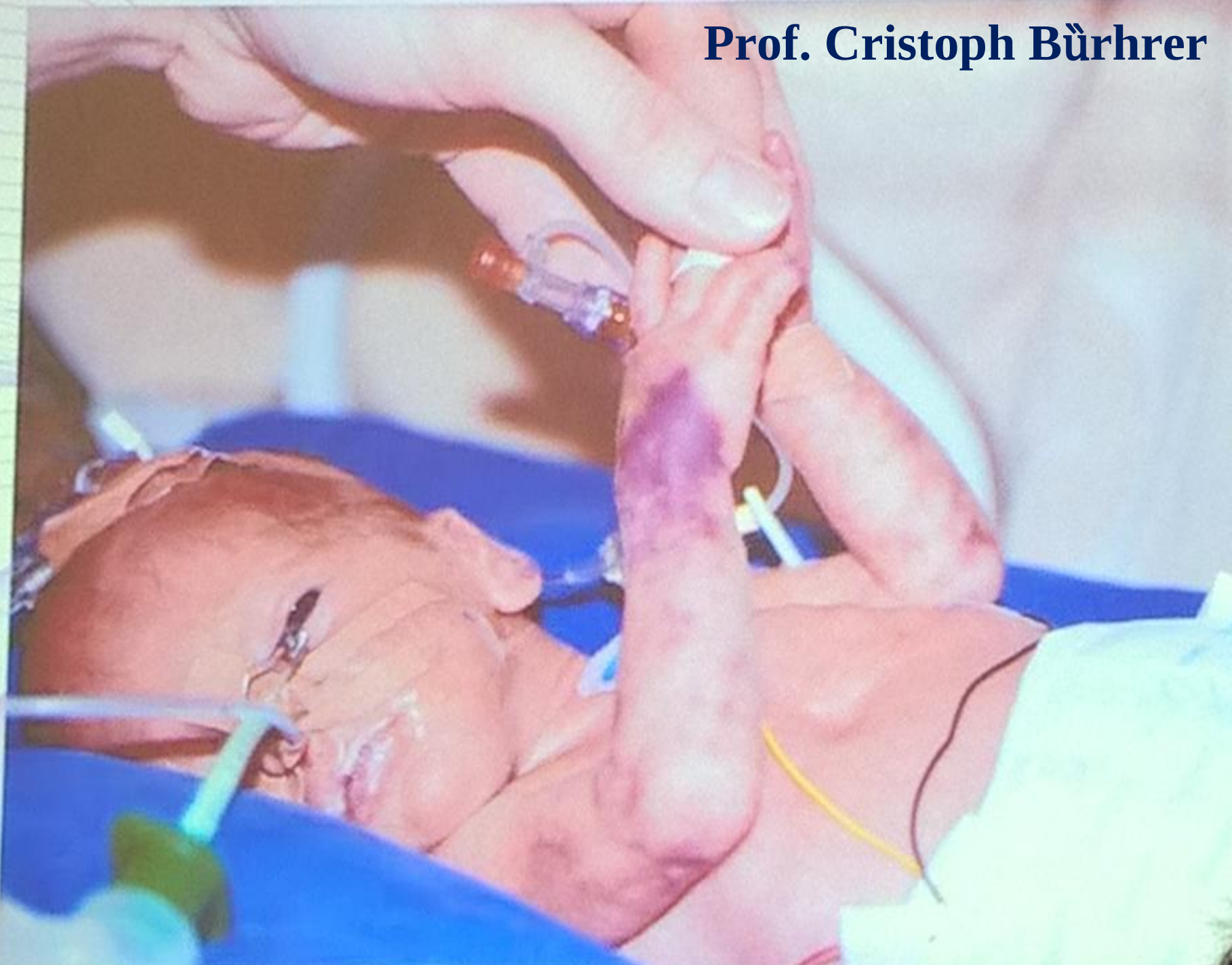




**Проф., доктор медицини
Крістоф Бюрер,
директор Клініки
неонатології**



Університетська клініка Шаріте





Неонатальний сепсис

★ There are ~3300 invasive early-onset sepsis cases and 390 deaths in the United states each year (2005-2008 data).

- Рівень захворюваності на сепсис – впродовж 10 років – не зменшився (США – 0,77/1000 , 2014-2015)
- III місце в структурі смертності дітей неонатального періоду
- Значно більше Сепсису – в розвиваючих країнах
- У недоношених дітей – у 20 разів частіше, ніж у доношених;
- GBS, E.coli – основні збудники сепсису



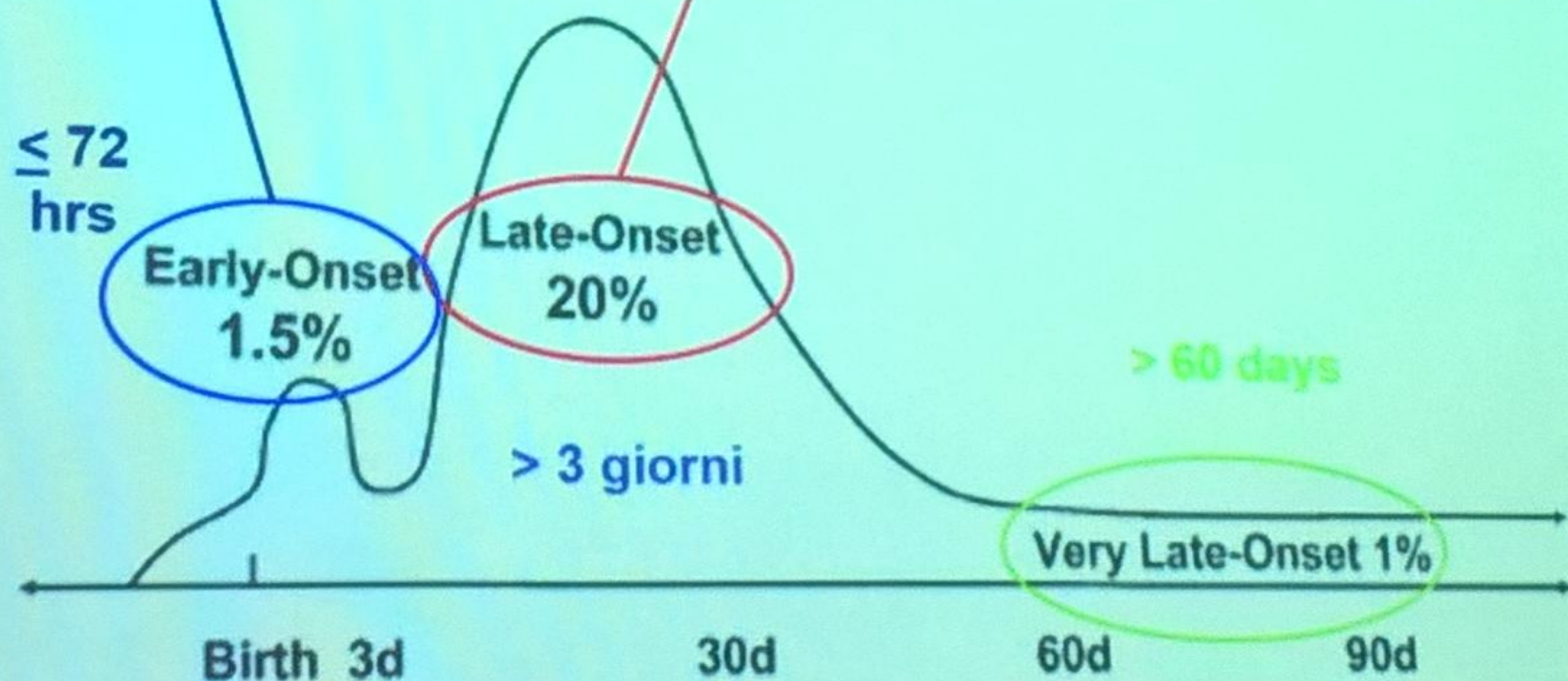
Dr Paolo Manzoni, MD, PhD
Neonatology and NICU
S. Anna Hospital .
Torino, Italy

SEPSIS in preterm VLBW Neonates in NICU: causative agents and timing

E. coli
SGB
CONS
H. influenzae

CONS
S. aureus
Candida spp
E. coli

(data from NICHD,
2002-2003)



EARLY-ONSET SEPSIS : causative pathogens

Barbara J. Stoll, Nellie Hansen, Avroy A. Fanaroff, et al
Changes in Pathogens Causing Early-Onset Sepsis in Very-Low-Birth-Weight Infants
NEJM 2002, Volume 347:240-247



The NEW ENGLAND
JOURNAL of MEDICINE

GBS
+
E.Coli

81%

TABLE 2. DISTRIBUTION OF PATHOGENS AMONG 84 CASES OF EARLY-ONSET SEPSIS OCCURRING IN 5447 INFANTS BORN BETWEEN SEPTEMBER 1, 1998, AND AUGUST 31, 2000.*

ORGANISM	No. with Sepsis (%)
Gram-negative organisms	
<i>Escherichia coli</i>	51 (60.7)
<i>Haemophilus influenzae</i>	37 (44.0)
<i>Citrobacter</i>	7 (8.3)
Other†	2 (2.4)
Gram-positive organisms	
Group B streptococcus	5 (6.0)
Viridans streptococcus	31 (36.9)
Other streptococci‡	9 (10.7)
<i>Listeria monocytogenes</i>	3 (3.6)
<i>Coagulase-negative staphylococcus</i> §	4 (4.8)
Other¶	2 (2.4)
Fungi	9 (10.7)
<i>Candida albicans</i>	4 (4.8)
Total	2 (2.4)
	84 (100)

*Seven of the 84 infants had two positive blood cultures for the same organism.

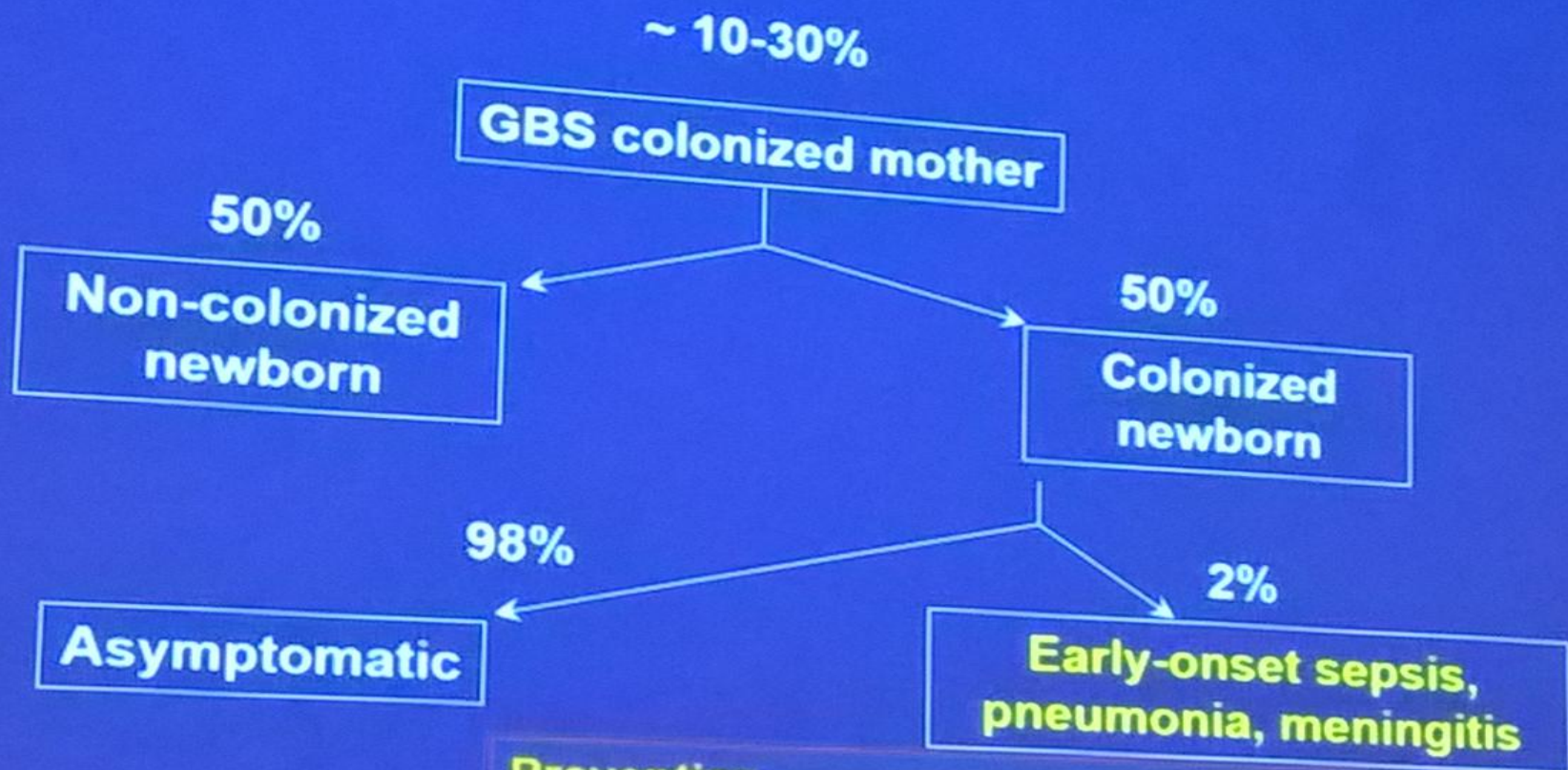
†Other gram-negative organisms included *Klebsiella* (in one infant), *Bacteroides* (in two infants), *Enterella corrodens* (in one infant), and *Streptococcus maltophilia* (in one infant).

‡Other streptococci included group A streptococcus (in one infant) and three cases in which the species was unknown.

§Of 18 positive blood cultures for coagulase-negative staphylococci, 1 met the criteria for definite infection and 8 for possible infection; in the other 9 cases, the organism was considered to be a contaminant (see the Methods section).

¶Other gram-positive organisms included *Staphylococcus aureus* (in one infant), *Bacillus* (in two infants), and *Peptostreptococcus* (in one infant).

GBS : Maternal to Infant Transmission (in absence of intervention)



Prevention

- Intrapartum antibiotic prophylaxis (IAP) with Ampicillin every 4 hrs
- Effectiveness 86-89% for preventing EOGBS

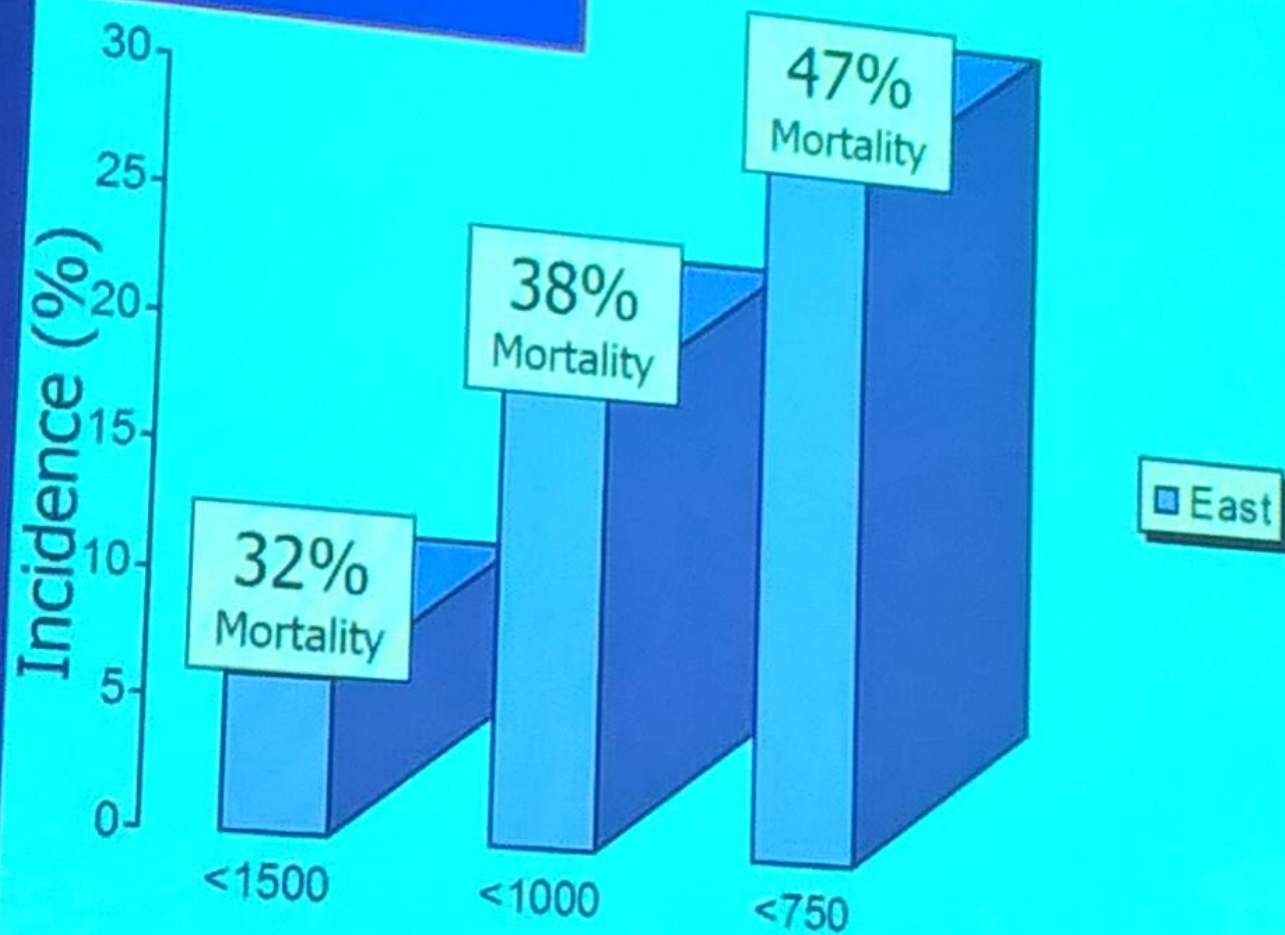
Epidemiology of LOS

Table 2 Incidence of LOS by birth weight

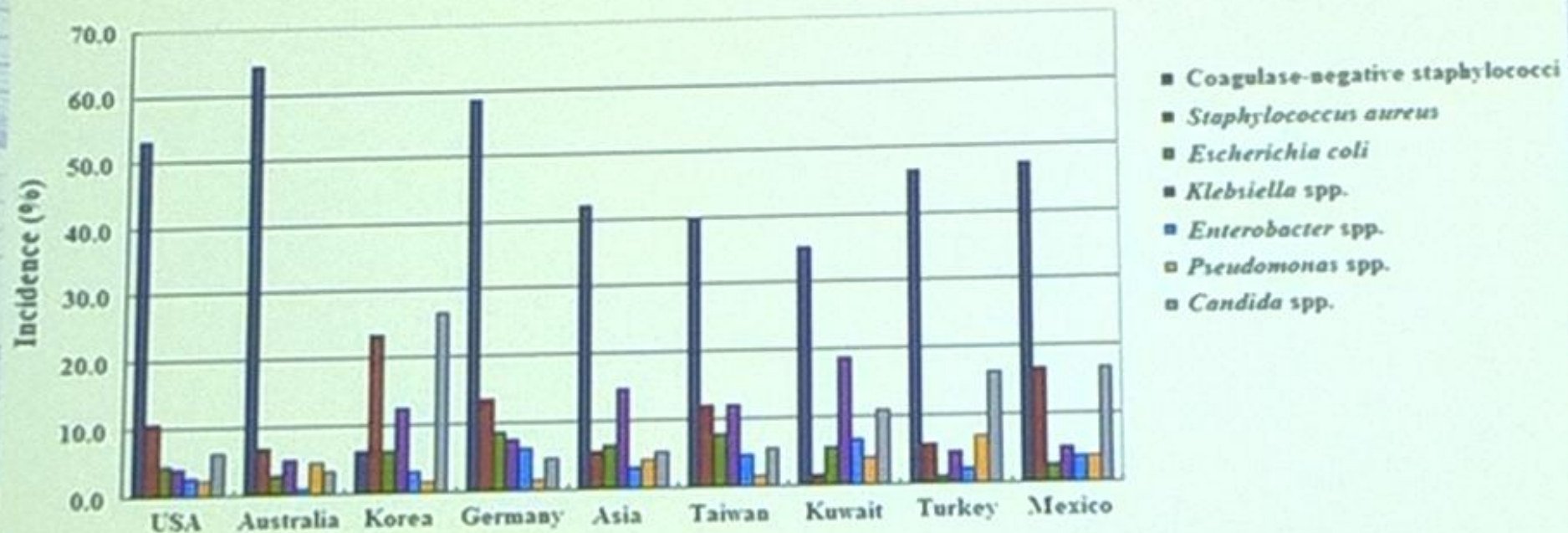
Reference	Birth weight (g)	No. of neonates	LOS, No. (%)
Boghossian <i>et al</i> , ² USA	400–500	223	146 (65.5)
	501–750	2680	1372 (51.2)
	751–1000	4030	1309 (32.5)
Vergnano <i>et al</i> , ³ England	1000–1499	1110	113 (10.2)
	1500–2500	2945	66 (2.2)
	>2500	5340	88 (1.6)

LOS, late-onset sepsis.

Why is it mandatory to prevent infections in the NICU?



Which organisms cause LOS in NNUs?



Mortality of late-onset sepsis in preterm infants < 1,500 g
NICHD-NRN 1998-2000

Coagulase-neg. Staph.	9
Enterococcus	11
Candida parapsilosis	16
Staph aureus	17
GBS	22
Klebsiella	23
Enterobacter	27
E. coli	34
Serratia	36
Candida albicans	44
Pseudomonas	74

Pathogens involved in Neonatal Sepsis are different between HIC and LMIC

In HIC - the most common causes of EONS are:

- group B streptococcus (GBS) and *Escherichia coli*;
- *S. aureus*, CoNS - *S. coagulase-negative*, *Listeria monocytogenes*, other Gram-negative bacteria;
- LONS (mainly in VLBW infants), the main pathogens are CoNS, *E. coli*, *Klebsiella* spp., *Candida* spp.

In LMIC - the commonest causes of neonatal bacteremia are:

- *S. aureus*, *E. coli*, *Klebsiella* spp.,
- *Acinetobacter* spp., GBS, CoNS;

The majority of nosocomial infections occur in preterm or term infants who require intensive care.



CORRECT MANAGEMENT OF CVC HELPS REDUCING UNNECESSARY ANTIBIOTIC EXPOSURE

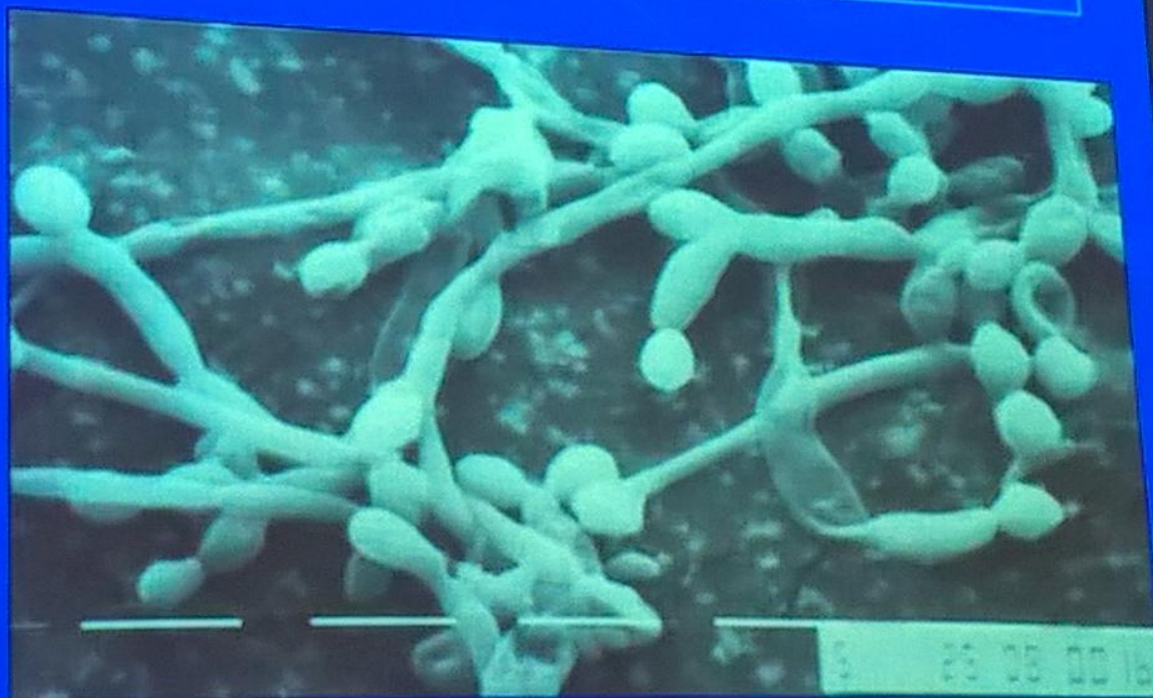
Having a CVC is a risk for infections
Many pathogens may form biofilms on prosthetic devices, and hence disseminate through the bloodstream through septic thrombi

OR = 2.0 (95% CI 1.1-3.9)
(Avila-Figueroa, 1998)

RR = 3.81 ($P < 0.001$)
(Pediatric Prevention
Network, 2001)

RR = 5.87 ($P = 0.001$)
(Auriti, 2003)

OR = 13.6 ($p = 0.01$)
(Rojas, 2005)



Fungal Biofilms

Antibiotic Use for Sepsis in Neonates and Children: 2016 Evidence Update

**Aline Fuchs^a, Julia Bielicki^{a,b}, Shrey Mathur^b,
Mike Sharland^b, Johannes N. Van Den Anker^{a,c}**

***^a Paediatric Pharmacology and Pharmacometrics, University Children's Hospital
Basel, Basel, Switzerland***

***^b Paediatric Infectious Disease Research Group, Institute for Infection and
Immunity, St George's University of London, London, United Kingdom***

***^c Division of Clinical Pharmacology, Children's National Health System,
Washington, DC, USA***

Неонатальний сепсис

- наявність щонайменше 2-х клінічних ознак + 2-х лаборатор. ознак при підозрі/доведеній інфекції (рос культура, мікроскопія, ПЛР):

Why empirical ? The Limits of blood cultures in the diagnosis of infections

- Failure to identify the various species of pathogens (eg., up to 15% of the microbiological samples can be actually contaminated with *Candida* spp.).
- Phases of bacteraemia are fleeting, or not protracted, in many cases of systemic infections (and this is true for *Candida* spp more than for bacterial sepsis)
- The aliquots of drawn blood are usually not suitable → a good blood culture would need at least 3 ml !
- Blood drawn from "peripheral" vs. "central" sites

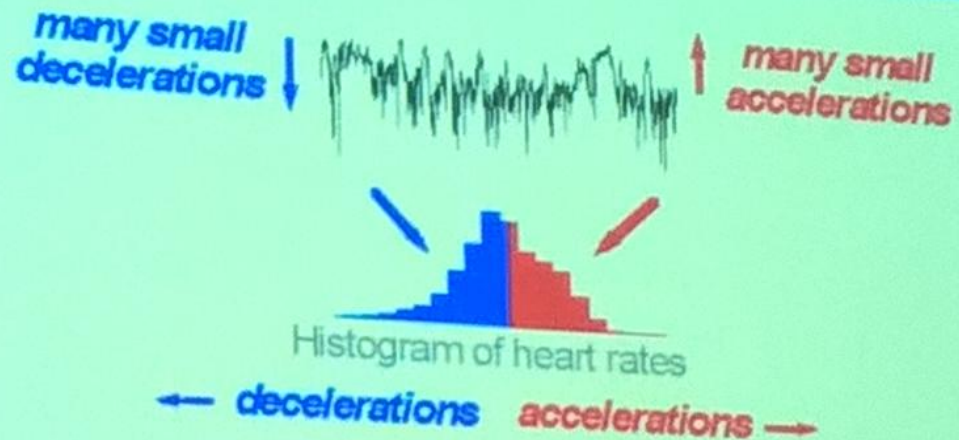
Why empirical ? Clinical Signs of Sepsis remain the most sensitive Indicator

Predictive Values of ANC, I:T Ratio, and Clinical Examination among newborns weighing ≥ 2000 g at birth evaluated for sepsis

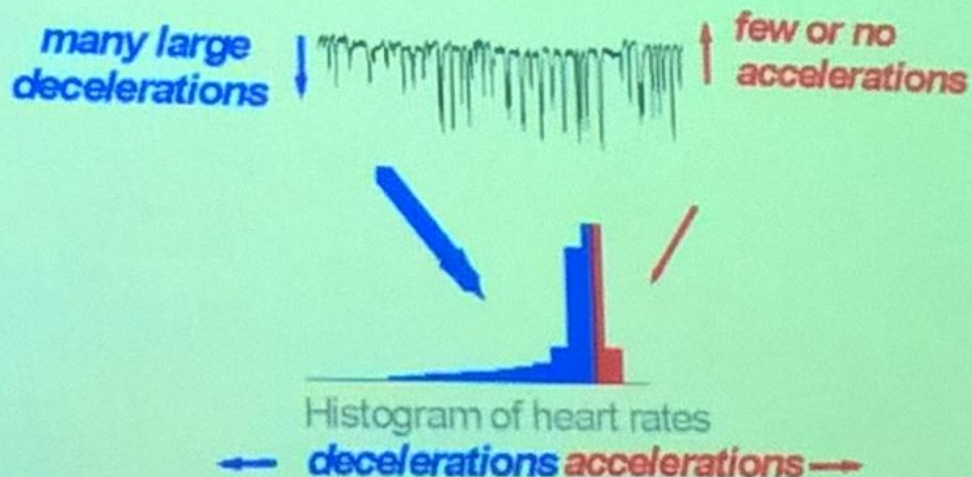
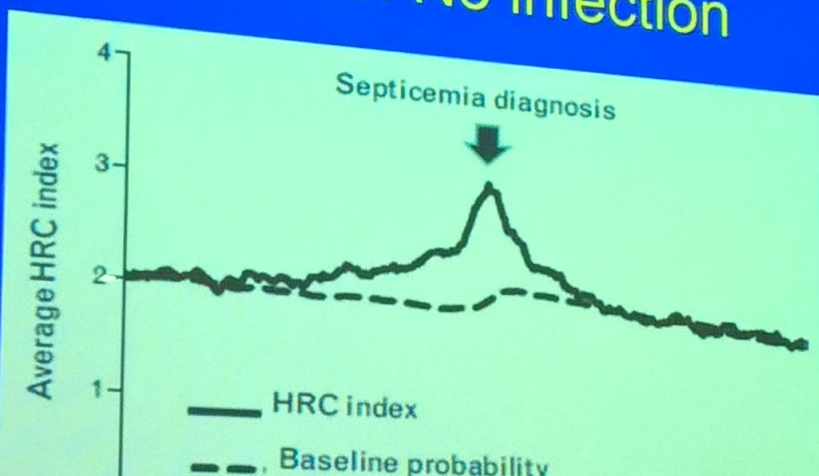
	Sensitivity	Specificity	+PV	-PV
Presence of clinical signs	92%	53%	4%	99%
Baby critically ill	31%	6%	10%	98%
ANC <10th percentile	48%	73%	4%	98%
ANC <10th percentile	16%	96%	8%	98%
Manroe et al				
I:T ratio, $\geq .25$ cutoff	45%	84%	6%	98%
I:T ratio, $\geq .30$ cutoff	35%	89%	7%	98%

Heart Rate Characteristics (HRC) : may they help diagnosis?

Normal: many small
decelerations and
accelerations – the
histogram is
symmetric



Sepsis vs. No infection



Клінічні ознаки

- 1. Зміна температури тіла** – температура тіла $> 38,5^{\circ}\text{C}/<36^{\circ}\text{C}$, температурна нестабільність;
- 2. Кардіоваскулярна нестабільність** - брадикардія (ЧСС < 10 -го центиля), тахикардія, порушення ритму, зниження діурезу ($< 1 \text{ mL/kg/h}$), гіпотензія (сер АТ < 5 -го центиля), мармуровість шкіри, порушення периферичної перфузії;
- 3. Зміни шкіри, підшкірної клітковини** – петехіальна висип, склерема;
- 4. Респіраторна нестабільність** – апноє, тахикардія, потреба O_2 -терапії, потреба вентиляційної підтримки;
- 5. Гастроінтестинальні порушення:** інтолерантність їжі, погане смоктання, вздуття живота;
- 6. Неспецифічні ознаки:** збудження, пригнічення, гіпотонія

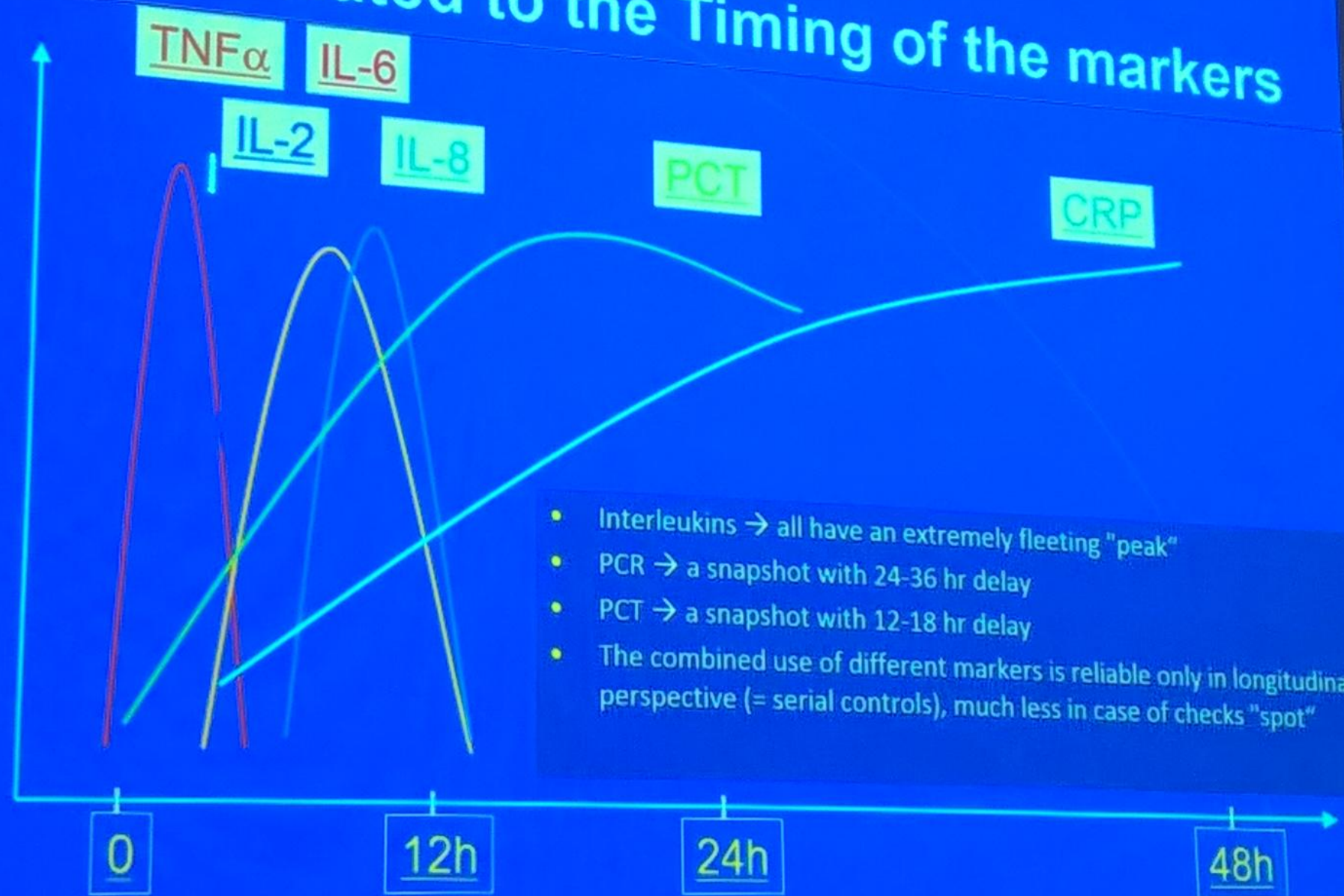
Laboratory signs

White blood cells count: $<4,000 \times 10^9$ cells/L OR $>20,000 \times 10^9$ cells/L

- **Immature to total neutrophil ratio (I/T)** greater than 0.2
- **Platelet** count $<100,000 \times 10^9$ cells/L
- **CRP** > 15 mg/L OR **procalcitonin** ≥ 2 ng/ml
- **Glucose intolerance** confirmed at least 2 times:
hyperglycaemia (blood glucose > 10 mMol/L or 180 mg/dL)
OR *hypoglycaemia* (glycaemia < 2.5 mMol/L or 45 mg/dL)
- **Metabolic acidosis**: Base excess (BE) < -10 mEq/L or
Serum lactate > 2 mMol/L

Why empirical?

Issues related to the Timing of the markers



Management of Neonates with Suspected or Proven Early-Onset Sepsis

Risk Factors

Chorioamnionitis^a or
PROM ≥ 18 h or IAP
indicated but Inadequate



Diagnostic Tests

Blood culture at birth
WBC/Diff $\pm$ CRP
at age 6-12 h



Antibiotics

Treat with broad-
spectrum antibiotics



Management



Blood culture positive



Continue antibiotics
Lumbar puncture^b

Blood culture negative
Infant remains well
Lab data abnormal



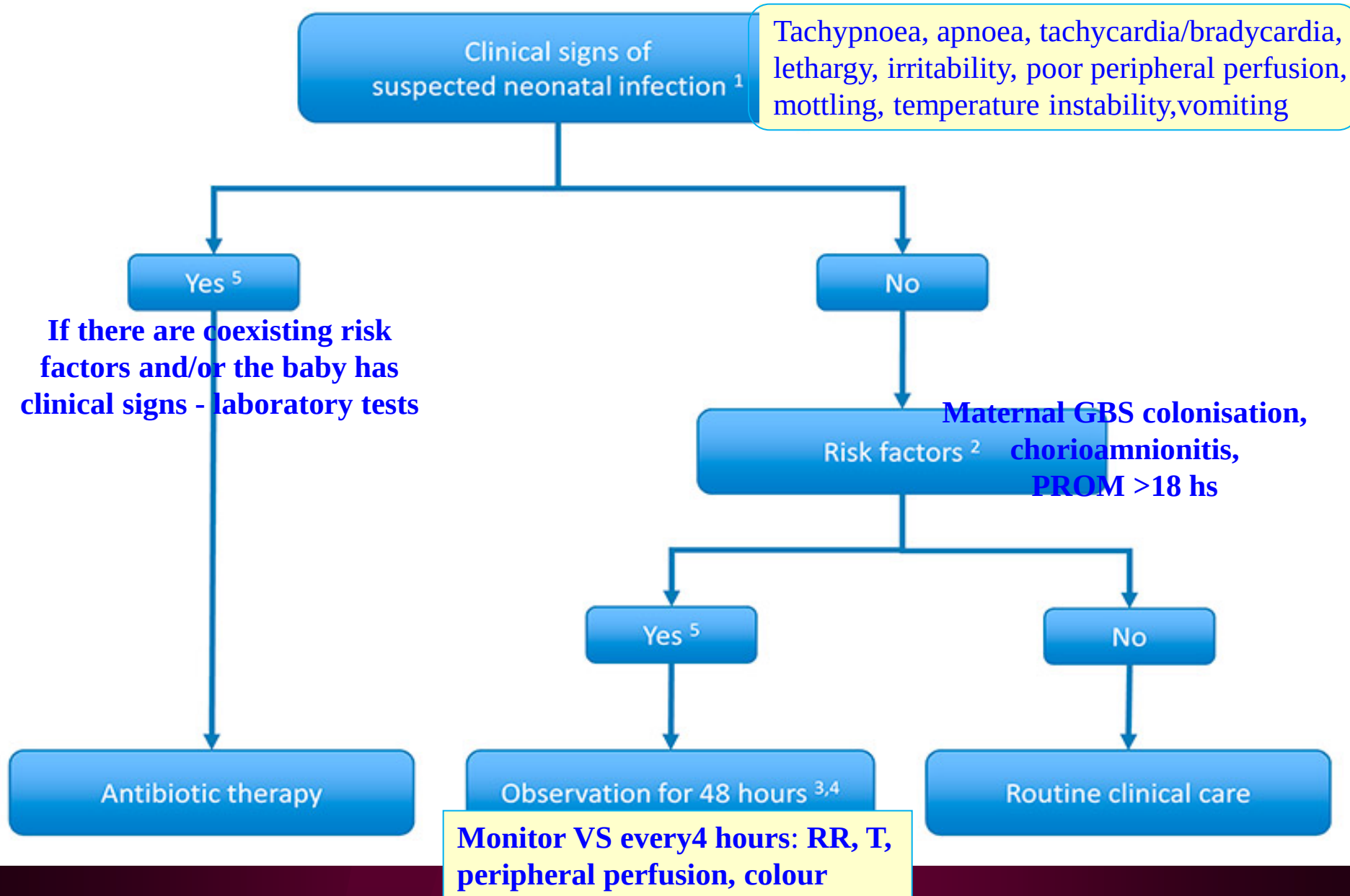
Continue antibiotics if mother
received antibiotics during
labor and delivery

Blood culture negative
Infant remains well
Lab data normal



Discontinue
antibiotics

Management of newborns at increased risk for early-onset sepsis



Reducing unnecessary antibiotic exposure in preterm neonates: an achievable goal

"Paolo Manzoni, Alberto Dall'Agnola
Neonatology and NICU, S Anna Hospital, Torino 10126, Italy (PM);
and Paediatrics and Neonatology, "Silvio Orlandi" Hospital,
Bussolengo, Verona, Italy (AD'A)

THE LANCET

Volume 379 | Number 10134 | Pages 1-98 | 3-6 July 2012

Four, main areas of antibiotic stewardship :

1. Avoid unnecessary prophylactic exposures (i.e., for UVC, CVC, etc), including better diagnosis
2. Discontinue ATBs after 48 hrs if sepsis is not confirmed
3. Try shorter duration of courses if sepsis is confirmed
4. Prevent infection / Reinforce prophylaxis to prevent infections thus bypassing any need for ATBs (e.g., bundles of care, CVC bundles, reinforced hygiene measures, prophylactic fluconazole, lactoferrin, probiotics, fresh human milk, etc)

Antibiotic Use for Sepsis in Neonates and Children: 2016 Evidence Update

**Aline Fuchs^a, Julia Bielicki^{a,b}, Shrey Mathur^b,
Mike Sharland^b, Johannes N. Van Den Anker^{a,c}**

***^a Paediatric Pharmacology and Pharmacometrics, University Children's Hospital
Basel, Basel, Switzerland***

***^b Paediatric Infectious Disease Research Group, Institute for Infection and
Immunity, St George's University of London, London, United Kingdom***

***^c Division of Clinical Pharmacology, Children's National Health System,
Washington, DC, USA***

Antibiotic therapy for suspected neonatal infection



The standard empiric therapy is aminoglycoside (amikacin or gentamicin) combined with amoxicillin IV

- Appropriate doses for neonates within the first week of life are: gentamicin 4–5 mg/kg/dose or amikacin 15 mg/kg/dose IV every 24 hours and amoxicillin 50–100 mg/kg/dose IV every 12 hours.
- There is a need for therapeutic drug monitoring for aminoglycoside therapy.
- **Cephalosporins should be avoided as first-line therapy** because of the high risk of developing resistance and should be restricted to special cases.

- As the clinical and laboratory signs of neonatal infection are nonspecific and symptomatic neonates are treated empirically with antibiotics, it is important to reevaluate the need for continued antibiotic therapy after 48 hours.
- In most cases, based on the clinical course, negative culture results and laboratory parameters, a decision can be made to stop safely antibiotic therapy after this time.
- The frequent observation that prolonged antibiotic therapy (>5 days) causes **increased mortality and a higher incidence of NEC in preterm** infants emphasises the need to stop empirical antibiotic therapy in the absence of proven infection (negative culture and negative acute phase reactants) as early as possible and at the latest after 48–72 hours.

Recommendations for term and late preterm infants at risk for perinatal bacterial infection

Revised guidelines of the Swiss Society of Neonatology in collaboration with the Paediatric Infectious Disease Group of Switzerland (PIGS): modified version based on a previous publication in the Journal of the Swiss Society of Paediatrics

- **According to guidelines- NICE, AAP, BMJ and WHO recommendations, for EONS - recommend the use of benzylpenicillin or ampicillin combined with gentamicin as empiric treatment and list third generation cephalosporins as an alternative.**

Current international guidelines for the empirical treatment of sepsis

Guideline	Recommendations
NICE, 2016	• Neonates presenting in hospital with suspected sepsis in their first 72 hours: IV benzylpenicillin 25 mg/kg 3 times daily and gentamicin (starting dose 5 mg/kg every 36 hours). Minimum 7 day course of IV; • Neonates, community acquired sepsis: - o ≤ 40 weeks corrected gestational age - cefotaxime 50 mg/kg - o > 40 weeks corrected gestational: ceftriaxone 50 mg/kg

Current international guidelines for the empirical treatment of sepsis

Guideline	Recommendations
AAP, 2015	<u>Early-onset sepsis:</u> - o Broad-spectrum antimicrobial agents (ampicillin 150 mg/kg per dose IV every 12 hours and an aminoglycoside (gentamicin 4 mg/kg per dose IV every 24 hours)). - o Third-generation cephalosporins (eg, cefotaxime) represent a reasonable alternative to an aminoglycoside. <u>Late-onset sepsis</u> admitted from the community: ampicillin 75 mg/kg per dose IV every 6 hours and gentamicin 4 mg/kg per dose IV every 24 hours • <u>Late-onset sepsis hospitalized</u> since birth: vancomycin: 10 to 20 mg/kg every 12 to 48 hours according serum creatinine and gentamicin 4 mg/kg per dose iv every 24 hours

Current international guidelines for the empirical treatment of sepsis

Guideline	Recommendations
BMJ Clinical Evidence , 2016 (British Medical Journal)	<u>Early-onset sepsis:</u> benzylpenicillin plus gentamicin (from NICE guidelines) OR ampicillin plus gentamicin <u>Late-onset sepsis:</u> - o ampicillin plus gentamicin OR cefotaxime, OR vancomycin plus gentamicin OR cefotaxime. - o Ceftazidime or piperacillin/tazobactam may be added to the empirical regimen if Pseudomonas is suspected. - o Metronidazole or clindamycin may be added to the empirical regimen to cover for anaerobes/necrotising enterocolitis. Infants and young infants, community-acquired infection: Third-generation cephalosporin (e.g., cefotaxime, ceftriaxone) Infants and young infants, hospital-acquired infection: Extended-spectrum penicillin (e.g., piperacillin/tazobactam) OR carbapenem (e.g. meropenem)

PREVENTION OF INFECTIONS HELPS REDUCING UNNECESSARY ANTIBIOTIC EXPOSURE: the example of Fluconazole

FLUCONAZOLE either dosage
(3mg or 6mg every 2nd day) vs. PLACEBO



The NEW ENGLAND
JOURNAL of MEDICINE

	<i>Fluconazole</i> N=216	<i>Placebo</i> n=106	<i>R.R.</i>	<i>95% C.I.</i>	<i>P-value</i>
Total invasive fungal infections (IFI; %)	3.2%	13.2%	0.25	0.10-0.59	0.001
Overall colonisation	8.8%	29.2%	0.30	0.18-0.51	<0.0001
Overall mortality	8.3%	9.4%			0.83
Mortality attributable to fungi	0%	1.9%			0.10

Manzoni P, et al. *N Engl J Med* 2007;356:2483-95.

Original Investigation

Effect of Fluconazole Prophylaxis on Candidiasis and Mortality in Premature Infants

A Randomized Clinical Trial

JAMA®

JAMA. 2014;311(17):1742-1749. doi:10.1001/jama.2014.2624

Daniel K. Benjamin Jr, MD, PhD; Mark L. Hudak, MD; Shahnaz Duara, MD; David A. Randolph, MD, PhD; Margarita Bidegain, MD, MHS-CL; Gratias T. Mundakel, MD; Girija Natarajan, MD; David J. Burchfield, MD; Robert D. White, MD; Karen E. Shuttuck, MD; Natalie Neu, MD, MPH; Catherine M. Bendel, MD; M. Roger Kim, MD; Neil N. Finer, MD; Dan L. Stewart, MD; Antonio C. Arrieta, MD; Kelly C. Wade, MD; David A. Kaufman, MD; Paolo Manzoni, MD; Kristi O. Prather, MPH; Daniela Testoni, MD, MHS; Katherine Y. Berezny, MPH; P. Brian Smith, MD, MPH, MHS; for the Fluconazole Prophylaxis Study Team

- ✓ Multicenter RCT
- ✓ 362 infants <750g
- ✓ 6mg/kg Fluconazole twice weekly vs placebo

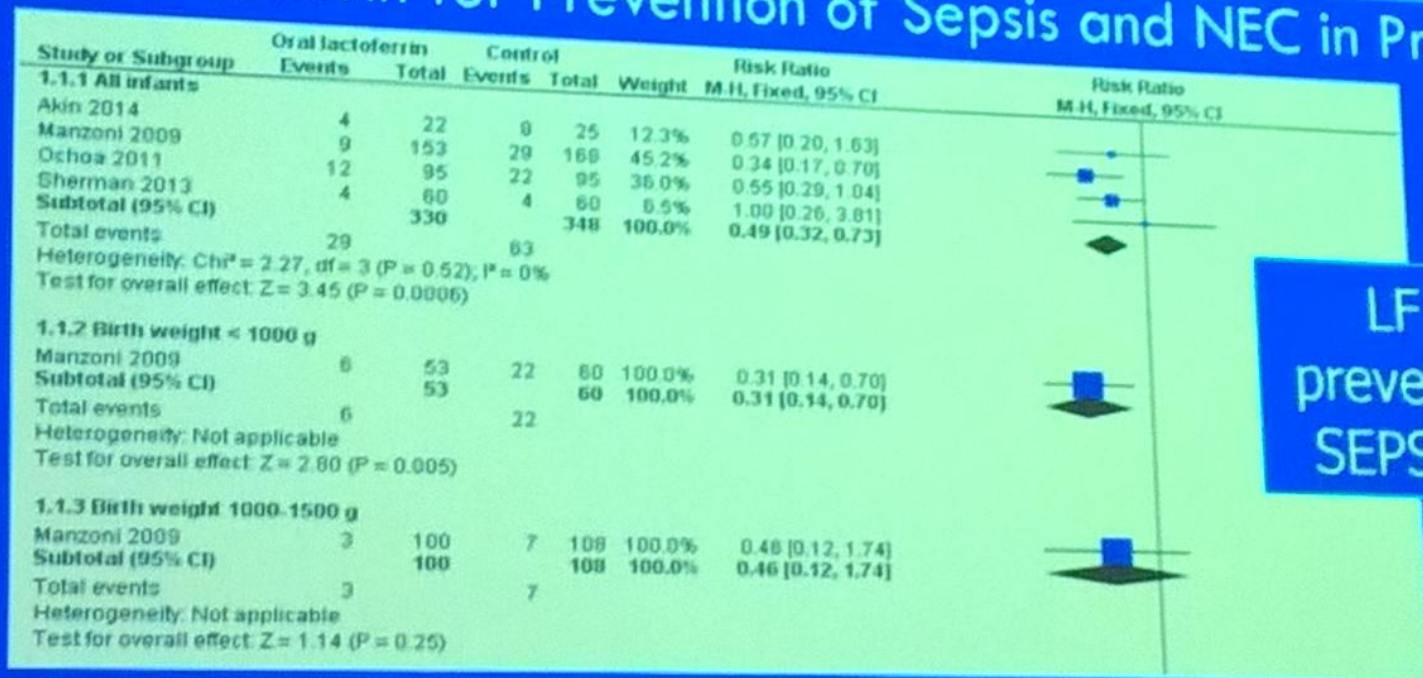
	Fluco	Placebo	95%CI	P-value
Invasive Candidiasis	3%	9%	-11 to -1	0.02
Death (any cause)	14%	14%	-7 to 7	0.98
Death OR Candidiasis	16%	21%	-13 to 3	0.24
Neurodevelopmental Impairment – composite at 18-22 months c.a.	31%	27%	-10 to 7	0.60

Is FLUCONAZOLE preferable to NYSTATIN ? YES

	Fluconazole	Nystatin
Effect on colonization	Decreased CVC, skin, GI and respiratory colonization	Decreased skin, GI and respiratory colonization
Level of evidence	Level A-I	Level A-I
Efficacy	RCT data 80% in all studies >90% in <1000 g	RCT data 50%-60%
Evidence in extremely preterm infants	Efficacy in the most extreme preterm infants (<25 weeks' gestation and <750 grams)	Fewer infants <750 g or <25 weeks' gestation have been studied
Effect on mortality	Candida-related mortality decreased by 96%	Lower mortality in one study
Administration with GI disease or ileus	Can be given in infants with NEC, ileus, or GI disease	Cannot be given if GI disease or ileus
Resistance	No resistance	Lack of data on resistance
Dosing	Twice a week dosing	Dosing 3-4 times/day
Route of administration	Given IV*	Oral/enteral administration
Osmolarity	300 mOsm/L	3002 mOsm/L
Start prophylaxis	Soon after birth	Soon after birth
End prophylaxis	No longer need IV access	Full enteral feedings
Cost	Cost effective	Cost effective Costs more in U.S. compared to fluconazole.

PREVENTION OF INFECTIONS HELPS REDUCING UNNECESSARY ANTIBIOTIC EXPOSURE: the example of Lactoferrin

Oral Lactoferrin for Prevention of Sepsis and NEC in Preterm Infants



LF
prevents
SEPSIS



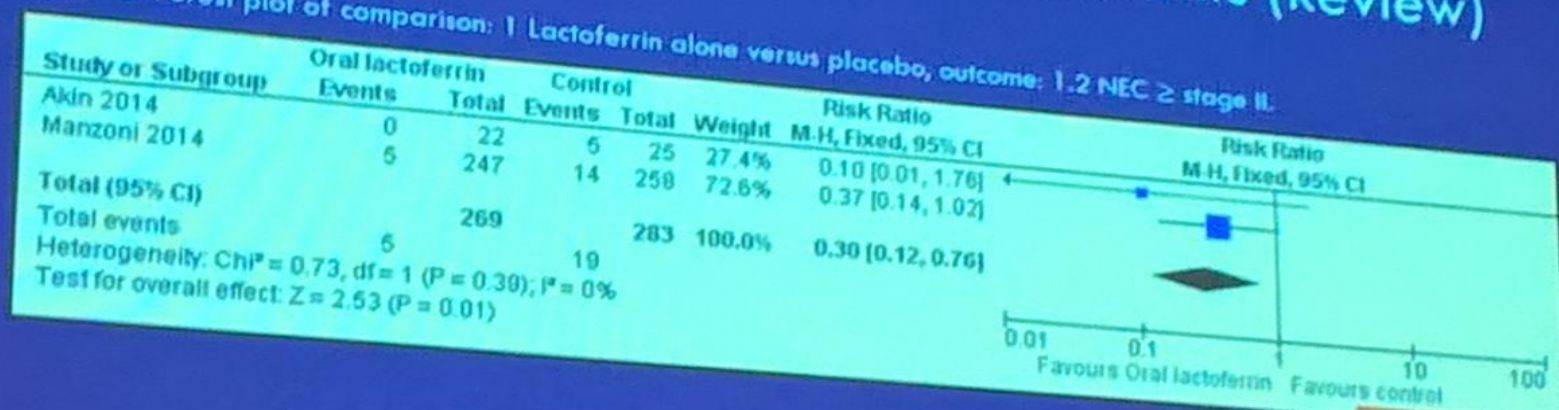
Pammi M, Abrams S A.
Cochrane Database Syst Rev. 2015 Feb
20;2:CD007137.

- ❑ 4 RCTs retrieved (3 BLF, 1 rHLF)
- ❑ 648 VLBW infants analysed. No heterogeneity
- ❑ R.R. 0.49
- ❑ NNT 11

Current available evidence graded as “moderate quality”

Oral Lactoferrin for Prevention of Sepsis and Necrotizing Enterocolitis in Preterm Infants (Review)

Figure 2. Forest plot of comparison: 1 Lactoferrin alone versus placebo, outcome: 1.2 NEC $\geq$ stage II.



LF and
NEC

- 2 RCTs retrieved (all with BLF)
- 552 VLBW infants analyzed. Moderate heterogeneity
- R.R. 0.30
- NNT 20
- Current available evidence graded as "low-to-moderate quality"



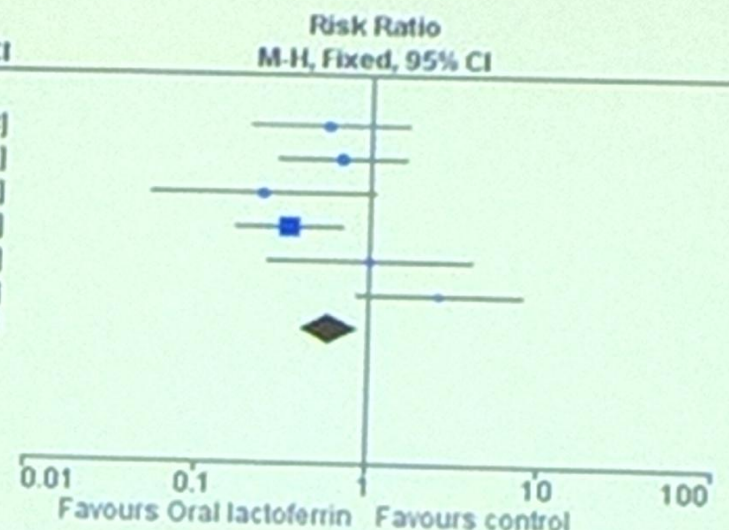
Oral lactoferrin in very preterm infants

Sepsis

Study or Subgroup	Oral lactoferrin		Control		Weight	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
1.1.1 All infants						
Akin 2014	4	22	8	25	12.1%	0.57 [0.20, 1.63]
Barrington 2016	7	40	10	39	16.3%	0.68 [0.29, 1.61]
Kaur 2015	2	63	9	67	14.1%	0.24 [0.05, 1.05]
Manzoni 2014	9	153	29	168	44.6%	0.34 [0.17, 0.70]
Ochoa 2015	4	95	4	95	6.5%	1.00 [0.26, 3.88]
Sherman 2016	10	59	4	60	6.4%	2.54 [0.84, 7.66]
Subtotal (95% CI)		432		454	100.0%	0.59 [0.40, 0.87]
Total events	36		64			

Heterogeneity: $\chi^2 = 11.14$, $df = 5$ ($P = 0.05$); $I^2 = 55\%$

Test for overall effect: $Z = 2.66$ ($P = 0.008$)



Trials **Patients**
6 **886**

Risk Ratio (95% CI)
0.59 (0.40-0.87)

$p = 0.008$

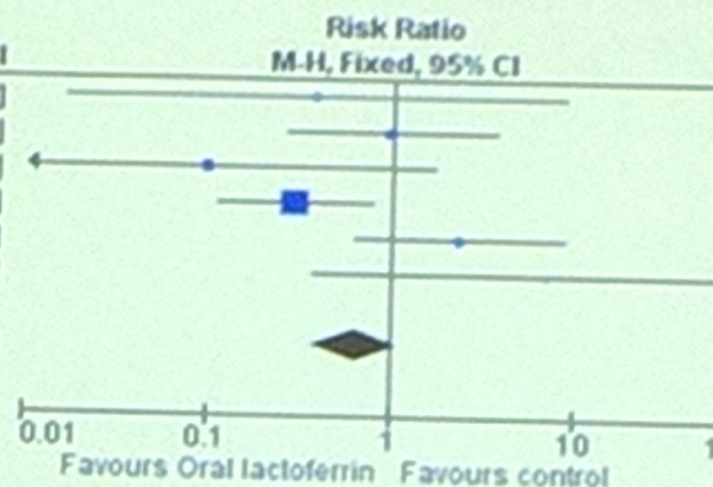
Oral lactoferrin in very preterm infants

Mortality

Study or Subgroup	Oral lactoferrin		Control		Weight	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Akin 2014	0	22	1	25	4.4%	0.38 [0.02, 8.80]
Barrington 2016	4	40	4	39	12.7%	0.97 [0.26, 3.63]
Kaur 2015	0	63	5	67	16.7%	0.10 [0.01, 1.71]
Manzoni 2014	5	247	18	258	55.2%	0.29 [0.11, 0.77]
Ochoa 2015	7	95	3	95	9.4%	2.33 [0.62, 8.75]
Sherman 2016	3	60	0	60	1.6%	7.00 [0.37, 132.66]
Total (95% CI)		527		544	100.0%	0.65 [0.37, 1.11]
Total events	19		31			

Heterogeneity: $\chi^2 = 10.90$, $df = 5$ ($P = 0.05$); $I^2 = 54\%$

Test for overall effect: $Z = 1.57$ ($P = 0.12$)



Trials

6

Patients

1.071

Risk Ratio (95% CI)

0.65 (0.37-1.11)

$p = 0.12$

PREVENTION OF INFECTIONS HELPS REDUCING UNNECESSARY ANTIBIOTIC EXPOSURE: the example of Human Fresh Milk

Human milk prevents:

- Infections *(Schanler 2005, Hylander 1998)*
- NEC *(Lucas 1990, Furman 2002, Schanler 2005)*

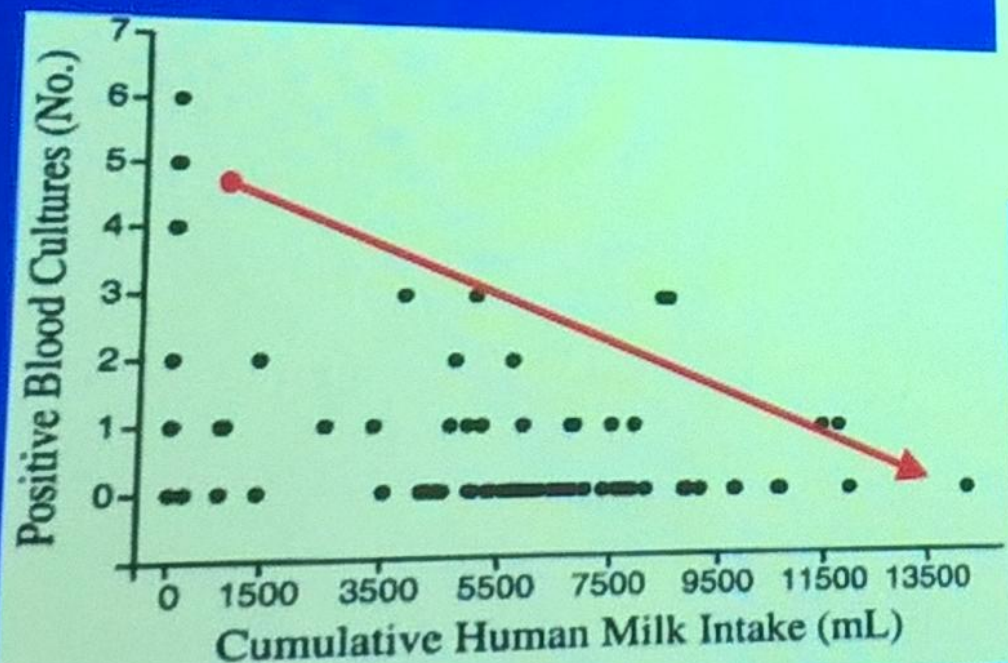


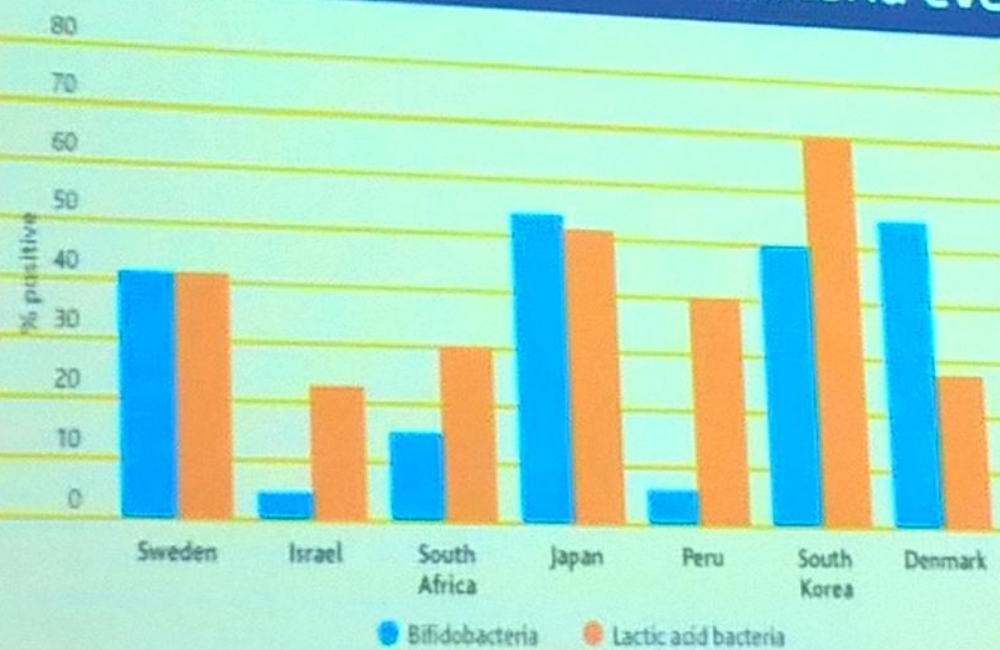
TABLE 5. Reduced Logistic Regression Model for Infection in Relation to Confounding Variables*

Variable	Odds Ratio	95% CI	P Value
Gestational age (wk)	0.80	(0.68–0.95)	.009
Apgar score at 5 minutes	0.93	(0.77–1.14)	.494
Days without enteral feedings (NPO)	1.03	(0.99–1.07)	.153
Mechanical ventilator days	1.01	(0.99–1.03)	.184
Human milk-fed 	0.43	(0.23–0.81)	.010

The beneficial effects of
human fresh milk depend
on intake volumes

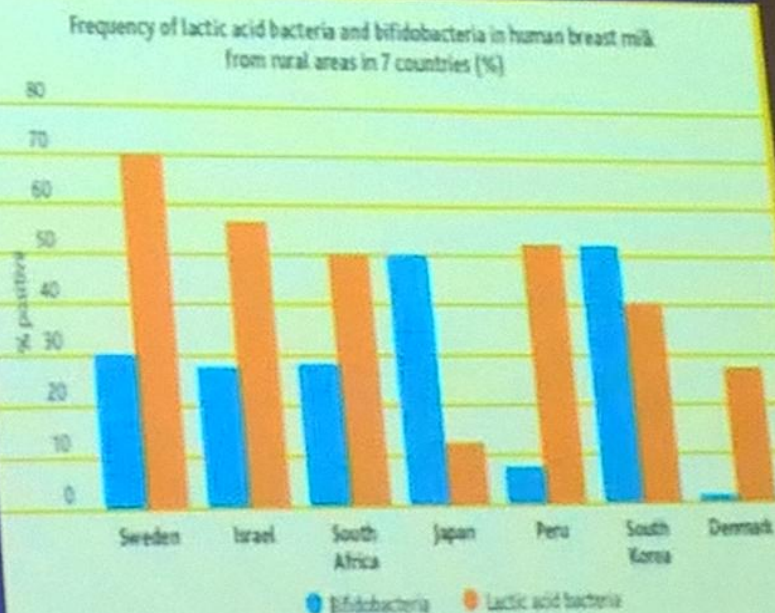
Maternal milk contains probiotics

An infant fed with 800 ml /day of maternal milk will ingest 10^5 - 10^7 bacteria every day



Bifidobacteria and Lactobacilli content in human milk: urban areas

Bifidobacteria and Lactobacilli content in human milk: rural areas



Probiotics are beneficial in promoting a "good" enteric microbiota in preterm neonates, preventing colonization by many pathogens including the various *Candida* spp (Neu et al, *Pediatr Res* 2010)

Lactobacilli are the probiotics that are effective in preventing *Candida* colonization in neonates

RCTs	Probiotic used	Primary outcome	Results in probiotic group	Results in placebo group	P-value
Manzoni et al, •Clin Infect Dis 2006 •JPGN 2007	Lactobacillus rhamnosus GG	<i>Candida</i> gut Colonization in <1500g neonates	23.1%	48.8%	0.01
Romeo et al, •J Perinatol 2011	Lactobacillus Reuterii	<i>Candida</i> gut Colonization in <2500g neonates	7.1%	22.9%	0.01
Romeo et al, •J Perinatol 2011	Lactobacillus rhamnosus GG	<i>Candida</i> gut Colonization in <2500g neonates	10.7%	22.9%	0.01

Possible "antibiotic-like" functions of *Lactobacillus* GG → a synergistic activity with Lactoferrin



BioMetals 17: 285-289, 2004.
© 2004 Kluwer Academic Publishers. Printed in the Netherlands.

Neonatal small bowel epithelia: enhancing anti-bacterial defense with lactoferrin and *Lactobacillus* GG

285

Michael P. Sherman^{1,*}, Stephen H. Bennett¹, Freda E.Y. Huang¹ & Camille Yu²

¹School of Medicine; University of California, Davis, California U.S.A.

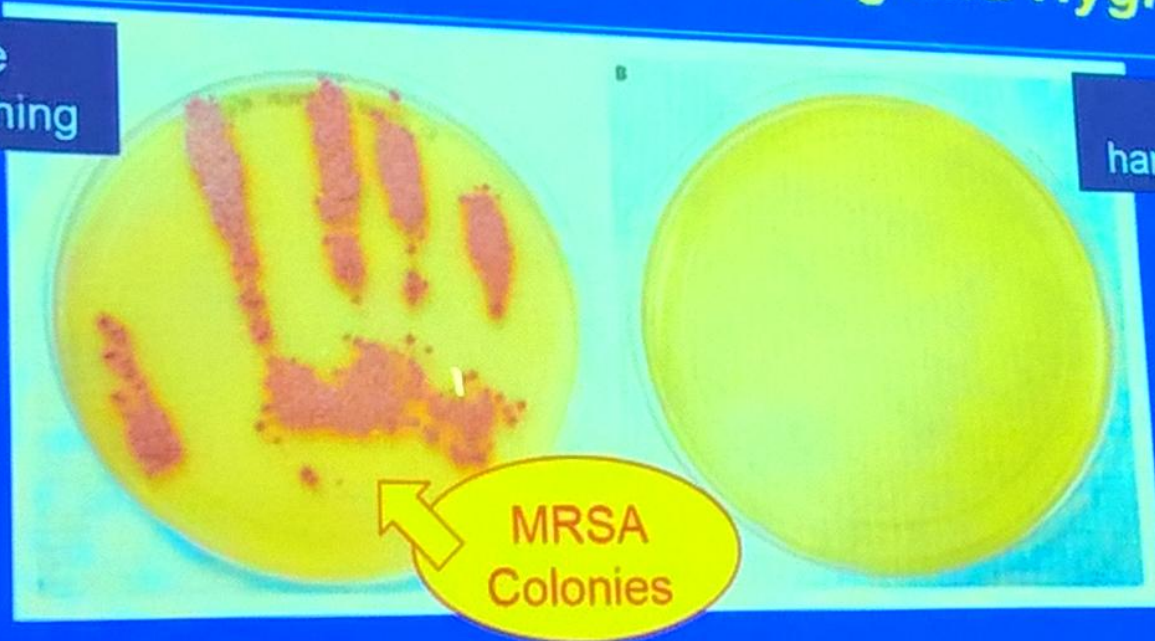
²School of Medicine; Washington University, St. Louis, Missouri U.S.A.

"In newborn rat pups, prophylactic therapy with Lactoferrin and *Lactobacillus* GG enhances defenses against invasive *E. coli* in the nascent small intestine".

"LF and LGG might be therapeutic agents for NEC and gut-related sepsis in preterm human infants".

PREVENTION OF INFECTIONS HELPS REDUCING UNNECESSARY ANTIBIOTIC EXPOSURE: the importance of Handwashing and Hygiene measures

Before
handwashing



After
handwashing

Donskey J et al
NEJM 2009 (360) e3

A 24-year-old man was found on routine surveillance cultures to have methicillin-resistant *Staphylococcus aureus* (MRSA) colonization of his anterior nares.

To assess the potential implications of the patient's MRSA carriage for infection control, an imprint of a health care worker's ungloved hand was obtained for culture after the worker had performed an abdominal examination of the patient, and repeated after the worker washed his hands.

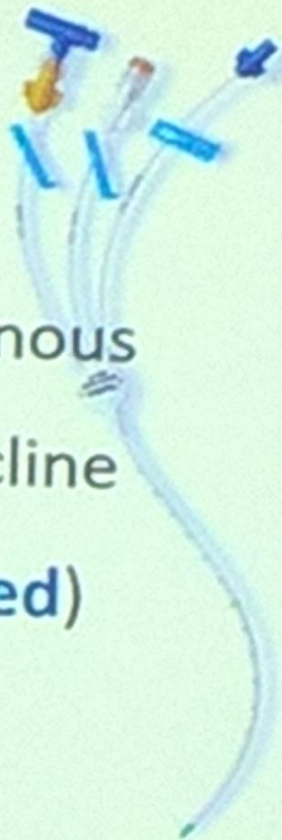
Inhibiting biofilm formation

- Prevent bacterial contact with CVC
 - Sterile insertion technique
 - Sterile CVC access
 - Antiseptic dressings
 - barrier
 - chlorhexidine impregnated
- Prevent bacterial adhesion to CVC
- Remove CVC as soon as possible

CATCH trial

Aim:

Head to head trial comparing **standard** central venous catheters (CVCs) with impregnated CVCs (minocycline and rifampicin **antibiotic coated** or **heparin bonded**)



Gilbert R et al. Impregnated central venous catheters for prevention of bloodstream infection in children (the CATCH trial): a randomised controlled trial. Lancet 2016;387:1732 - 1742





PREVenting infection using Antimicrobial
Impregnated Long lines

- P – in infants for whom placement of a 1Fr PICC line is planned
- I – does placement of an AM-PICC
- C – as compared to a standard PICC
- O – reduce bloodstream infection

Triangle of injury in sepsis



**Injury of cardiomyocytes and
endothelium**

Summary on pentoxifylline in the treatment of sepsis in neonates



- ❧ PTX when given as the adjunct therapy seems to be safe and beneficial in the treatment of sepsis in preterm infants.
- ❧ PTX should be introduced at the beginning of the therapy so as to prevent or treat the microcirculation disorders
- ❧ Recommended dose: infusion of 5 mg/kg/h continued for 6 or 12 hours is well tolerated and has no adverse effects even in the critically ill infants

2nd jENS

Congress of joint European
Neonatal Societies

58th ESPR Annual Meeting
7th International Congress of UENPS
3rd International Congress of EFCNI

Venice 2017

POWERED BY MCA

October 31st
November 4th

www.jenscongress.eu

Organising Institutions:



TENTH EDITION

Workbook in

PRACTICAL NEONATOLOGY

POLIN & YODER



7-8 листопада 2017, Київ



Richard A. Polin

Чи можуть діти з факторами ризику чи клінічними ознаками – не потребувати а/б ???

- Дитина >35 тижнів, без клініки, з факторами ризику (хоріоамніоніт) - ???
- Дитина з клінікою тяжкого захворювання (РДС, ТТН) та без факторів ризику - ???

Клінічна ситуація

- Жінка 22 років, I вагітність. У 37 тижнів - розрив НПО, через 26 год госпіталізовано у клініку. Підвищення температури тіла до 38С, лабораторні показники - без порушень. Запідозрено хоріоамніоніт. Призначено а/б (ампіцилін+гентаміцин) за 2 год до пологів. Пологи - епідуральна анестезія.
- Дитина народилась в легкими дихальними розладами;

Яка тактика ведення новонародженого???

Вибір лікувальної тактики

- А. Підтримуюча терапія, без а/б, лабораторні тести, культура крові
- В. Культура крові + а/б широкого спектру
- С. Загальний ан.крові, культура крові

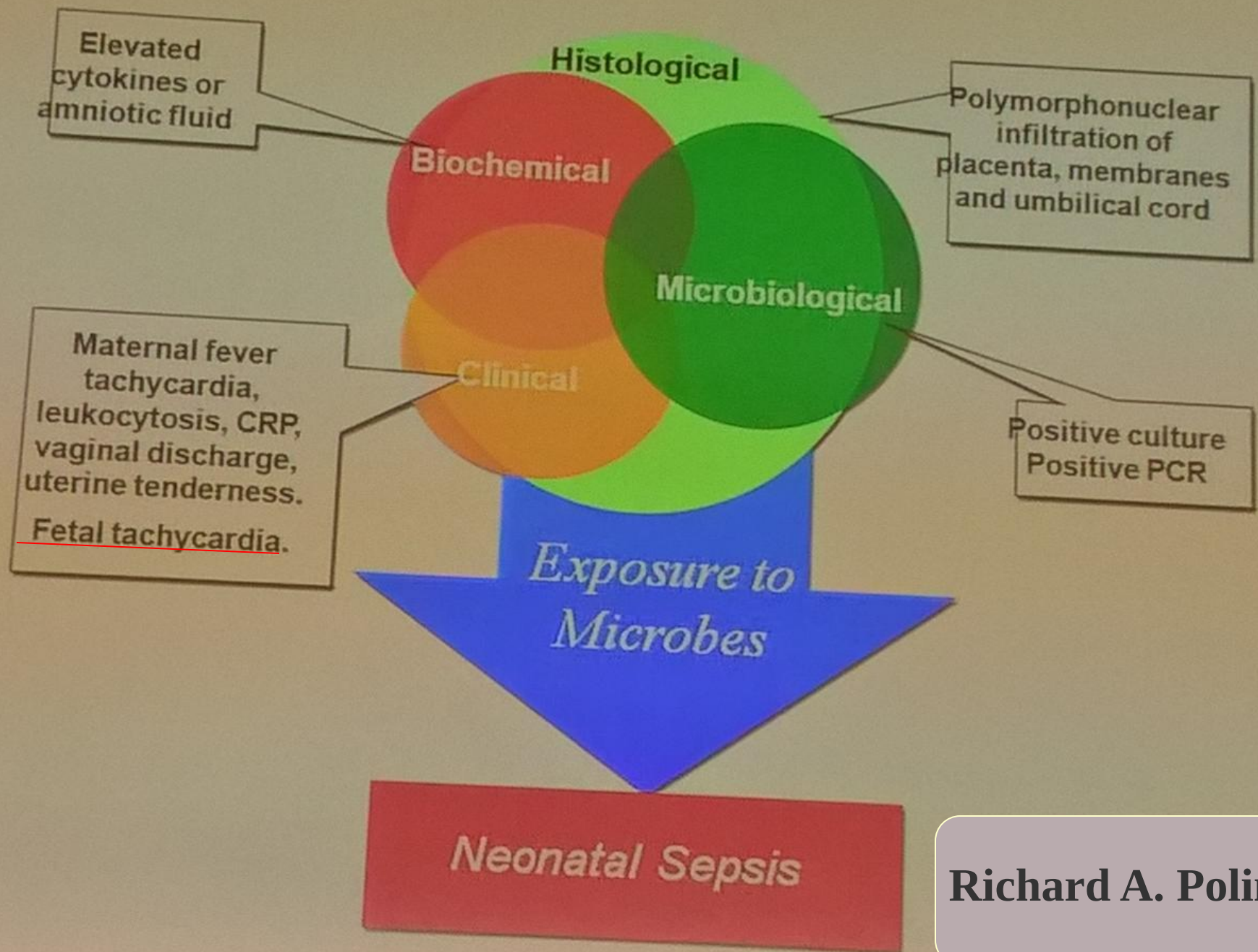
Клінічний хоріоамніоніт: діагностичні критерії

Presence of otherwise unexplained maternal fever (greater than or equal to 100.4°F, or 38.0°C) *plus* at least 2 of the following additional clinical findings:

- ★ Maternal tachycardia (> 100 bpm)
- ★ Fetal tachycardia (>160 bpm) 10 хв і більше
- ★ Elevated maternal white blood cell count (> 15,000 cells/m³)
- ★ Uterine tenderness
- ★ Foul smelling amniotic fluid

без ГКК

Mukhopadhyay et al Pediatrics 2014; Mukherjee et al AD-FNN 2014; Kiser et Pediatrics 2014



Richard A. Polin

Клінічна ситуація

- Дитина народилась в 37^{2/7} тижнів;
- Оц. Апгар 6/8 балів, дихальні розлади.
- NPSRAP з 21% киснем, швидко купувалися дихальні розлади – самостійне дихання

Яка тактика ведення новонародженого???

Probability of Neonatal Early-Onset Infection Based on Maternal Risk Factors for Infants ≥ 35 weeks gestation

★ Gestational age (weeks/days)	37 weeks 2 days
★ Temperature	38.0° C
★ ROM (Hours)	26 hours
★ GBS status (positive, negative, uncertain)	Positive
★ Maternal intrapartum treatment	Broad spectrum
★ Was LAP given 2.0-3.9 hours prior to delivery	Yes

Predicted probability(/1,000 live births) = 1.61

*Sepsis is much less likely in a well-appearing infant
With identical risk factors*

<i>Well</i>	Predicted probability(/ 1,000 live births) =	0,66
<i>Equivocal</i>	Predicted probability(/ 1,000 live births) =	7,98
<i>Clinical Illness</i>	Predicted probability(/ 1,000 live births) =	32,78

<http://www.dor.kaiser.org/external/DORExternal/research/InfectionProbabilityCalculator.aspx>

Escobar et al Pediatrics 133: 30-36, 2014

Achieving a Treatment Threshold for Early-Onset Sepsis



*Critically Ill
Symptomatic*



Treatment

Observe



No risk factors
(not critically ill)

*Diagnostic
testing*

*Asymptomatic
and Risk Factors*



Treatment



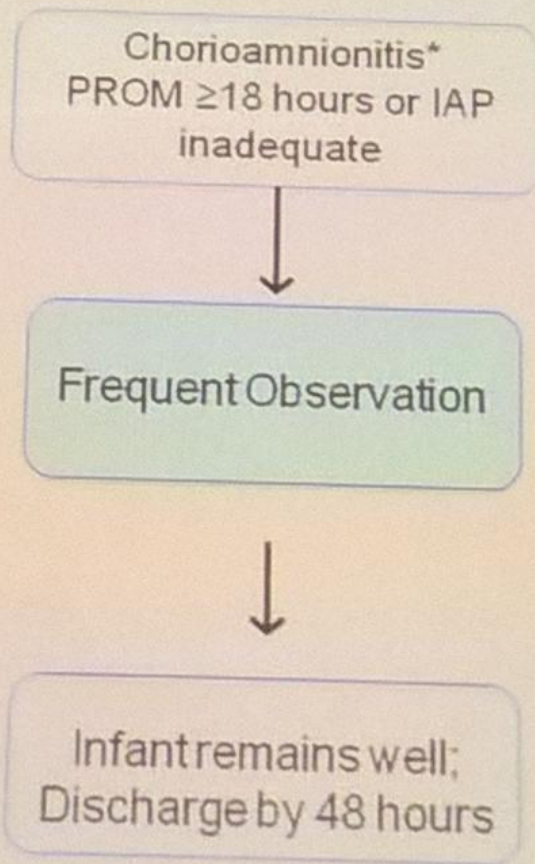
*Diagnostic
testing*



Observation

Evaluation of Asymptomatic Infants ≥ 35 Weeks Gestation with Risk Factors for Sepsis (including chorioamnionitis):

Risk Factors



Duration of Antimicrobial Therapy

- * Whenever possible, antibiotics should be stopped by 48 hours if the cultures are negative and the infant remains asymptomatic.
- * Antibiotics should be continued for 7 days in any critically ill infant
- * Consider automatic stop orders in infants with negative cultures.

Клінічна ситуація

- Культура крові – негативна
- Лабораторні показники – без відхилень
- Дитина отримувала лікування – 48 год!

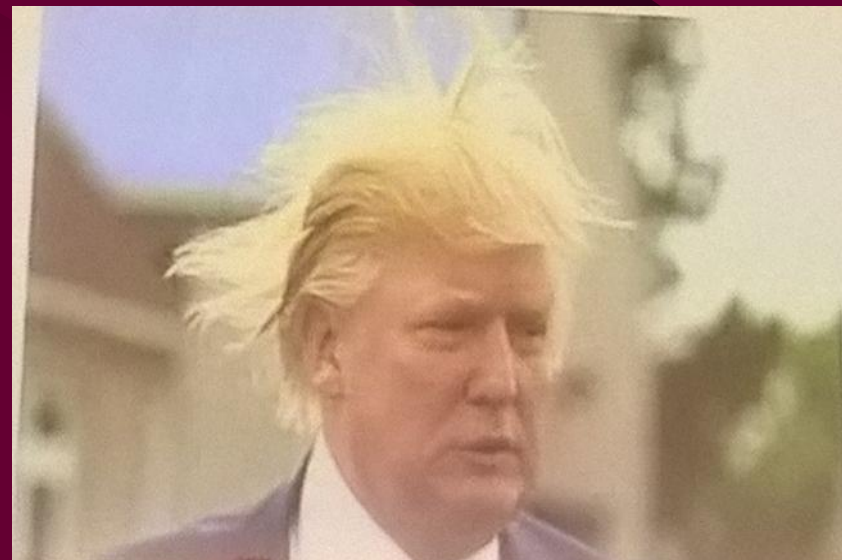
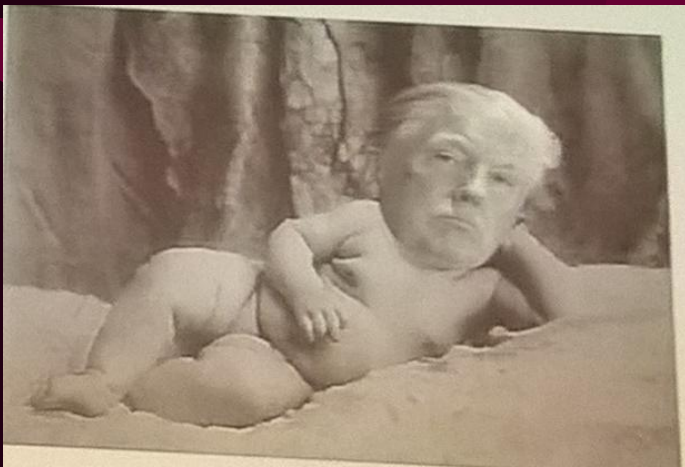
Катамнез дитини

???

Клінічна ситуація

- Культура крові – негативна
- Лабораторні показники – без відхилень
- Дитина отримувала лікування – 48 год!

**Дитина виросла – стала мільярдером, а
потім Президентом США!**









Andrew Ewer



**Cochrane
Library**

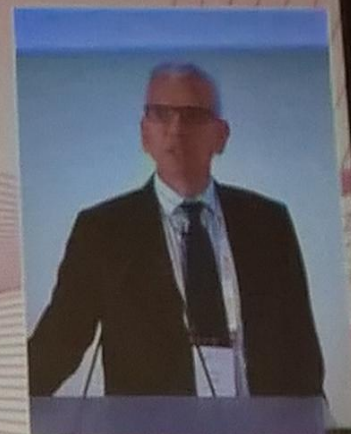
Cochrane Database of Systematic Reviews

Diagnostic accuracy of pulse oximetry screening for critical congenital heart defects (Review)

Plana MN, Zamora J, Suresh G, Fernandez-Pinero L, Thangaratinam S, Ewer AK

Submitted June 2017. Resubmitted Oct 2017

21 studies; 457 202 patients studied



20:17

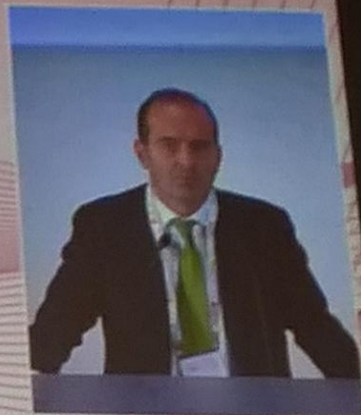
Practical aspects
of Pulse Oximetry Screening
for Critical Congenital Heart defects:
any hurdles for implementation?

Dr Paolo Manzoni, MD, PhD

Neonatology and NICU

S. Anna Hospital .

Torino, Italy



Let us take a look to the epidemiology and to the rationale of PO screening

- CCHD are the most common congenital malformations: 0,8-0,9 % ~ 50% of infant mortality (due to malformation)
- 10-30 % do not have diagnosis before necropsy
- **Prenatal diagnosis accuracy and availability vary widely : accuracy may range 15 - 50% according to centres (Ewer, 2012) .**

Let us take a look to the epidemiology and to the rationale of PO screening

The rationale of PO Screening :

- Hypoxaemia (low saturations) presents in the majority of CCHD, being frequently clinically undetectable, and that PO may detect babies with CCHD early, before they collapse
- Clinical diagnosis is not enough accurate (not visible cyanosis if $SpO_2 > 80-85\%$, clinical signs not always detected, very complex changes from fetal to normal circulation after birth)
- Detection through physical examination may be $< 50\%$
 - ✓ Auscultation – Many FP and FN
 - ✓ Palpation of Pulses – Depends on patency of PDA
 - ✓ Cyanosis – Difficult for HCP to detect

False positives: pros and cons

- ✓ Not negligible rates of False Positives with PO Screening → even better!
 - The ability of pulse oximetry screening to detect non-CCHD 'secondary conditions' is an added benefit, which may support the value of screening
- ✓ False positives are babies with low oxygen levels → No baby should have unexplained persistent hypoxaemia
- ✓ Examples of False Positives:
 - ✓ Pneumonia
 - ✓ Sepsis
 - ✓ PPHN
- ✓ Added benefits of detection of false positives:
 - ✓ Earlier and timely diagnosis of respiratory/infective cases
 - ✓ Increasing discharges within 24 hours
 - ✓ Less Echocardiography for murmurs to investigate

Cost-effectiveness – may it be a barrier to implementation of CCHD screening ?

PLUS:

- ✓ Average only 3.5 minutes to screen CCHD
- ✓ A number of non-cardiac hypoxemic diseases can be detected through CCHD screening
- ✓ It may be paired with other screening routinary activities (Transcutaneous bilirubinometry, acoustic otoemission, metabolic diseases, etc.)
- ✓ It may save unnecessary EchoCardio assessments for murmurs

WEAKNESSES:

- ✓ Need for training sessions for the Staff
- ✓ Need for sensors

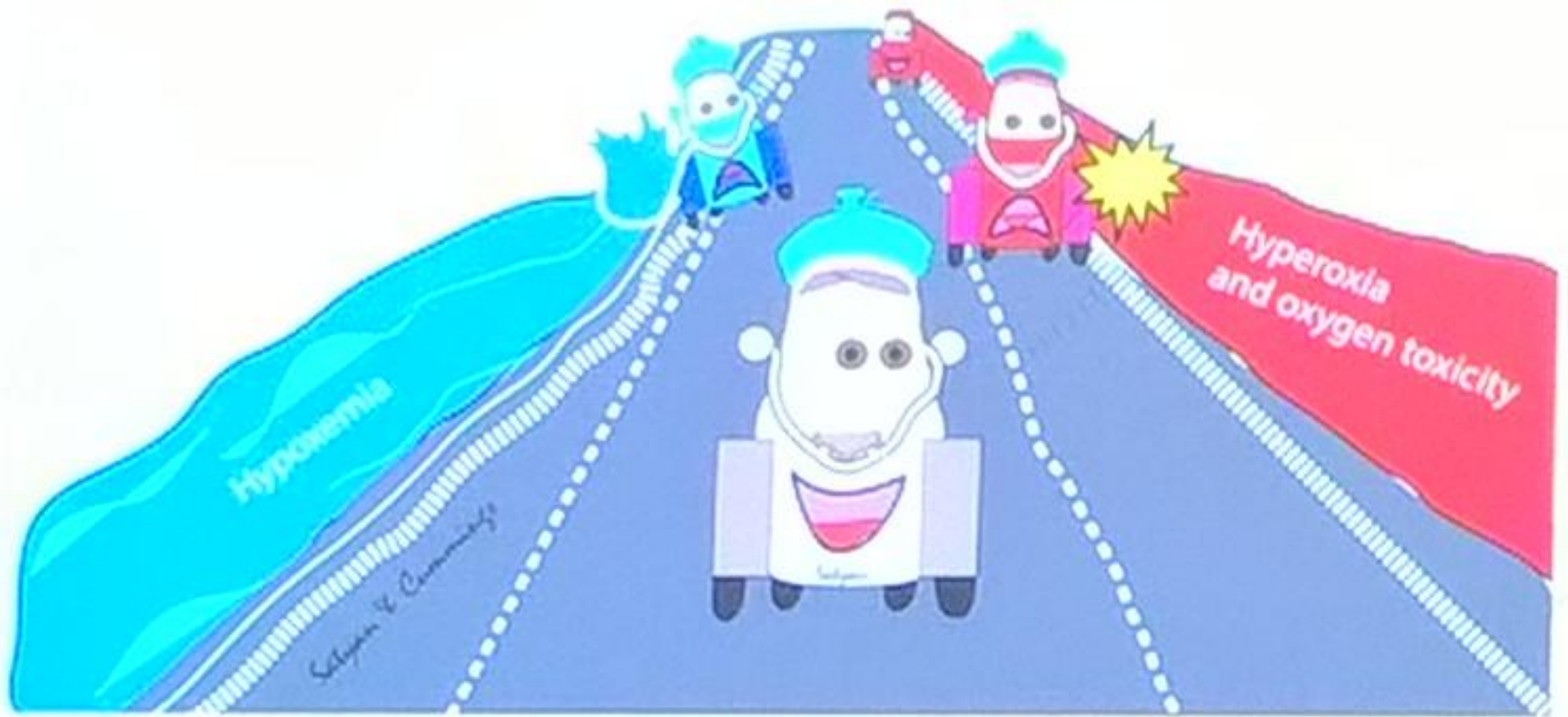
Although CCHD screening looks intuitively cost-effective, health economic analyses are scarce, and further evidence of the favourable cost-benefit profile of CCHD screening is needed.

Early or late screening (<24 or >24 hrs)

- Most babies have 'normal' sats within 2 hr
- FP lower if PO screening >24 hr
0.05 vs 0.5%

Panel: Recommendations from The European Pulse Oximetry Screening Workgroup

- Pulse oximetry screening (POS) for critical congenital heart defects should be recommended for all European countries
- POS should be done with new-generation equipment that is motion tolerant
- Screening should occur after 6 h of life or before discharge from the birthing centre (preferably within 24 h after birth)
- Screening should be done in two extremities: the right hand and either foot
- Each country should consider the advantages and disadvantages of the two available protocols⁴⁵ and use that which best suits their population



Alarm - lower limit

Target

Alarm - upper limit

Summary: High or Low SpO₂ < 28 w GA

beyond the delivery room

Oxygen targets 91-95% increase ROP in need of therapy but not severe vision injury

Oxygen targets 85-89% increase mortality and NEC

Long term follow-up: no differences between the arms regarding Death/disability, blindness, hearing loss

European Guidelines

- In preterm babies receiving oxygen, the saturation target should be between 90-94% (B2).
- To achieve this, suggested alarm limits should be 89% and 95% (D2)
- Sweet D et al European RDS Guidelines 2016



Co warto robić, gdy już „nic nie można zrobić”?

Postępowanie paliatywne po urodzeniu dziecka z nieuleczalną wadą rozwojową

Agnieszka Jalowska
Katedra i Klinika Neonatologii
Uniwersytecki Szpital Kliniczny we Wrocławiu



1. Wada jednoznacznie letalna

- ▶ z. genetyczne:, np. abberacje chromosomowe: trisomia 18 (Z. Edwardsa), trisomia 13 (Z. Pataua), triploida...
- ▶ aencefalia, holoprosencefalia,
- ▶ brak nerek,
- ▶ dysplazja tanatoforyczna,
- ▶ letalne wady serca izolowane lub w zespołach genetycznych...

2. Wada o potencjalnie niepomyślnym rokowaniu bez pełnej diagnostyki prenatalnej

- ▶ np. wodogłowie/wodomózgowie, zespół wad bez oznaczenia karyotypu prenatalnie, itp.

**INTERDYSCYPLINARNY
ZESPOŁ PERINATALNY !!!**

NASI PACJENCI

Co możemy im zaoferować: - *medyczna opieka*
- *psychologiczna opieka*
- *duchowa opieka*
- *socjalna/dokumentacyjna opieka*

OPIEKA MEDYCZNA

1. Ustalenie możliwości odstąpienia od uporczywej terapii/terapii daremnej po urodzeniu się dziecka.

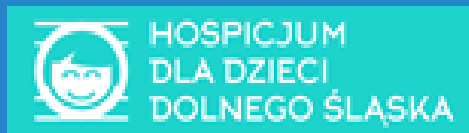
OPIEKA MEDYCZNA

2. Łagodzenie objawów:

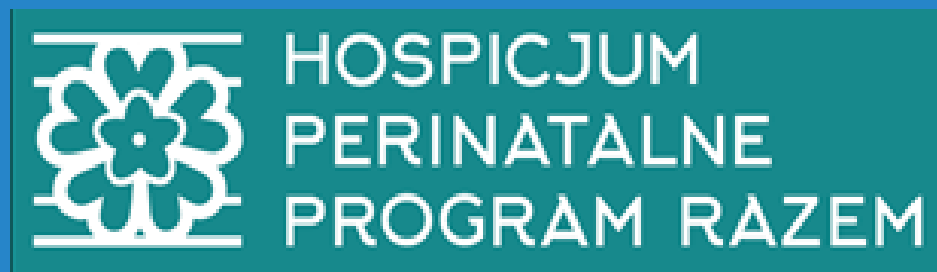
- bólu (morfina p.o, fentanyl)
- duszności (morfina p.o, tlen, ...)
- objawów neurologicznych (np. drgawki: fenobarbital, midazolam)
- gorączka (paracetamol)

3. Komfort cieplny (skóra do skóry)

4. Karmienie (pierś, sonda, smoczek)



PROGRAM „RAZEM”



DAR CZASU

Dzięki wczesnej diagnozie rodzice mogą świadomie lepiej wykorzystać **czas ciąży** – często jedyne **chwile** **wspólnego życia z dzieckiem**.

komunikacja prenatalna – słuchanie muzyki,
rozmawianie z dzieckiem, zachęcenie
rodzeństwa do „przebywania” z dzieckiem,
przeżywanie wspólnie uroczystości
zachęcenie rodziny do nadania imienia dziecku
już w okresie prenatalnym;



«Чи на правду це важливо?»



Dziewczynka, 38 tygodni,
30 minut

„Pani doktor, była taka śliczna, a ja mogąc ją tulić, byłam szczęśliwa”

„Mąż przez pół godziny nosił ją na rękach, tulił i śpiewał...”

„Córeczko, żyłaś krótko,
ale w wielkiej miłości...”

Chłopiec umarł w wieku 35 tygodni przed narodzeniem. .



„[...] urodziłam i przytuliłam wczoraj mojego synka.
Wspaniałe uczucie, szkoda tylko, że tak krótko. Jestem
szczęśliwa, że mogłam zostać Jego mamą”

Głos rodziców

Not important «**How many good things have you done in your life?**», but very importantly
«**How much LOVE did you put into what you did?**»

Keep close
to Jesus
He loves you
Let us pray
God bless you
Lu Teresa me



“God will NOT ask, How many good things have you done in your life?, He will ask, How much LOVE did you put into what you did?”

Keep close
to Jesus
He loves you
Let us pray
God bless you
Lu Teresa M.C.



"If we want a love message to be heard, it has got to be sent out. To keep a lamp burning, we have to keep putting oil in it."

Keep close
to Jesus
He loves you
Let us pray
God bless you
Lu Teresa M.C.

