Sistema Socio Sanitario

Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ASST Pavia

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UNIVERSITÀ DI PAVIA

GRAND ROUNDS CLINICI DEL MERCOLEDÌ

con il Policlinico San Matteo

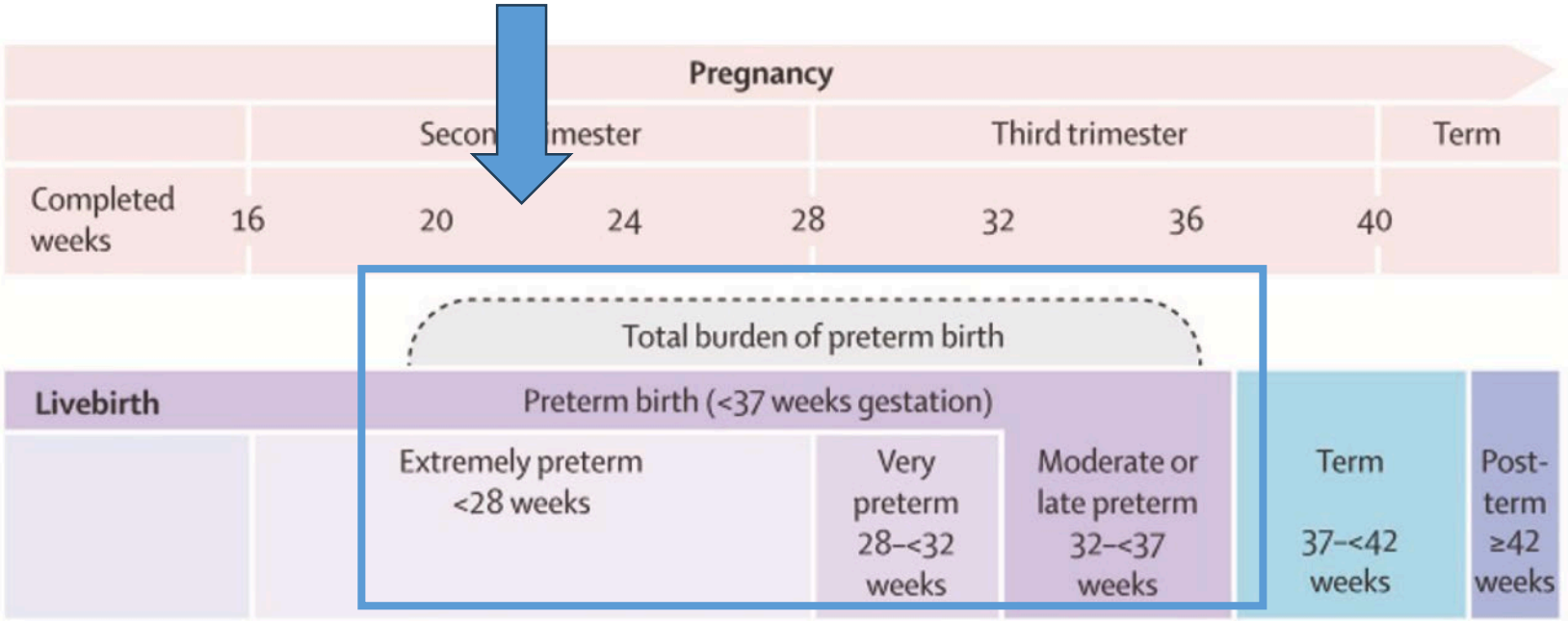
Aula Magna "C. Golgi" & WEBINAR

Rischi e speranze della prematurità: complicanze, interventi e prospettive future

Dott. Stefano Ghirardello
Terapia Intensiva Neonatale e Neonatologia

I numeri della prematurità

La prematurità è definita come la nascita **prima della 37° settimana** di età gestazionale



- extremely preterm (<28 settimane di età gestazionale)
- very preterm (28-32 settimane di età gestazionale)
- moderate to late preterm (32-36 settimane di età gestazionale)

Platt MJ. Outcomes in preterm infants. Public Health. 2014
Blencowe *et al*. *Reproductive Health* 2013

I numeri della prematurità

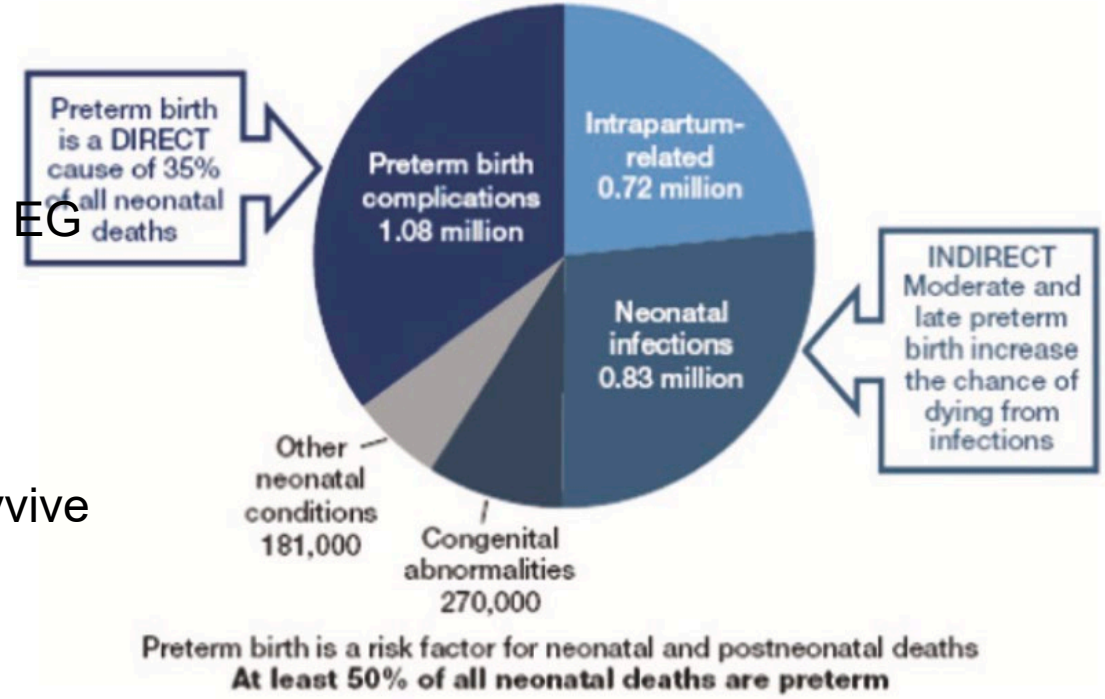
La prematurità è la **causa più frequente di morte in epoca neonatale** e la seconda causa di morte sotto i 5 anni.

Nel mondo, **la prevalenza della prematurità è di circa il 10%**

L'85% delle nascite premature avviene dopo le 31 settimane di EG

Nei paesi ad alto income, circa il 50% dei nati a 24 settimane sopravvive

Nei paesi ad alto income, il 90% dei nati a 28 settimane sopravvive

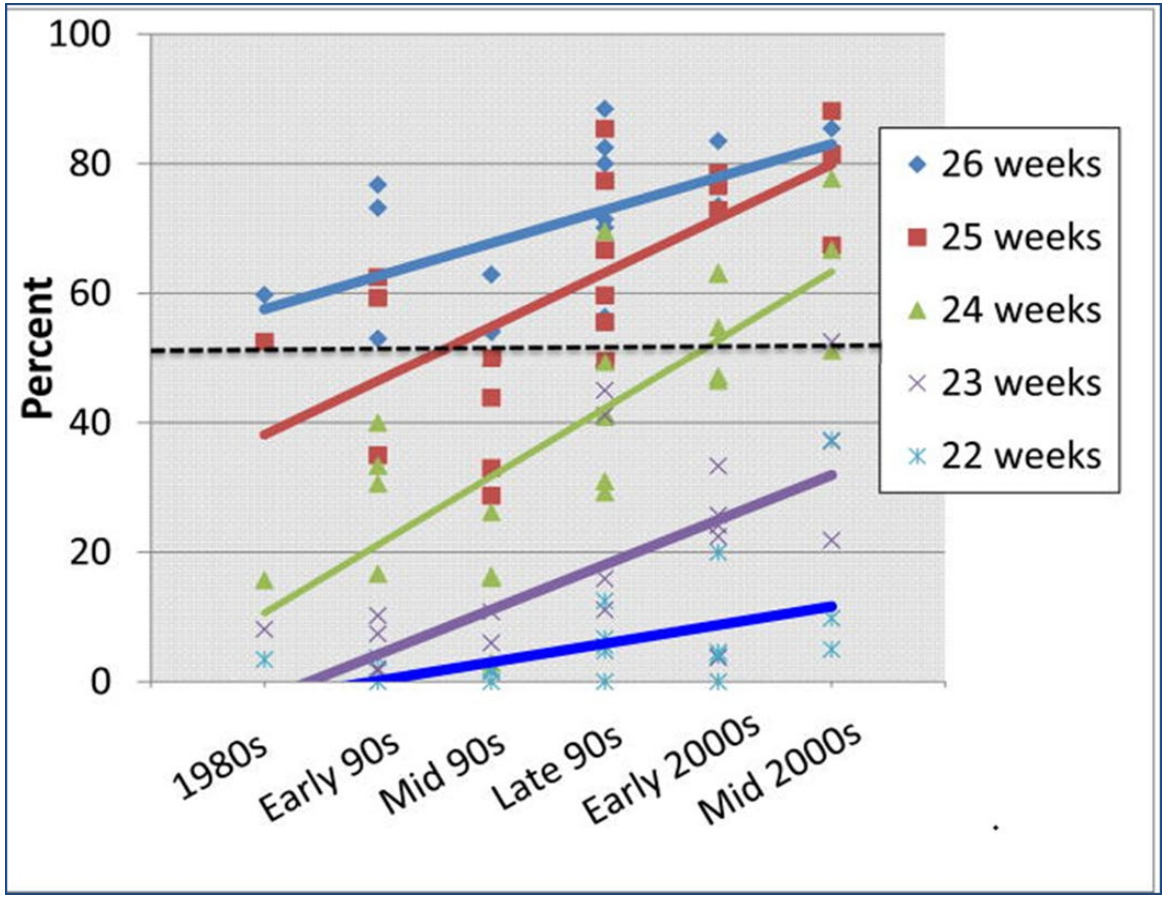


Platt MJ. Outcomes in preterm infants. Public Health. 2014
Blencowe *et al*. *Reproductive Health* 2013

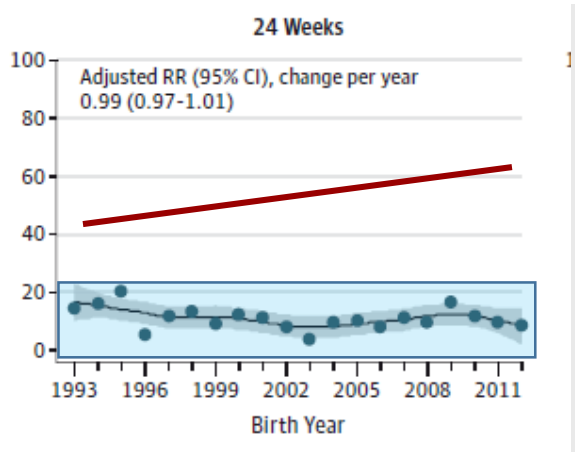
Non solo neonati prematuri

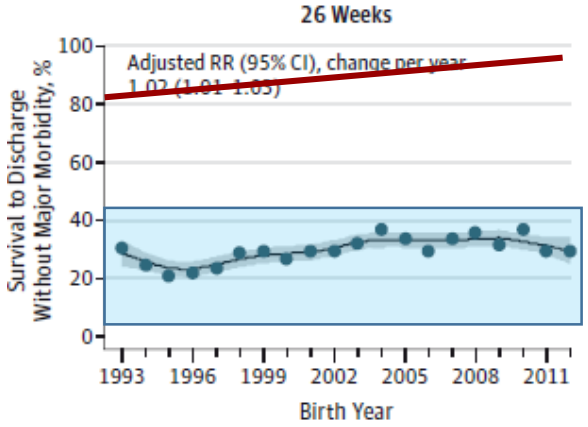
	BIRTH WEIGHT in grams	Corresponding Gestational Age (approx.)	Incidence in ITA (estimat.)
TERM neonate	>2500 g	37 wks g.a.	93%
LBW (low birth weight)	>1500 <2500 g	32+0 – 37+0 wks g.a.	5.5%
VLBW (very low birth weight)	>1000 <1500 g	29+0 -32+0 wks g.a.	1.0%
ELBW (extremely low birth weight)	<1000 g	23+0 – 28+0 wks g.a.	0.5%

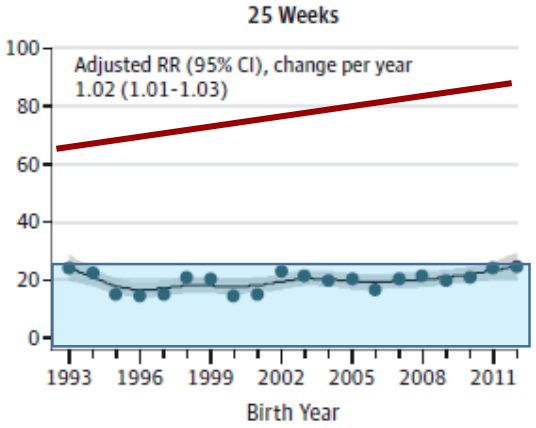
Sopravvivenza negli anni

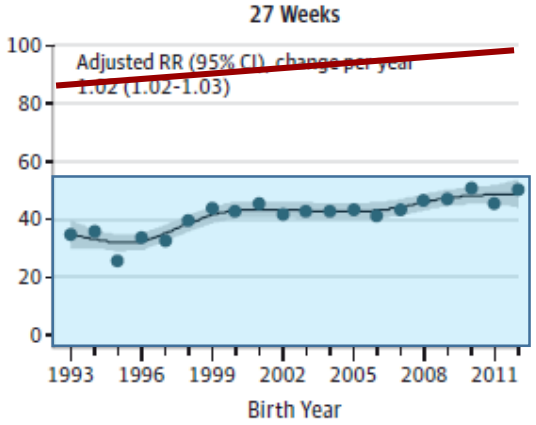


Come si sopravvive?









Comorbidità ed outcomes a lungo termine

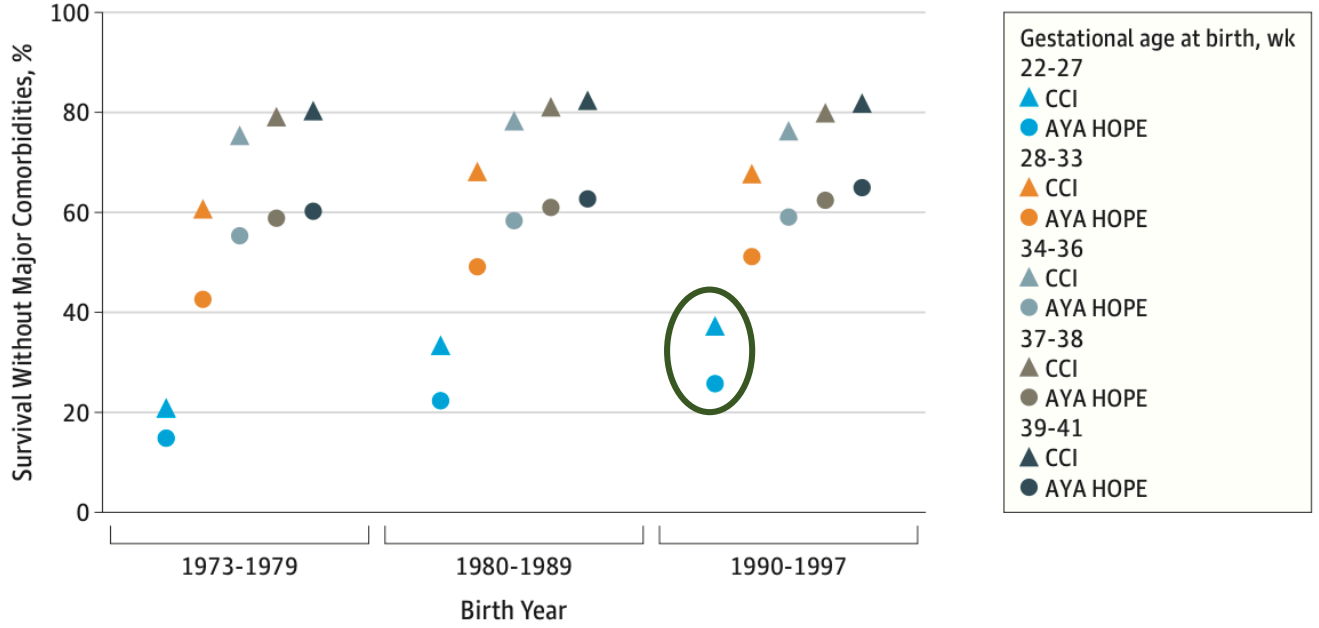
Key Points

Question What is the prevalence of survival without major comorbidities in adulthood among persons born prematurely?

Findings In this population-based cohort study of more than 2.5 million persons born in Sweden from 1973 to 1997, 54.6% of those born preterm (gestational age <37 weeks) and 22.3% of those born extremely preterm (22-27 weeks) were alive with no major comorbidities at ages 18 to 43 years, compared with 63.0% of those born full-term. The prevalences were statistically significantly lower in those born at earlier gestational ages vs full-term.

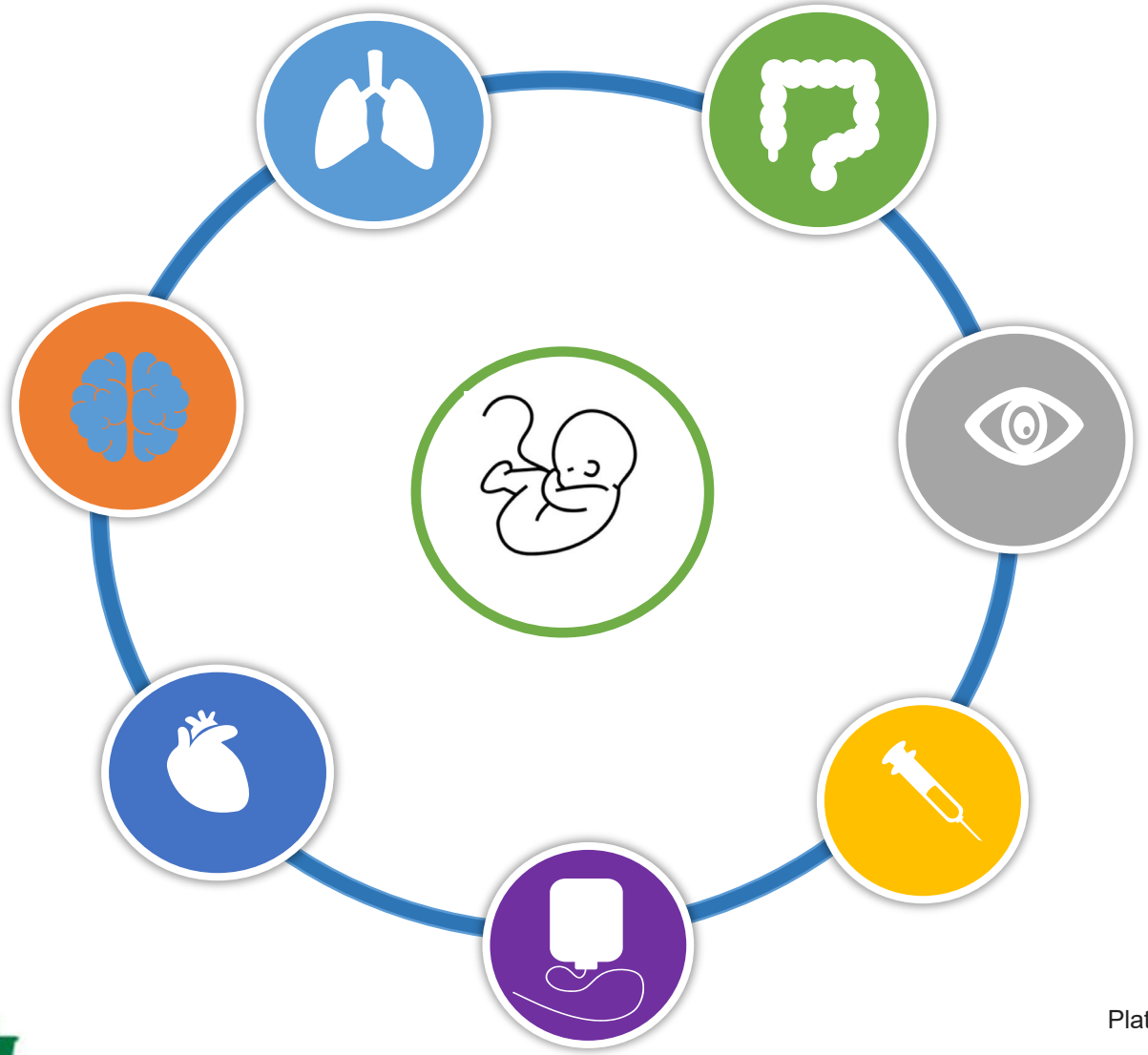
Meaning Among Swedish persons born prematurely, a large percentage survived into adulthood and had no major comorbidities.

Figure. Prevalence of Survival Without Major Comorbidities



Crump et al, *JAMA* 2019

Comorbidità ed outcomes a lungo termine



Platt MJ. Outcomes in preterm infants. Public Health. 2014

Gli adulti nati pretermine

Preterm birth and the risk of chronic disease multimorbidity in adolescence and early adulthood: A population-based cohort study

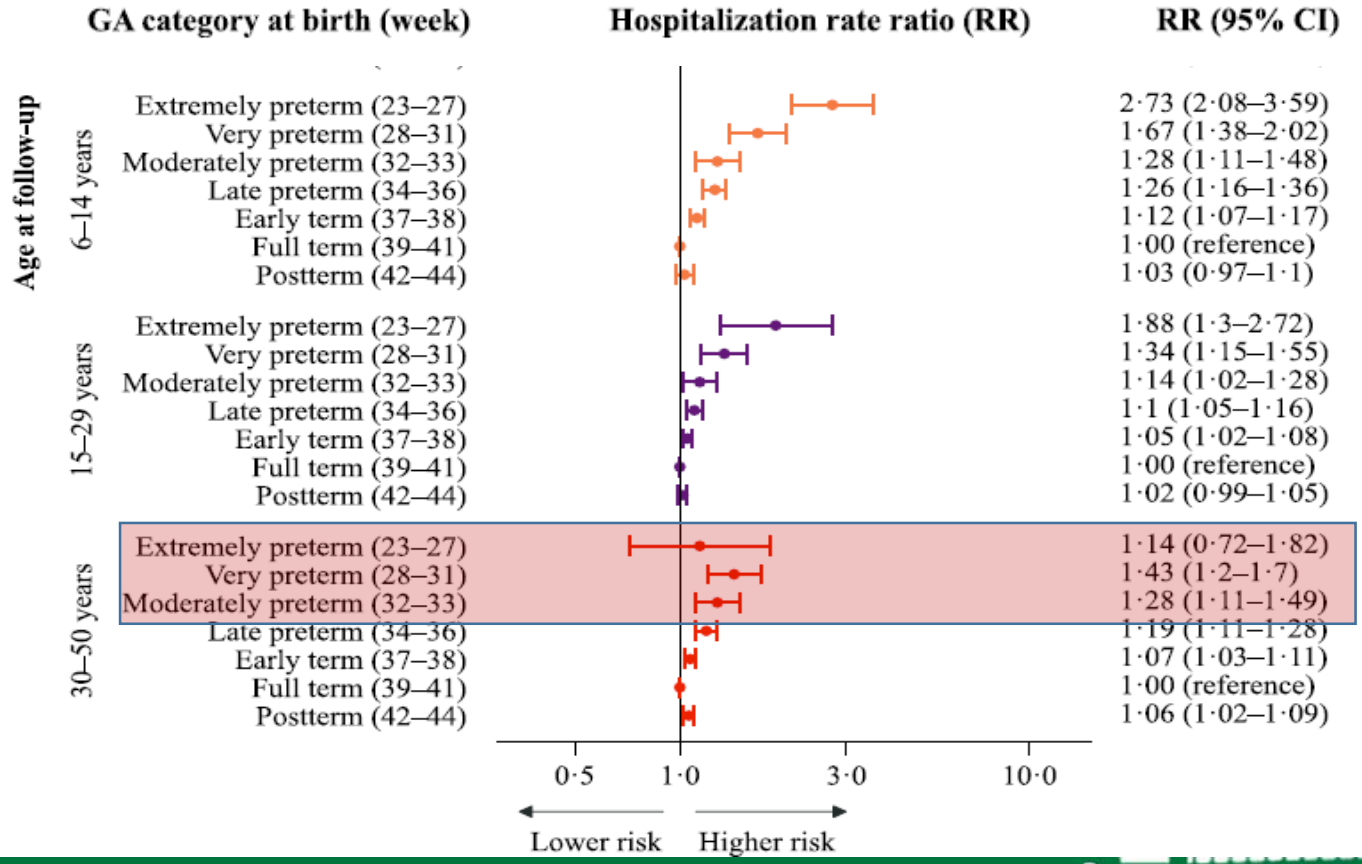
PLOS ONE 2021

Our findings, based on nationwide register data in Finland, suggest that compared to individuals born full-term, preterm born individuals have ~1.5- to 7-fold increased risks of chronic disease multimorbidity in adolescence and 1.2- to 3-fold increased risk of multimorbidity in early adulthood, with the estimated risks increasing in a dose-response manner with increasing prematurity. The risk patterns were broadly similar in males and females. There was also some

Gli adulti nati pretermine

Gestational age at birth and hospitalisations for infections among individuals aged 0–50 years in Norway: a longitudinal, register-based, cohort study

eClinicalMedicine
2023;62: 102108



Gli adulti nati pretermine

Preterm or early term birth and long-term risk of asthma into midadulthood: a national cohort and cosibling study

Crump C, *et al*. *Thorax* 2023;

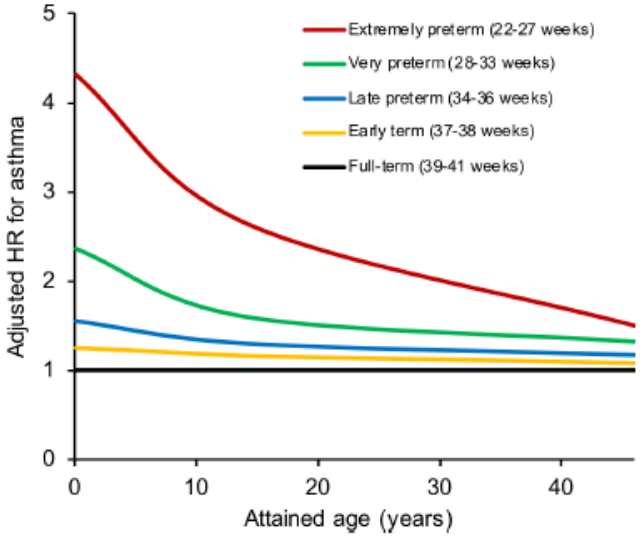
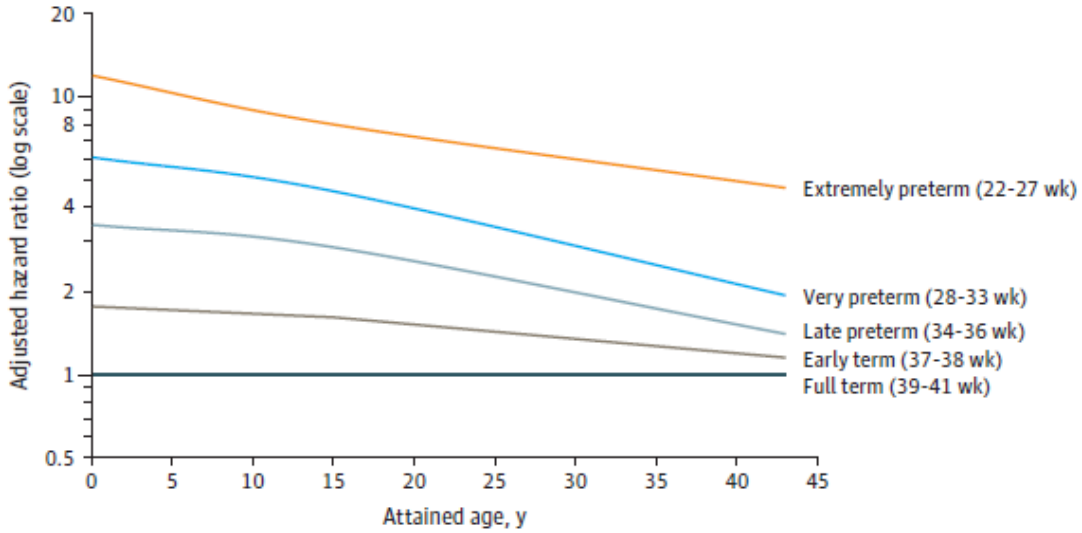


Figure 1 Adjusted HRs for asthma by gestational age at birth compared with full-term birth, Sweden, 1973–2018.

JAMA Pediatrics | Original Investigation

Association of Preterm Birth With Long-term Risk of Heart Failure Into Adulthood

Figure 1. Adjusted Hazard Ratios for Heart Failure by Gestational Age at Birth Compared with Full-term Birth, Sweden, 1973 Through 2015



Gli adulti nati pretermine

Stroke Risks in Adult Survivors of Preterm Birth

National Cohort and Cosibling Study

Stroke. 2021;

Table 3. Associations Between Gestational Age at Birth (1973–1994) and Risk of Hemorrhagic or Ischemic Stroke (1991–2015), Sweden

			Unadjusted	Adjusted*	
	Cases	Rate†	HR (95% CI)	HR (95% CI)	*P* value
Hemorrhagic stroke					
Preterm (<37 wk)	156	12.1	1.20 (1.02–1.42)	1.15 (0.97–1.35)	0.10
Early preterm (<34 wk)	40	15.0	1.51 (1.10–2.06)	1.42 (1.04–1.94)	0.03
Late preterm (34–36 wk)	116	11.3	1.13 (0.93–1.36)	1.08 (0.89–1.30)	0.44
Early term (37–38 wk)	469	10.5	1.05 (0.95–1.17)	1.02 (0.92–1.13)	0.73
Full-term (39–41 wk)	1199	10.2	Reference	Reference	
Ischemic stroke					
Preterm (<37 wk)	104	8.0	1.35 (1.11–1.66)	1.31 (1.07–1.60)	0.009
Early preterm (<34 wk)	22	8.2	1.40 (0.92–2.14)	1.33 (0.87–2.03)	0.18
Late preterm (34–36 wk)	82	8.0	1.34 (1.07–1.68)	1.30 (1.04–1.63)	0.02
Early term (37–38 wk)	271	6.0	1.04 (0.91–1.19)	1.02 (0.89–1.16)	0.78
Full-term (39–41 wk)	1180	6.1	Reference	Reference	
Post-term (≥42 wk)	174	5.9	0.89 (0.76–1.04)	0.90 (0.76–1.05)	0.18

Gli adulti nati pretermine

Preterm birth and risk of chronic kidney disease from childhood into mid-adulthood: national cohort study

Casey Crump,[1] Jan Sundquist,[2] Marilyn A Winkleby,[3] Kristina Sundquist[2]

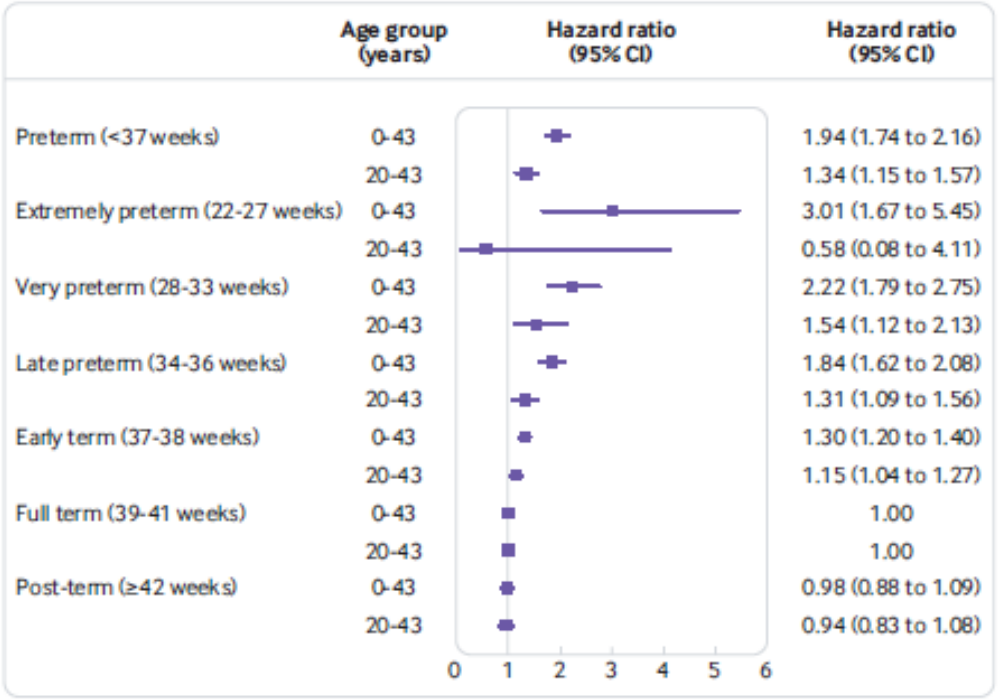
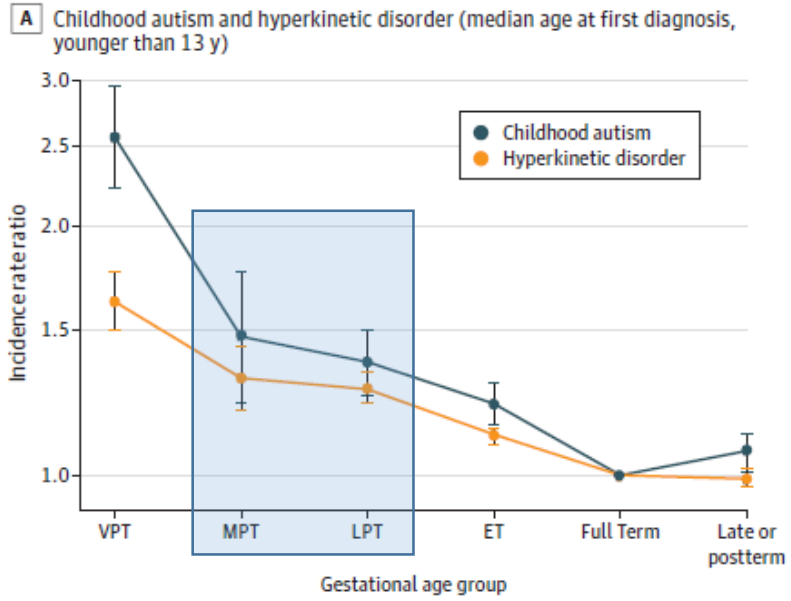


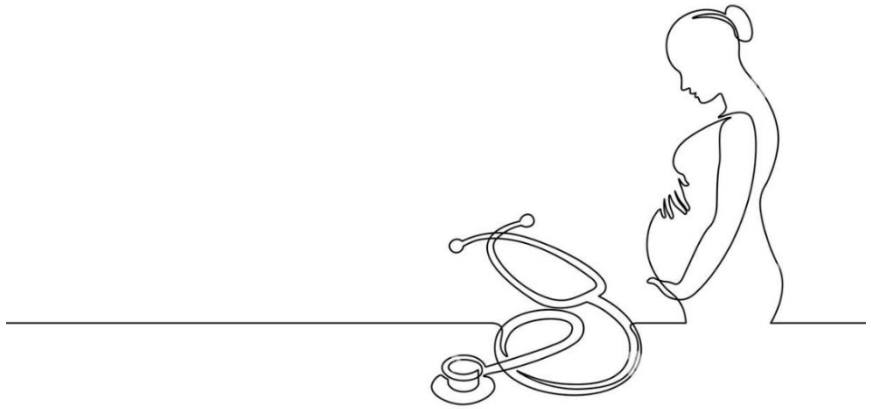
Fig 2 | Adjusted hazard ratios for chronic kidney disease at ages 0-43 and 20-43 years by gestational age at birth compared with full term birth, Sweden, 1973-2015. Whiskers are 95% confidence intervals

Preterm or Early Term Birth and Risk of Autism



Un caso clinico

- **N.M., maschio, EG 24 settimane + 1 giorno, PN 880gr**
- **Outborn:** H.di Lodi, trasporto mediante STEN, h 4:00



Anamnesi ostetrica e peripartum:

- Ipotiroidismo in terapia, no diabete, no pre-eclampsia
- IVU febbrili ricorrenti (UK positive per GBS e E. Coli)
- Travaglio precipitoso inarrestabile, sospetta corionamniosite
- Tipo di parto: eutocico
- Profilassi corticosteroidea: incompleta
- Profilassi antibiotica intrapartum: incompleta
- Solfato di magnesio: non somministrato

Cosa abbiamo imparato: *prevenzione*

Profilassi corticosteroidea: riduzione del rischio di RDS del 30-50% nei pretermine < 34 settimane di EG

Profilassi antibiotica intrapartum: riduzione del rischio di RDS del 40-60% nei pretermine < 34 settimane di EG

Solfato di magnesio: neuroprotettivo, riduzione del rischio di paralisi cerebrale (30-40%, EG < 30 settimane), miglioramento dell'outcome neurologico a lungo termine intellettivo e motorio

Anamnesi ostetrica e peripartum:

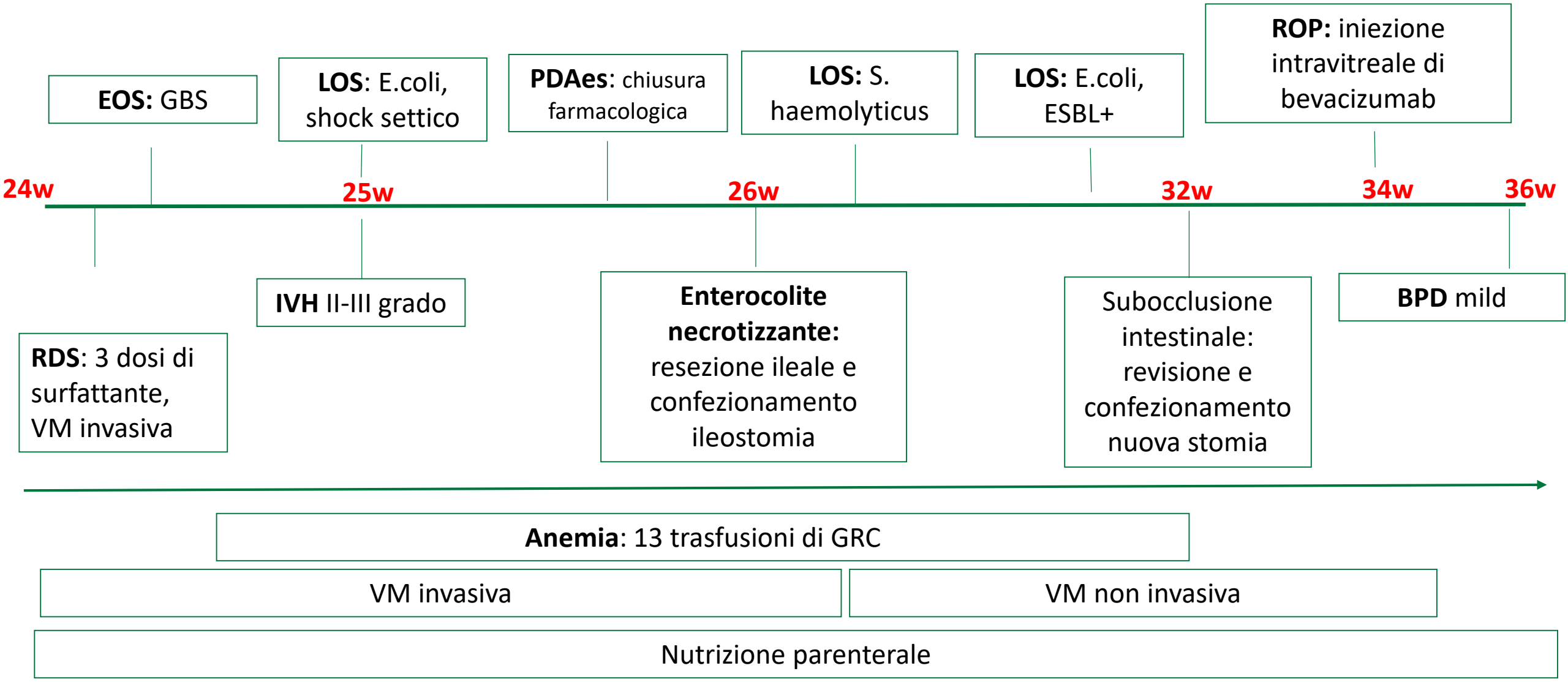
- Ipotiroidismo in terapia, no diabete, no pre-eclampsia
- **IVU febbrili ricorrenti (UK positive per GBS e E. Coli)**
- Travaglio precipitoso inarrestabile, sospetta corionamniosite
- Tipo di parto: eutocico
- Profilassi corticosteroidea: **incompleta**
- Profilassi antibiotica intrapartum: **incompleta**
- Solfato di magnesio: **non somministrato**

Sala Parto

- DCC ✖
- Indice di Apgar: 1’ 1; 5’5
- IPPV, intubazione, massaggio cardiaco
- 1° dose di surfattante endotracheale 200mg/kg

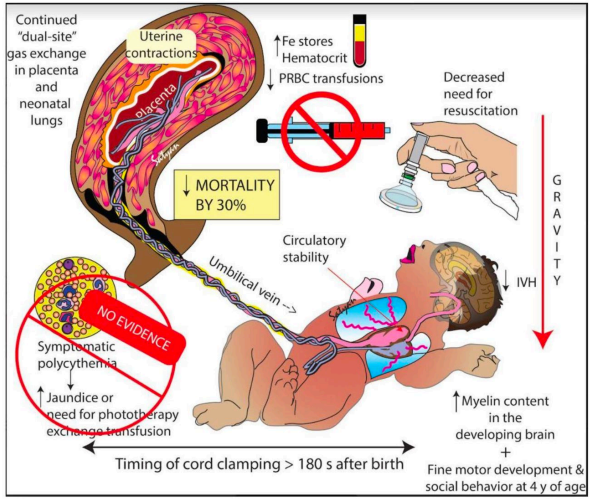
Trasferimento mediante STEN

Decorso Clinico



Cosa abbiamo imparato: *Ritardato clampaggio*

Nella fase di transizione feto-neonatale, il ritardato clampaggio del cordone ombelicale si è dimostrato **aumentare la stabilità cardiocircolatoria e ridurre la mortalità neonatale intraospedaliera.**



Un neonato **a termine** che esegue il ritardato clampaggio del cordone ombelicale riceve circa **30 ml/kg** di volume ematico trasfusionale

Un neonato prematuro di EG 24-32 settimane con il ritardato clampaggio riceve un volume ematico medio di circa **20ml/kg in più rispetto al** clampaggio immediato

Rabe H et al. What does the evidence tell us? Revisiting optimal cord management at the time of birth. Eur J Pediatr. 2022.

Cosa abbiamo imparato: *Ritardato clampaggio*

Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis

Michael Fogarty; David A. Osborn; Lisa Askie; Anna Lene Seidler; Kylie Hunter; Kei Lui; John Simes; William Tarnow-Mordi

JANUARY 2018 American Journal of Obstetrics & Gynecology

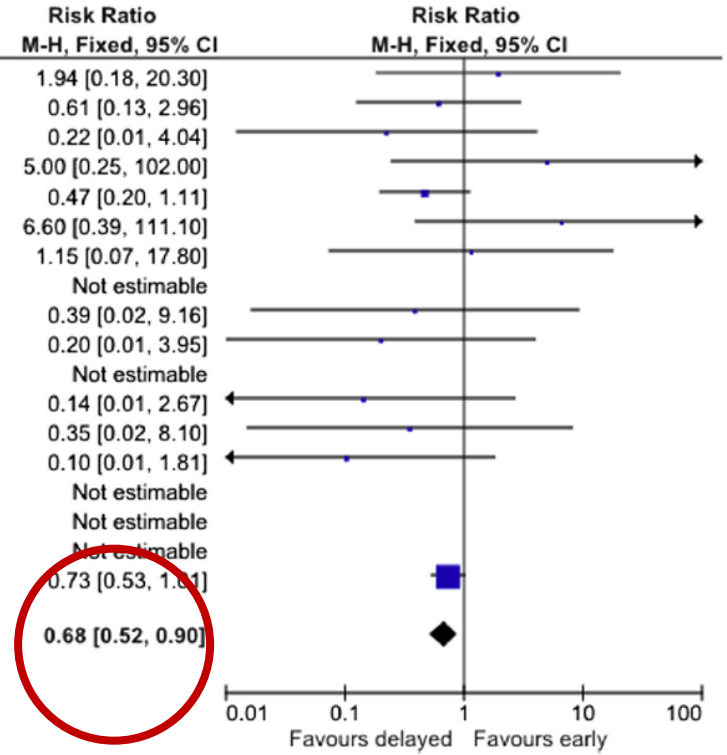
2834 neonati DCC vs ICC infants <37wks EG

Neonati < 28 settimane:
HIGH QUALITY of EVIDENCE: ↓ Mortalità 30%

FIGURE 3
Meta-analyses showing effect of delayed clamping on mortality

Study or Subgroup	Delayed Events	Delayed Total	Early Events	Early Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Armanian 2017	2	32	1	31	0.9%	1.94 [0.18, 20.30]
Backes 2016	2	18	4	22	3.1%	0.61 [0.13, 2.96]
Baenziger 2007	0	15	3	24	2.3%	0.22 [0.01, 4.04]
Datta 2017	2	60	0	60	0.4%	5.00 [0.25, 102.00]
Duley 2016	7	135	15	135	12.8%	0.47 [0.20, 1.11]
Hofmeyr 1988	5	24	0	14	0.5%	6.60 [0.39, 111.10]
Hofmeyr 1993	1	40	1	46	0.8%	1.15 [0.07, 17.80]
Kinmond 1992	0	17	0	19		Not estimable
Kugelman 2007	0	30	1	35	1.2%	0.39 [0.02, 9.16]
McDonnell 1997	0	23	2	23	2.1%	0.20 [0.01, 3.95]
Mercer 2003	0	16	0	16		Not estimable
Mercer 2006	0	36	3	36	3.0%	0.14 [0.01, 2.67]
Rabe 2000	0	19	1	20	1.2%	0.35 [0.02, 8.10]
Ranjit 2015	0	44	5	50	4.4%	0.10 [0.01, 1.81]
Strauss 2003	0	45	0	60		Not estimable
Tanprasertkul 2016	0	42	0	44		Not estimable
Ultee 2008	0	18	0	19		Not estimable
WTM APTS 2017	58	784	79	782	67.3%	0.73 [0.53, 1.01]
Total (95% CI)		**1398**		**1436**	**100.0%**	**0.68 [0.52, 0.90]**
Total events	77		115			

Heterogeneity: Chi² = 10.28, df = 12 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)



Meta-analyses showing effect of delayed vs early cord clamping on risk ratio for hospital mortality in 18 trials in 2834 infants <37 weeks' gestation (top) and 3 trials in 996 infants ≤28 weeks' gestation (bottom).

Cosa abbiamo imparato: *Ritardato clampaggio*

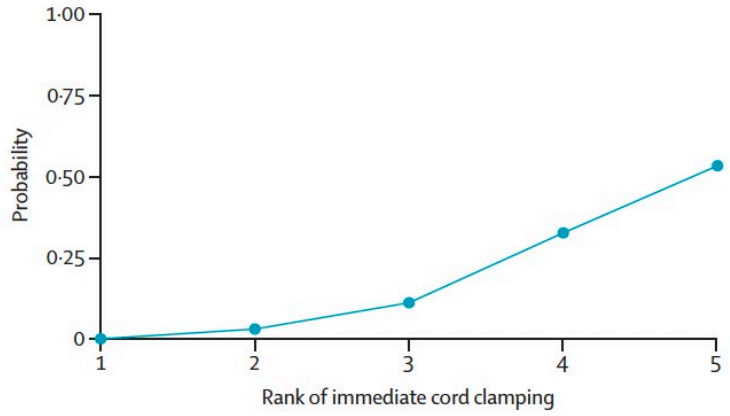
Short, medium, and long deferral of umbilical cord clamping compared with umbilical cord milking and immediate clamping at preterm birth: a systematic review and network meta-analysis with individual participant data

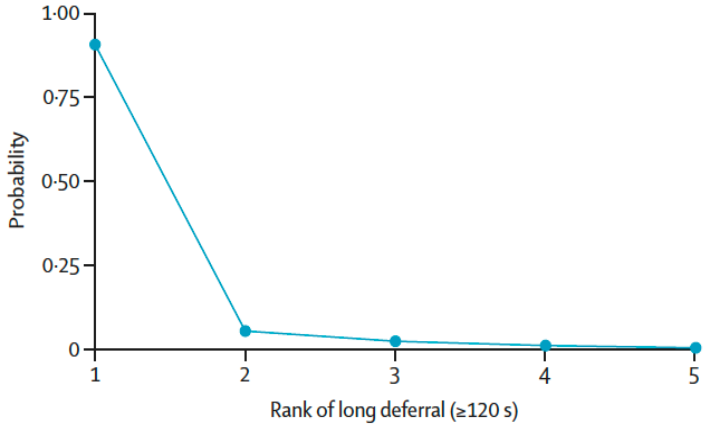
Anna Lene Seidler, Sol Libesman, Kylie E Hunter, Angie Barba, Mason Aberoumand, Jonathan G Williams, Nipun Shrestha, Jannik Aagerup, James X Sotiropoulos, Alan A Montgomery, Gillian M L Gyte, Lelia Duley, Lisa M Askie*, and iCOMP Collaborators†*

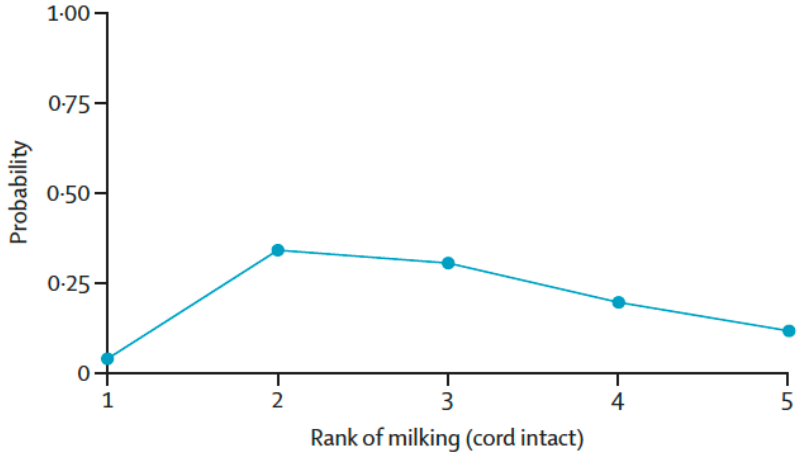
The Lancet, **Published online November 14, 2023**

6094 partecipanti (47 trials), EG < 37wks
Short (≥15 - < 45s)
Medium (≥ 45 - < 120)
Long (≥ 120s)
Intact cord miliking

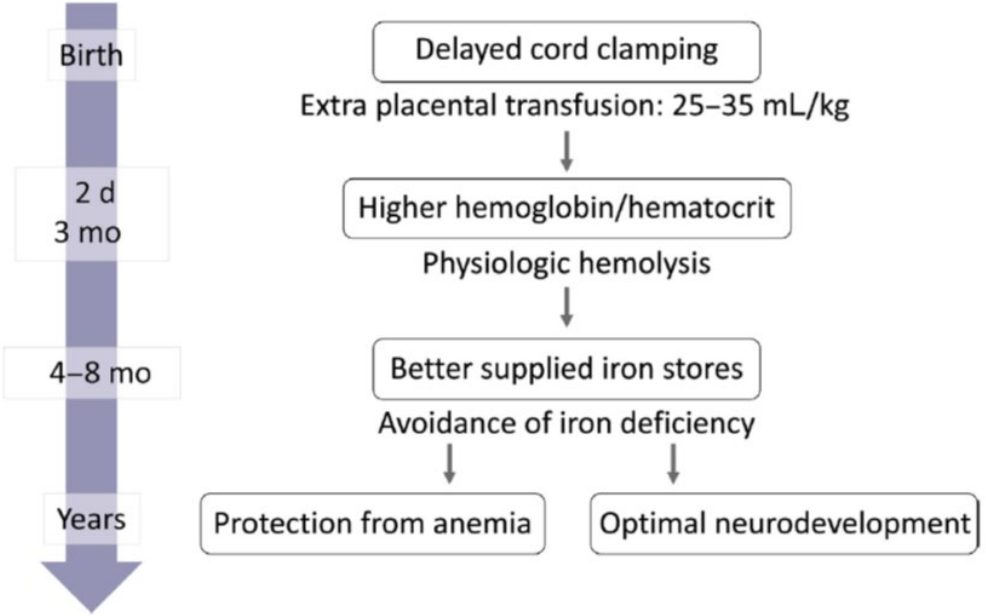
Outcome primario: morte prima della dimissione







Cosa abbiamo imparato: *Ritardato clampaggio*



- Miglior neurosviluppo a 1 anno di vita nei neonati a termine sani da madri anemiche (paesi a basse risorse)
- Miglior abilità motoria e funzionamento sociale a 4 anni nei neonati a termine sani (paesi ad alte risorse)

Cosa abbiamo imparato: *STAM vs STEN*

M. Hohlagschwandtner · P. Husslein · K. Klebermass
M. Weninger · A. Nardi · M. Langer

Perinatal mortality and morbidity

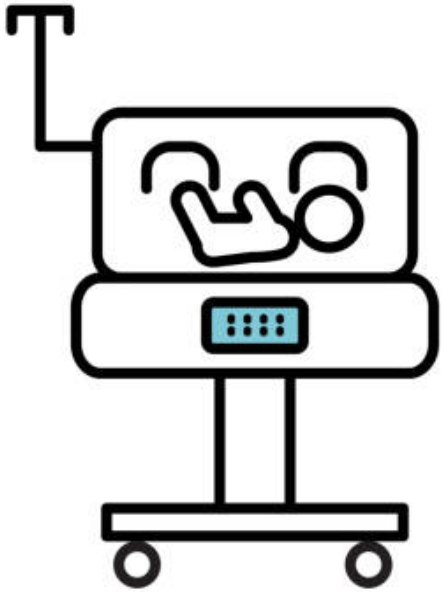
Comparison between maternal transport, neonatal transport and inpatient antenatal treatment

«..The results of the present study show that antenatal transfer guaranteed a better fetal outcome concerning severe neonatal morbidity than postnatal transport, and compared favorably with inborn admissions, even given the higher gestational age and birth weight in the NTI group.»

- ❑ Instabilità respiratoria e cardiovascolare
- ❑ Compromissione della termoregolazione, con conseguenti danni metabolici e neurologici
- ❑ Danno neurologico ed aumento rischio di IVH: movimenti bruschi, vibrazioni, cambiamento della posizione
- ❑ Infezioni: esposizione a vari ambienti, manipolazioni durante il trasporto
- ❑ Stress fisico e fisiologico

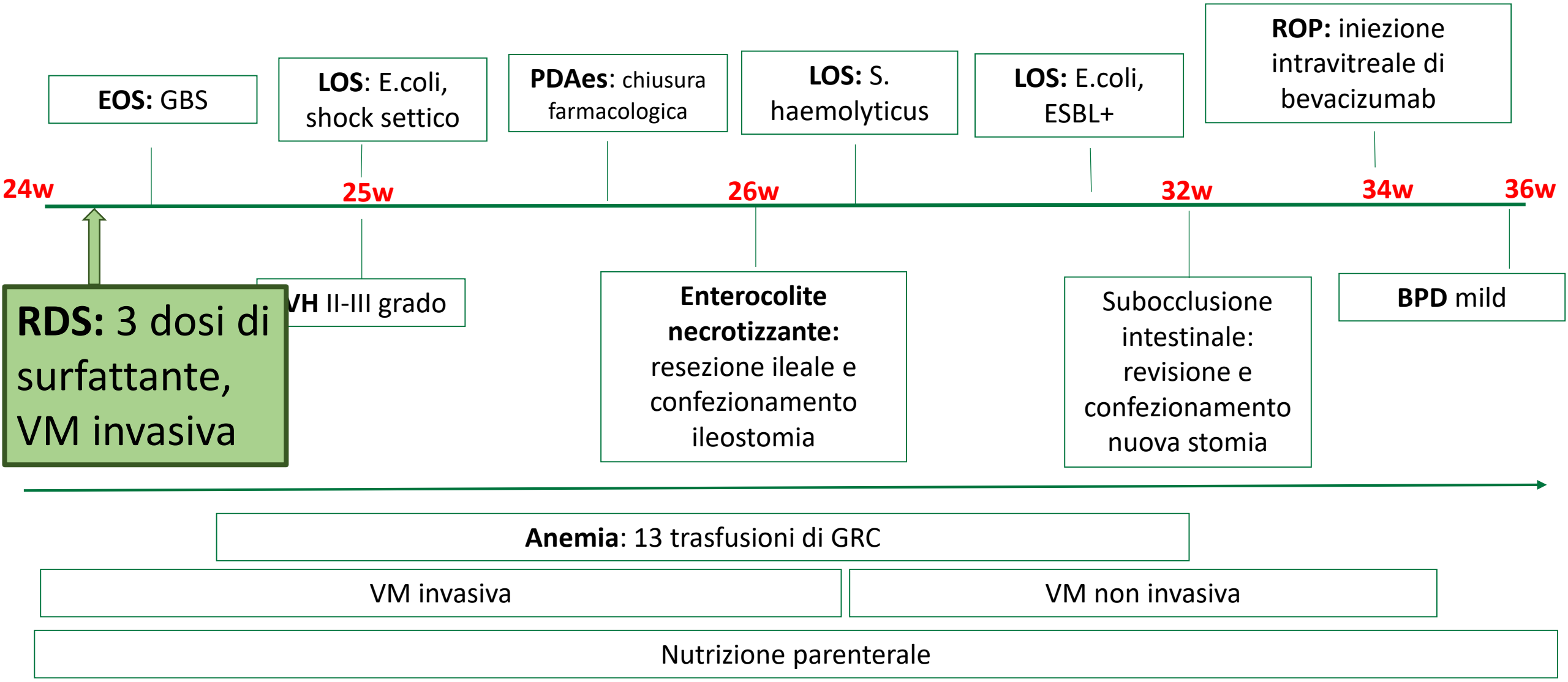
- **N.M., maschio, EG 24 settimane + 1 giorno, PN 880gr**
- **Outborn:** H.di Lodi, trasporto mediante STEN, h 4:00

Cosa abbiamo imparato: *danno iatrogeno*



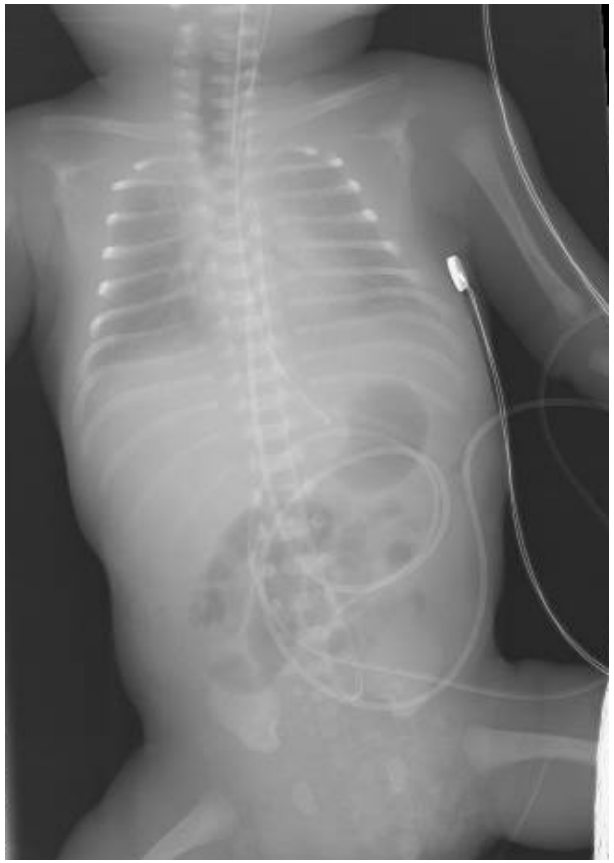
- ❑ Ventilazione meccanica
- ❑ Ossigeno
- ❑ Cateteri venosi ed arteriosi
- ❑ Terapia antibiotica
- ❑ Scarsa crescita di peso
- ❑ Trasfusione di emocomponenti
- ❑ Interventi chirurgici
- ❑ Farmaci sedativi ed analgesici
- ❑ Ambiente terapia intensiva

Decorso Clinico



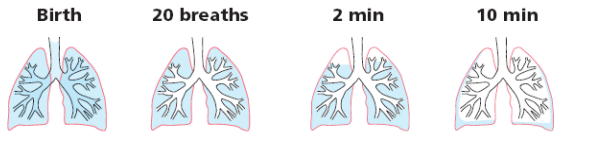
Cosa abbiamo imparato: *RDS, ottimizzare outcome*

- ❑ Minimizzare rischio di parto pretermine (tocolisi, progesterone)
- ❑ Trasferimento della madre in un centro di III livello
- ❑ Appropriata profilassi corticosteroidea



Sala parto →

Figure 2: A model of overdistension of the lung within the first 10 minutes after delivery.



	Birth	20 breaths	2 min	10 min
PEEP	0 ml	3 ml airway FRC	3 ml airway FRC + 4 ml FRC in UL	5 ml airway FRC + 15 ml FRC in parenchymal
V_T	0 ml	+5 ml to airways	5 ml to 20% of parenchyma = 25 ml/kg	5 ml to 100% of parenchyma = 5 ml/kg
Outcome	Airless lung	Overdistend airway	Focal overdistention	Non-injurious ventilation

Figure is based on a 1 kg preterm infant, intubated at delivery and volume ventilated with PEEP 5 ml and V_T 5 ml/kg.
PEEP: positive end-expiratory pressure; FRC: functional residual capacity; UL: upper lung; V_T: tidal volume.

European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update

Cosa abbiamo imparato: *RDS, less is more*

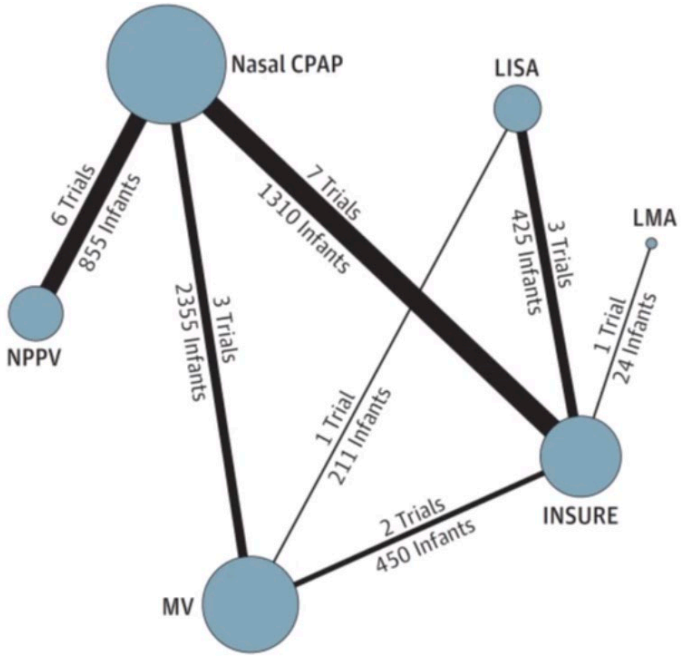
1.Intubazione selettiva	**2015**
2.Percentuale O2 durante rianimazione	**2010**
3.Saturazione ottimale	**2015**
4.Ventilazione «gentile», ipercapnia permissiva	**2008**
5.Somministrazione precoce di surfattante	**2014**
6.Tecniche di somministrazione di surfattante meno invasive	**2015**

European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update

Recommendations

1. If a preterm baby <30 weeks of gestation requires intubation for stabilisation, they should be given surfactant (A2).
2. Babies with RDS needing treatment should be given an animal-derived surfactant preparation (A1).
3. LISA is the preferred method of surfactant administration for spontaneously breathing babies on CPAP (A1).
4. Laryngeal mask surfactant may be used for more mature infants >1.0 kg (B2).
5. An initial dose of 200 mg/kg of poractant alfa is better than 100 mg/kg of poractant alfa or 100 mg/kg beractant for rescue therapy (A1).
6. Rescue surfactant should be given early in the course of the disease (A1). Suggested protocol would be to treat worsening babies with RDS when $FiO_2 > 0.30$ on CPAP pressure ≥6 cm H_2O or if lung ultrasound suggests surfactant need (B2).
7. A second and occasionally a third dose of surfactant should be given if there is ongoing evidence of RDS such as persistent high oxygen requirement and other problems have been excluded (A1).

Cosa abbiamo imparato: *surfattante*

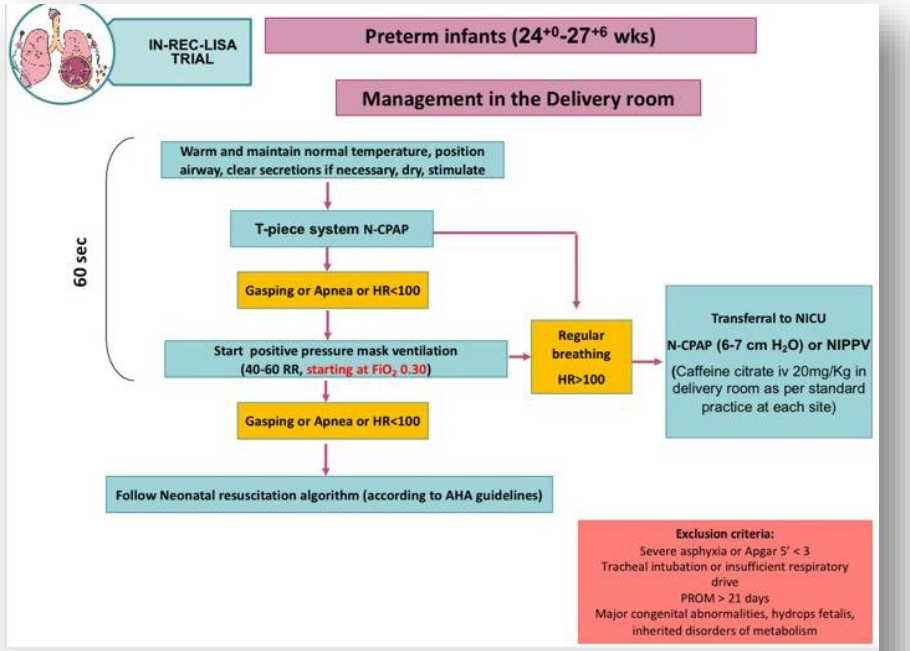


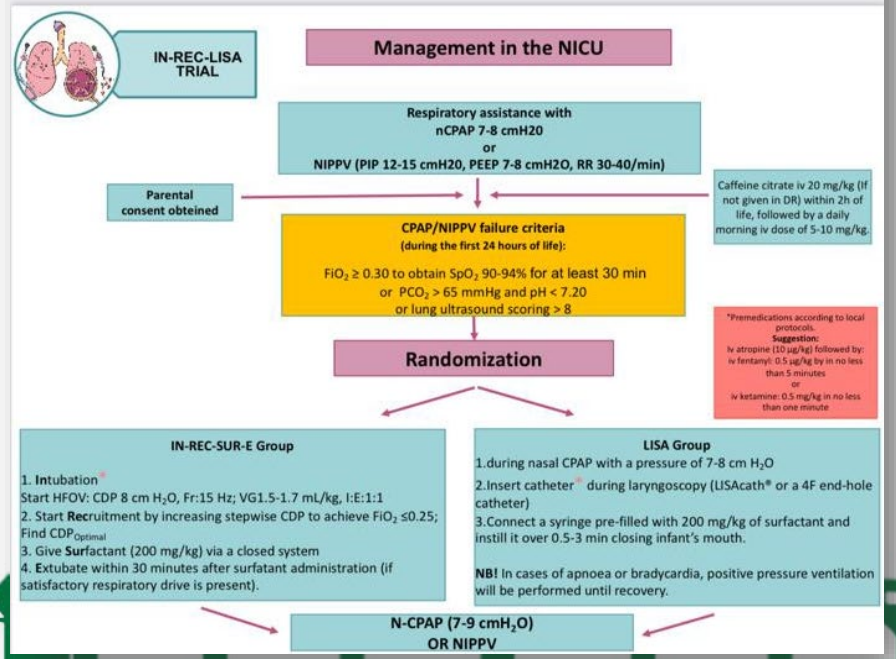
Vento *et al. Trials* (2024) 25:433
https://doi.org/10.1186/s13063-024-08240-4

Trials

STUDY PROTOCOL Open Access

Comparison of "IN-REC-SUR-E" and LISA in preterm neonates with respiratory distress syndrome: a randomized controlled trial (IN-REC-LISA trial)





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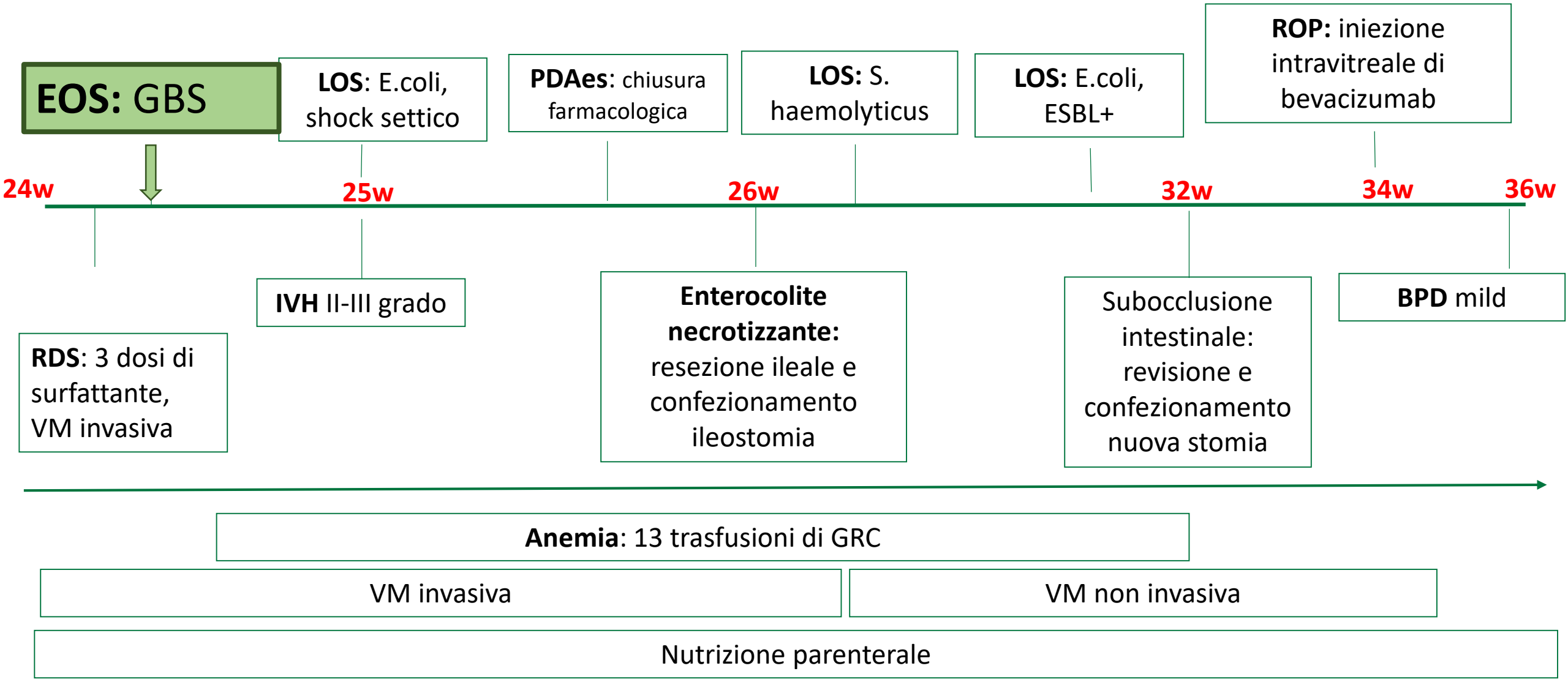


Cosa abbiamo imparato: *EOS*

Incidenza: ~0,8 casi/1000 nati vivi.
20 casi ogni 1000 nati di età gestazionale < 29 settimane

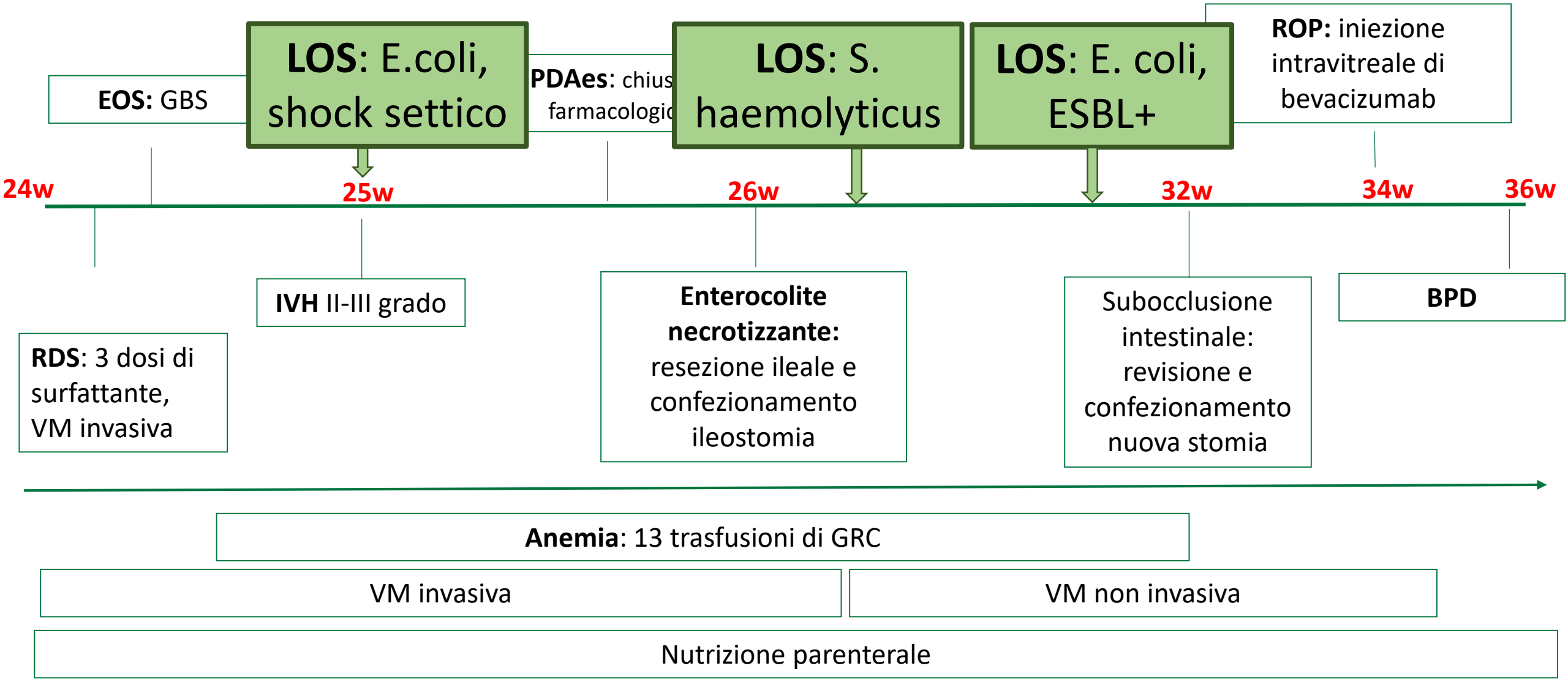
↓ Profilassi antibiotica intrapartum

Mortalità: 1,6% a EG > 37 settimane, 30% a EG 25-28, 50% a EG 22-24

Fattori di rischio: incontinenza cervicale, travaglio pretermine, PROM, IAI /corioamnionite, esordio acuto e inspiegato di stato non rassicurante del feto

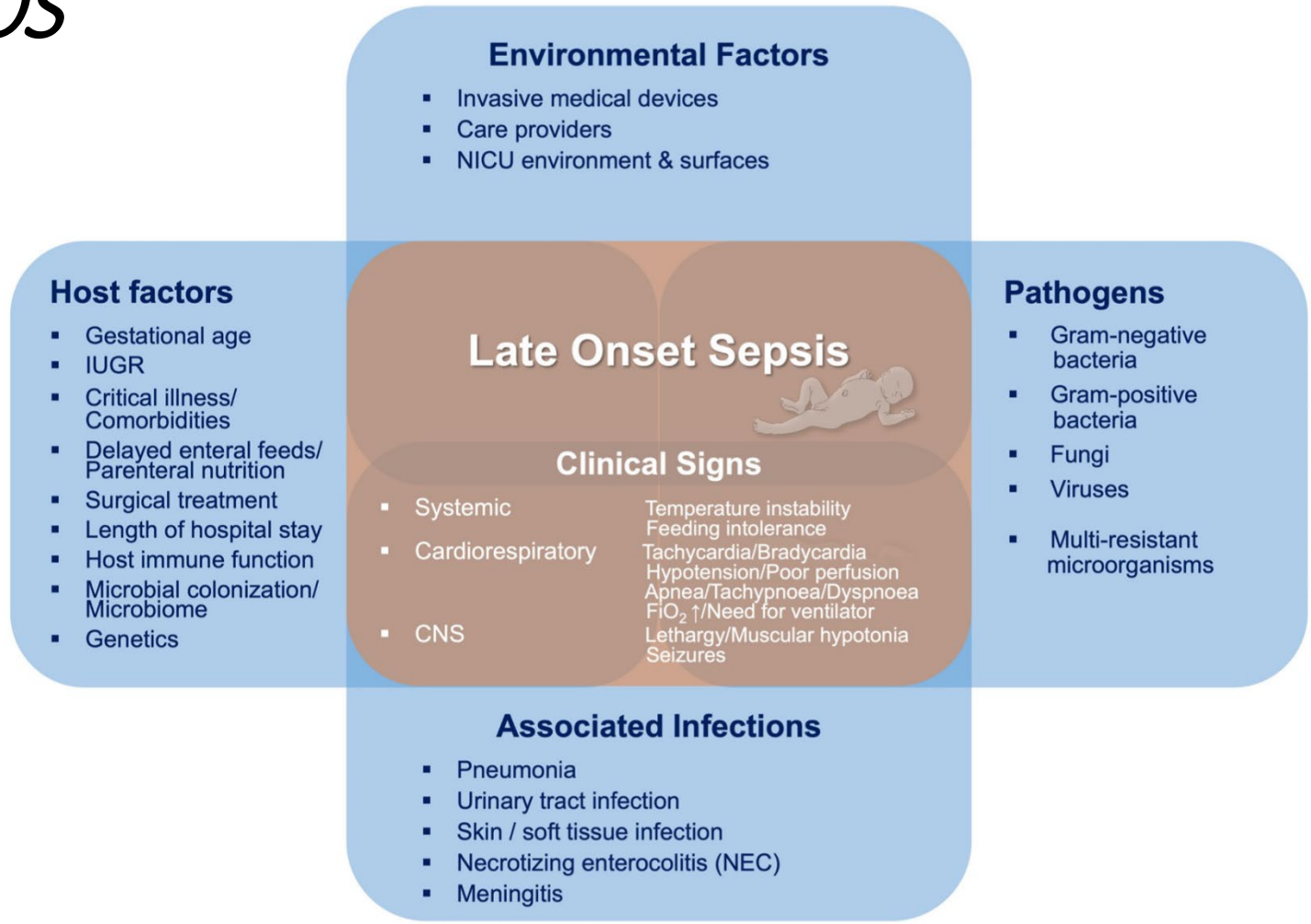
GBS, E. Coli, Listeria

Decorso Clinico



Cosa abbiamo imparato: *LOS*

- I neonati pretermine e i neonati VLBW rappresentano fino al 50% dei casi di LOS nei paesi ad alto reddito.
- Le misure igieniche estese basate sullo screening di routine della colonizzazione dei pazienti in TIN e le strategie di prevenzione delle CLABSI sono state associate a tassi ridotti di LOS.

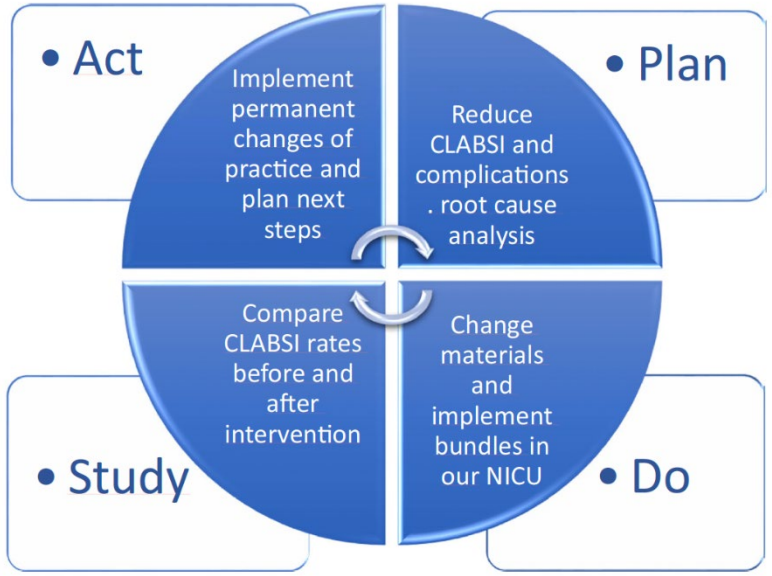


Coggins SA. Updates in Late-Onset Sepsis: Risk Assessment, Therapy, and Outcomes. Neoreviews. 2022

Cosa abbiamo imparato: *LOS - CLABSI*

CLABSI - *Central-line associated bloodstreem infection*

- ❑ Maggiore causa di mortalità e morbidità in TIN
- ❑ Prolungamento della durata della degenza
- ❑ Impatto su outcome a lungo termine (neurosviluppo)



STUDY PROTOCOL — Open Access

Effect of in-line filtration in newborns: study protocol of the Intravenous Neonatal Central Access Safety (INCAS) randomized controlled trial

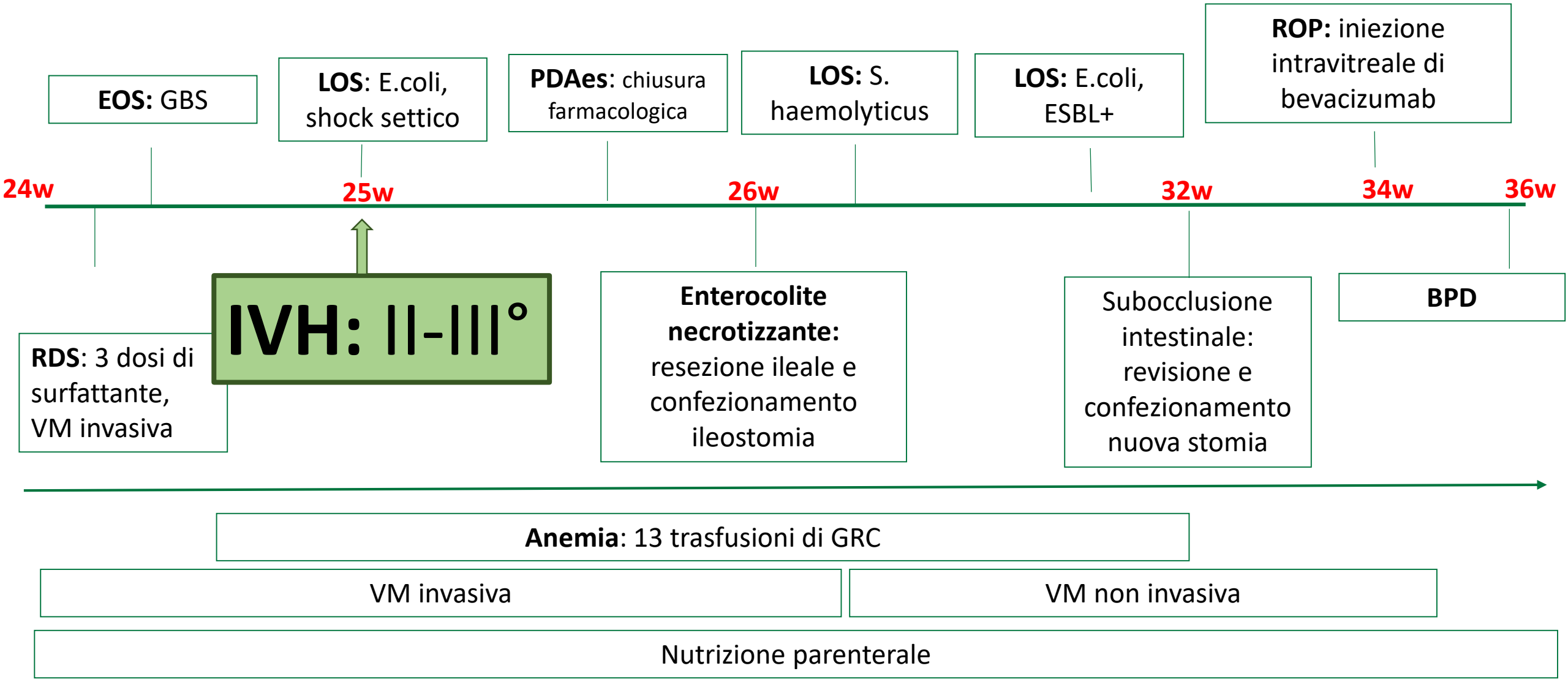
Francesco Cresi[1,2†], Elena Maggiora[1,2*†], Cecilia Capetti[3†], Martina Capitanio[1,2], Mattia Ferroglio[1], Elena Spada[1], Francesca De Matteis[2], Sara Cosimi[2], Fabio Mosca[4,5], Alessandra Coscia[1,2] and INCAS Trial Research Group

Outcomes

The primary outcome is the frequency of patients with at least one sepsis-like event, defined by any association of suspected sepsis symptoms with a level of c-reactive protein (CRP) > 5 mg/L in a negative-culture contest, from the beginning up to 48 h after discontinuation of infusion therapy.

Bierlaire S. How to minimize central line-associated bloodstream infections in a neonatal intensive care unit: a quality improvement intervention based on a retrospective analysis and the adoption of an evidence-based bundle. Eur J Pediatr. 2021 Feb

Decorso Clinico



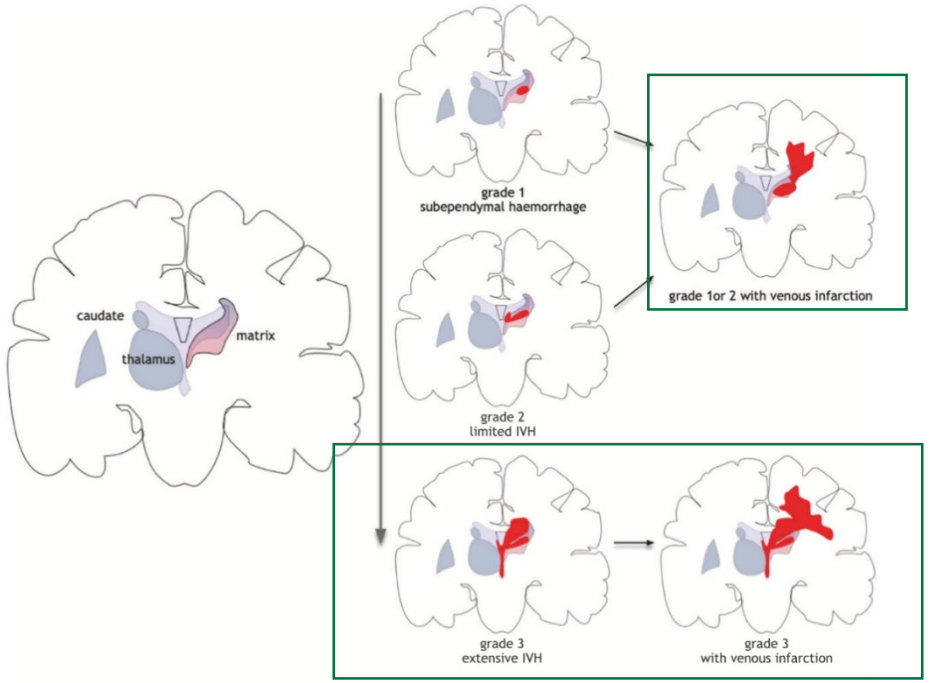
Cosa abbiamo imparato: *danno neurologico, IVH*

Incidenza: 20-25% (ELBW); EG dipendente (EG > 28wks incidenza < 5%)

Multifattoriale: scarsa autoregolazione vascolare, instabilità cardio-circolatoria, inotropi, danno ipossico- ischemico, infezioni, RDS severa, pneumotorace

Insorgenza e progressione: 24-72h di vita

Complicanze: infarto parenchimale, idrocefalo post emorragico



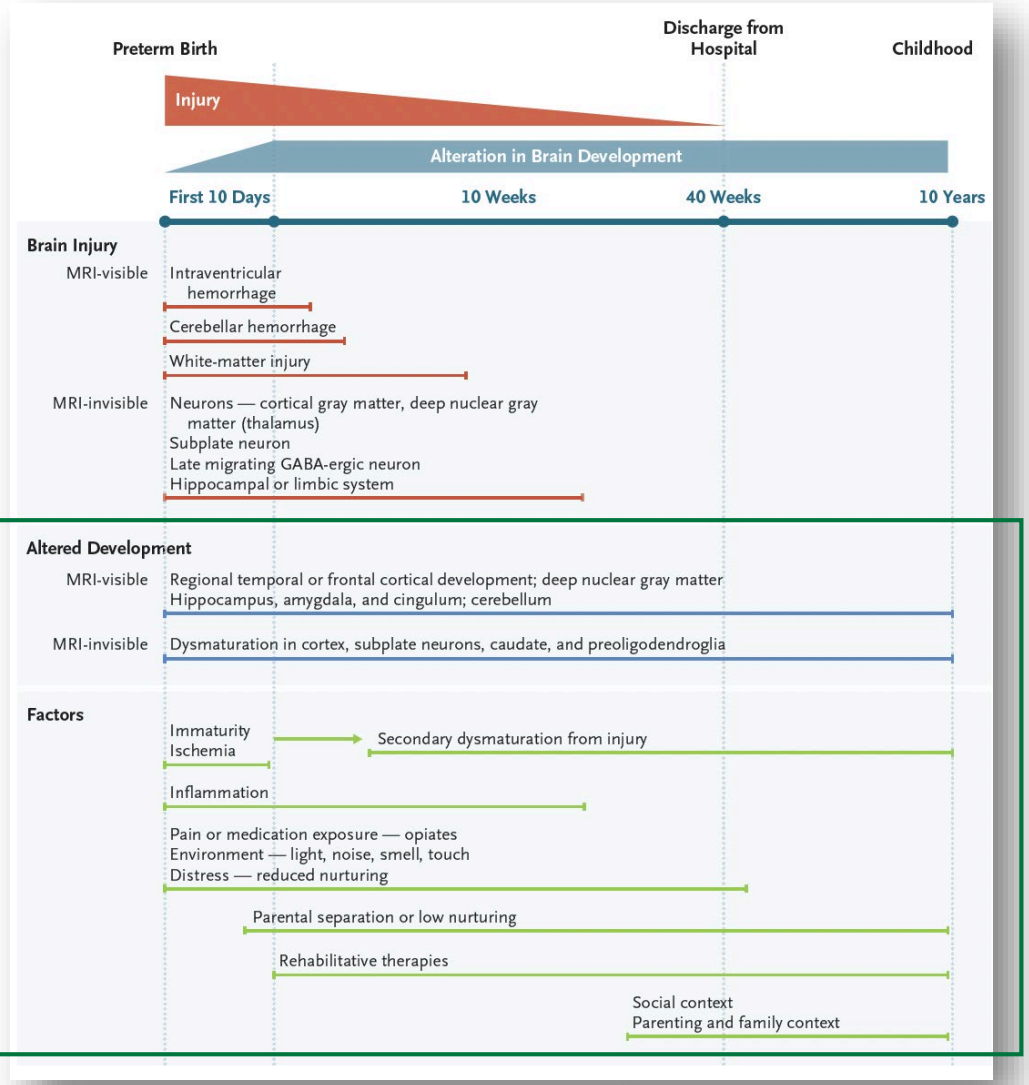
Alto grado (III o infarto parenchimale):
Paralisi cerebrale (6 volte maggiore)
Danno visivo (11 volte maggiore)
Sordità centrale (4 volte maggiore)

Parodi A, eurUS.brain group. Cranial ultrasound findings in preterm germinal matrix haemorrhage, sequelae and outcome. Pediatr Res. 2020 Mar

Cosa abbiamo imparato: *Danno neurologico, non solo IVH*

Danno neurologico del pretermine:

- ❑ Danno della sostanza bianca
- ❑ GMH/IVH
- ❑ Emorragia cerebellare



N ENGL J MED 389;5 NEJM.ORG AUGUST 3, 2023

Defining the Neurologic Consequences of Preterm Birth

Terrie E. Inder, M.B., Ch.B., M.D., Joseph J. Volpe, M.D., and Peter J. Anderson, Ph.D.

Cosa abbiamo imparato: *Danno neurologico, prevenire*

Anamnesi ostetrica e peripartum:

- Ipotiroidismo in terapia, no diabete, no pre-eclampsia
- **IVU febbrili ricorrenti (UK positive per GBS e E. Coli)**
- Travaglio precipitoso inarrestabile, sospetta corionamniosite
- Tipo di parto: eutocico
- Profilassi corticosteroidea: **incompleta**
- Profilassi antibiotica intrapartum: **incompleta**
- Solfato di magnesio: **non somministrato**

NIRS, TCpCO2, care infermieristica minimal touch
TIN aperta ai genitori h24
logopedista, fisioterapista
Follow up a breve e lungo termine

Table 1. Evidence of Association of Brain Injury and Dysmaturation with Functional Impairment in Preterm Infants and Potential Interventions to Improve Outcomes.*

Functional Impairment	Brain Injury				MRI-Defined Brain Dysmaturation		
	High-Grade Intraventricular Hemorrhage	Cystic White-Matter Injury	Diffuse White-Matter Injury	Cerebellar Hemorrhage	Frontal or Temporal Region	Basal Ganglia or Thalamus	Cerebellum
Early development	Strong	Strong	Strong	Moderate	Moderate	NC	Moderate
Motor function	Strong	Strong	Moderate	Strong	ND	Moderate	Moderate
IQ	Strong	Strong	Moderate	Strong	Moderate	Moderate	Moderate
Language	Moderate	Strong	Moderate	Moderate	Moderate	NC	Moderate
Visuospatial function	Moderate	Strong	Moderate	Weak	NC	NC	Weak
Memory	Moderate	Moderate	Moderate	NC	Moderate	Moderate	Weak
Attention and executive function	Moderate	Moderate	Moderate	NC	Moderate	Weak	Weak
Academic performance	Moderate	Strong	Moderate	NC	NC	Moderate	NC
Behavior	Moderate	Moderate	Moderate	Moderate	NC	Moderate	Moderate
Interventions	Antenatal glucocorticoids, magnesium sulfate, delayed cord clamping NICU: physiological stability — prevent fluctuations in carbon dioxide, glucose, blood pressure Cerebrovascular monitoring to ensure stable cerebral perfusion Neurorehabilitation with parent–infant interaction and infant developmental therapy				Provide appropriate nutrition: macronutrients and micronutrients, maternal breast milk Minimize distress and stressful or painful experiences Enhance nurturing: skin-to-skin care, parental presence and engagement, exposure to human voices Home-based developmental programs		

Defining the Neurologic Consequences of Preterm Birth

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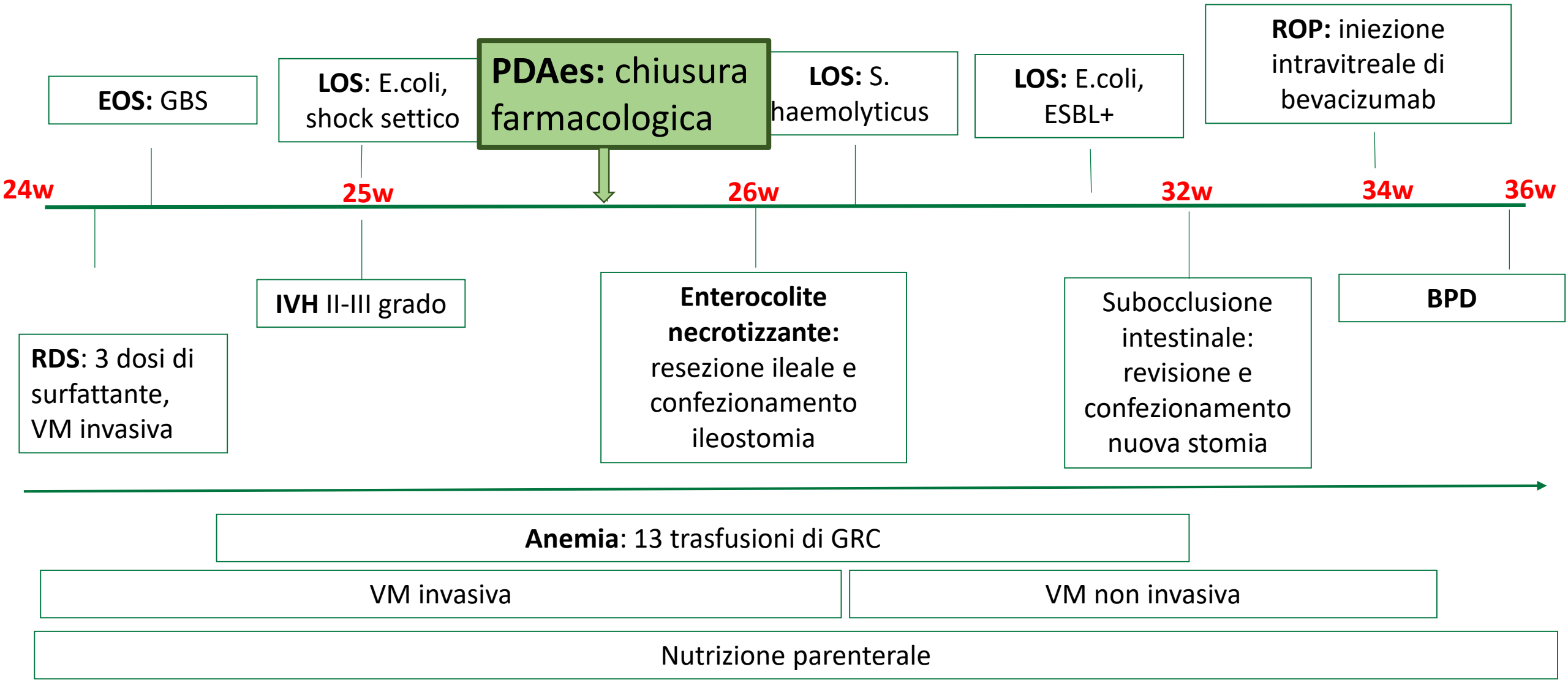
Decorso Clinico

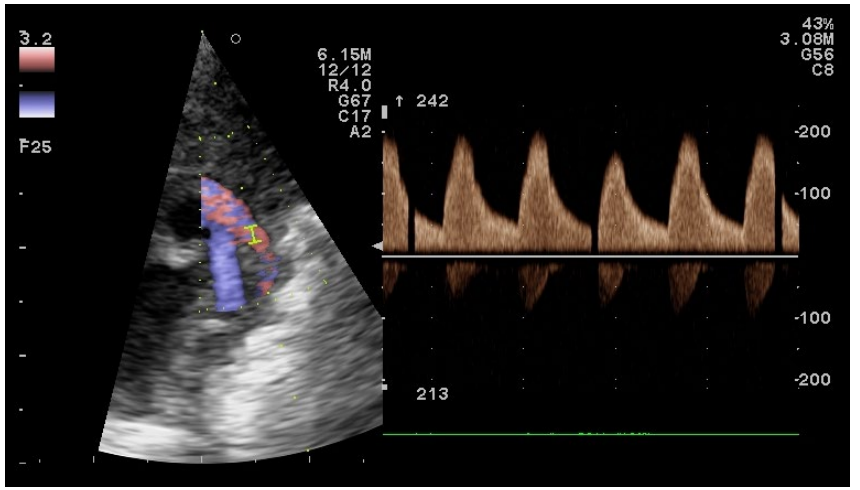


Cosa abbiamo imparato: *PDA emodinamicamente significativo*

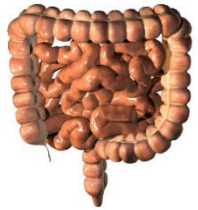
- Aumentato rischio di mortalità:

Failure of Ductus Arteriosus Closure Is Associated With Increased Mortality in Preterm Infants

Noori et al. *Pediatrics* 2009



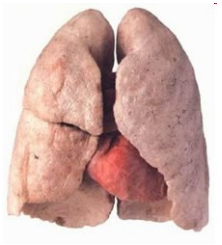
- Aumentato rischio di complicanze multiorgano:



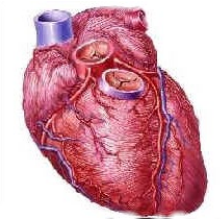
NEC

IVH

IRA



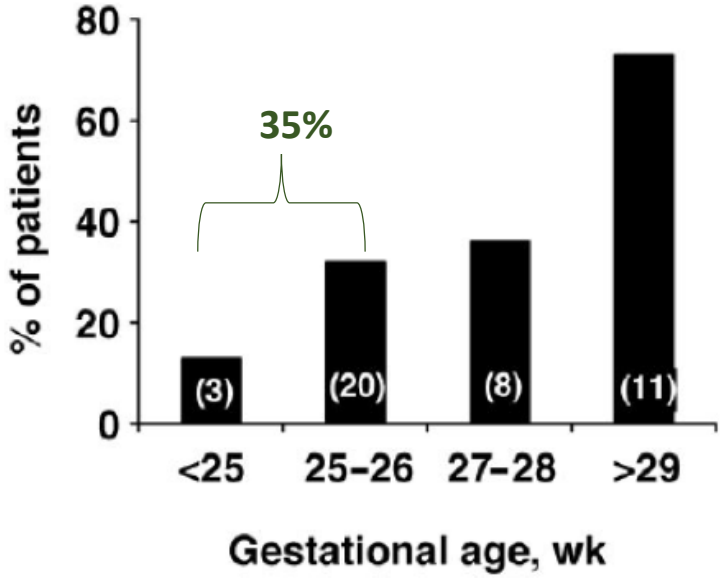
Emorragia polmonare & BPD



Scompenso cardiaco & ipotensione sistemica refrattaria agli inotropi

Cosa abbiamo imparato: PDA to treat or not to treat?

Prevalence of Spontaneous Closure of the Ductus Arteriosus in Neonates at a Birth Weight of 1000 Grams or Less Koch J, *Pediatrics* 2006



Cochrane Library

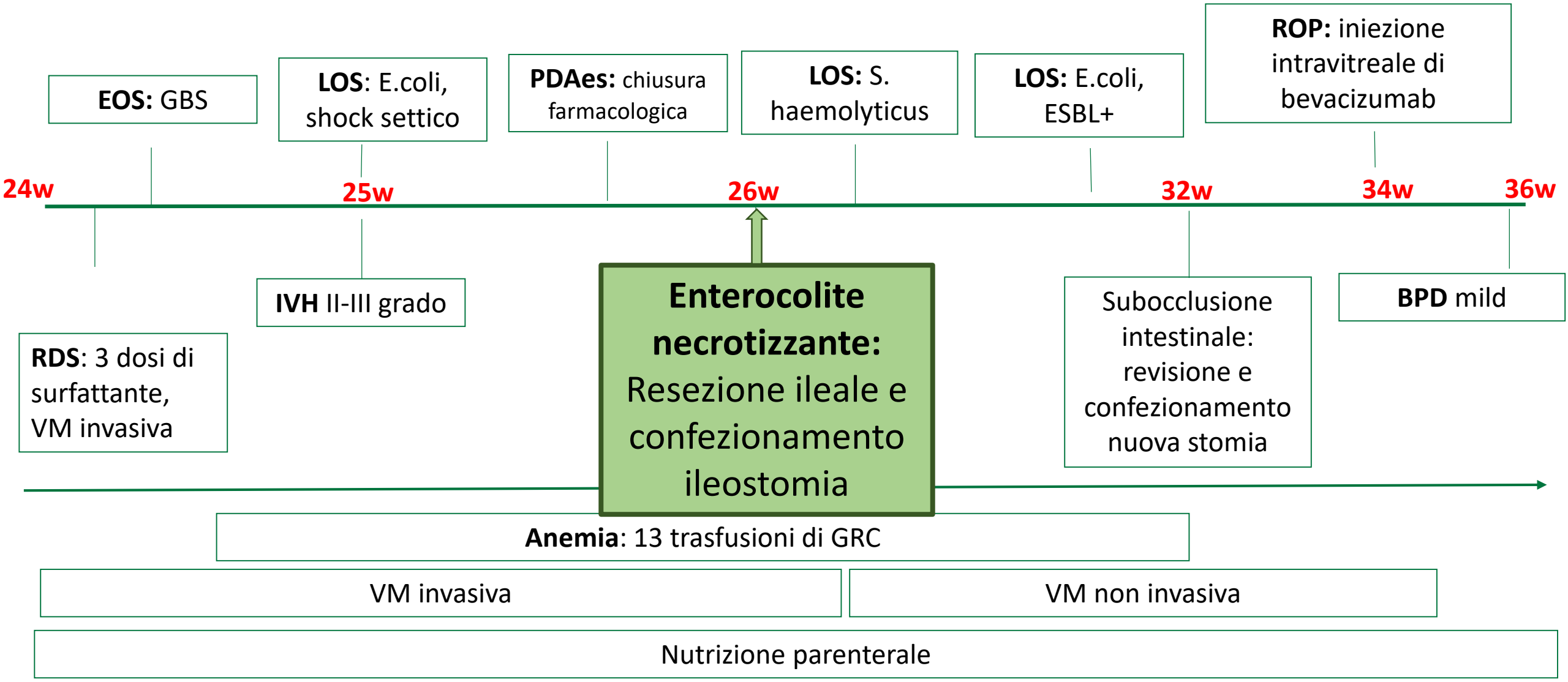
Cochrane Database of Systematic Reviews

Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus for preterm infants (Review)

- ❑ Trattamento profilattico
- ❑ Trattamento dopo la comparsa dei sintomi
- ❑ Trattamento precoce mirato

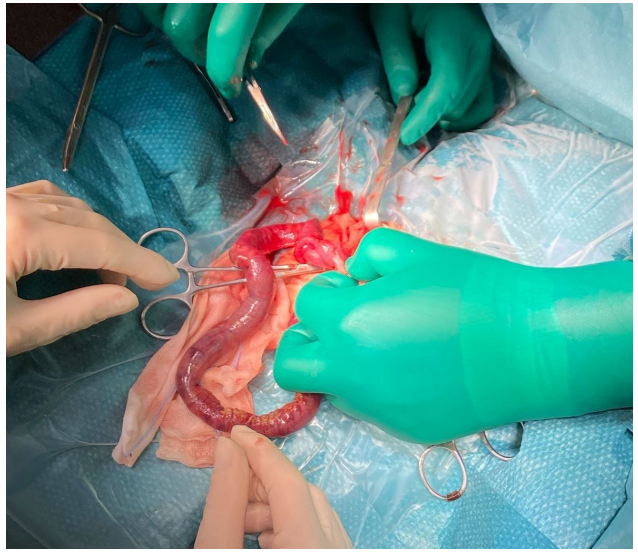
Valutazione ecografica precoce
Migliore selezione dei pazienti

Decorso Clinico



Cosa abbiamo imparato: *Enterocolite necrotizzante*

- Alta incidenza: 7-10% dei neonati con peso inferiore a 1500 gr
- Alta mortalità: 25-30%, fino al 50% nei pazienti che vanno incontro a chirurgia



Cosa abbiamo imparato: *Enterocolite necrotizzante*

- Sequele a lungo termine fortemente impattanti sulla qualità di vita, es. nutrizione parenterale prolungata, scarsa crescita, necessità di reintervento

- Strategie di prevenzione limitate (es. banca del latte umano donato)

- Assenza di trattamenti specifici, studi preclinici e traslazionali in corso

Human Bone Marrow-Derived Mesenchymal Stromal Cells Reduce the Severity of Experimental Necrotizing Enterocolitis in a Concentration-Dependent Manner

cells

Livia Provitera [1,†], Andrea Tomaselli [1,2,†], Genny Raffaeli [1,2,*], Stefania Crippa [3], Cristina Arribas [4], Ilaria Amodeo [1], Silvia Gulden [5], Giacomo Simeone Amelio [1], Valeria Cortesi [1,2], Francesca Manzoni [1,2], Gaia Cervellini [1,2], Jacopo Cerasani [1,2], Camilla Menis [1,2], Nicola Pesenti [1,6,7], Matteo Tripodi [1], Ludovica Santi [3], Marco Maggioni [8], Caterina Lonati [9], Samanta Oldoni [9], Francesca Algieri [10], Felipe Garrido [4], Maria Ester Bernardo [3,11,12], Fabio Mosca [1,2] and Giacomo Cavallaro [1,*]

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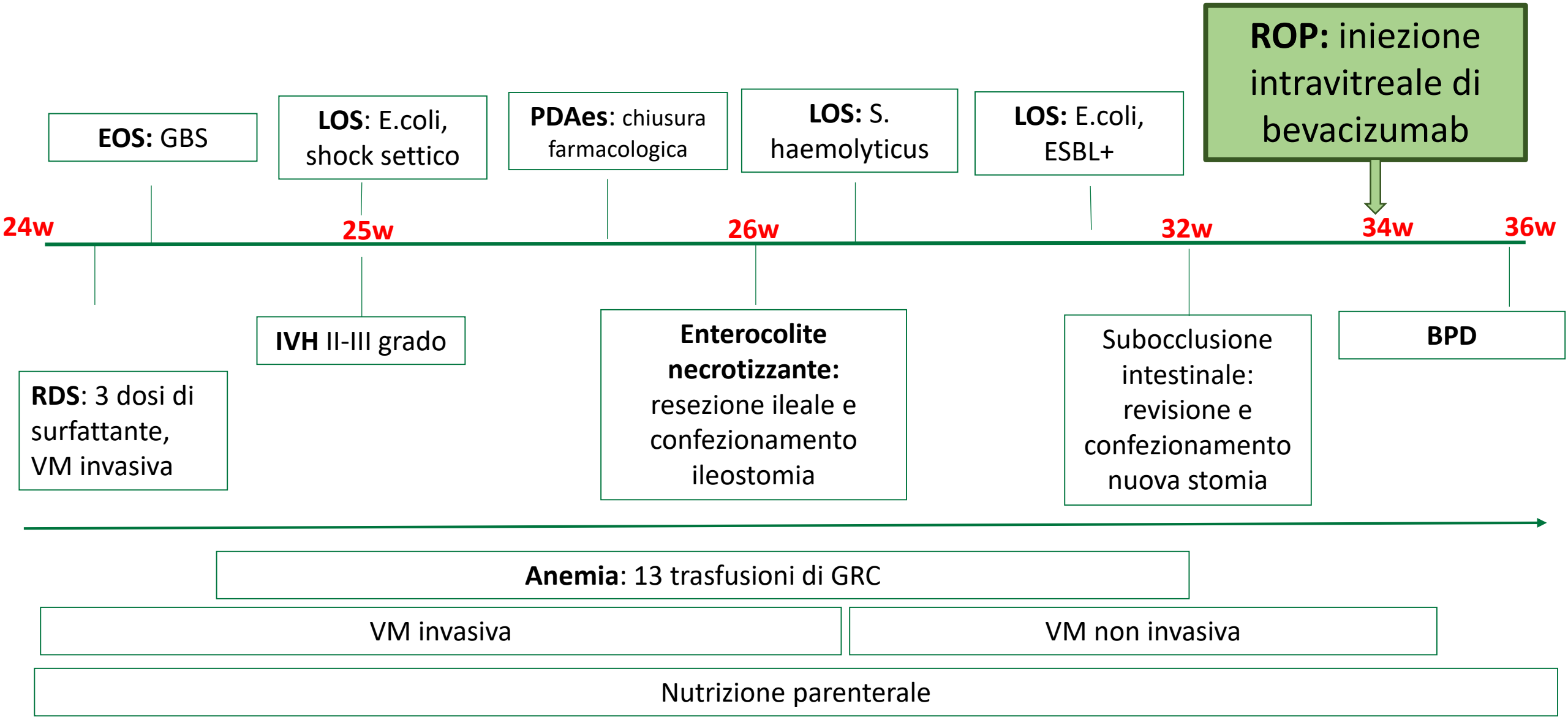
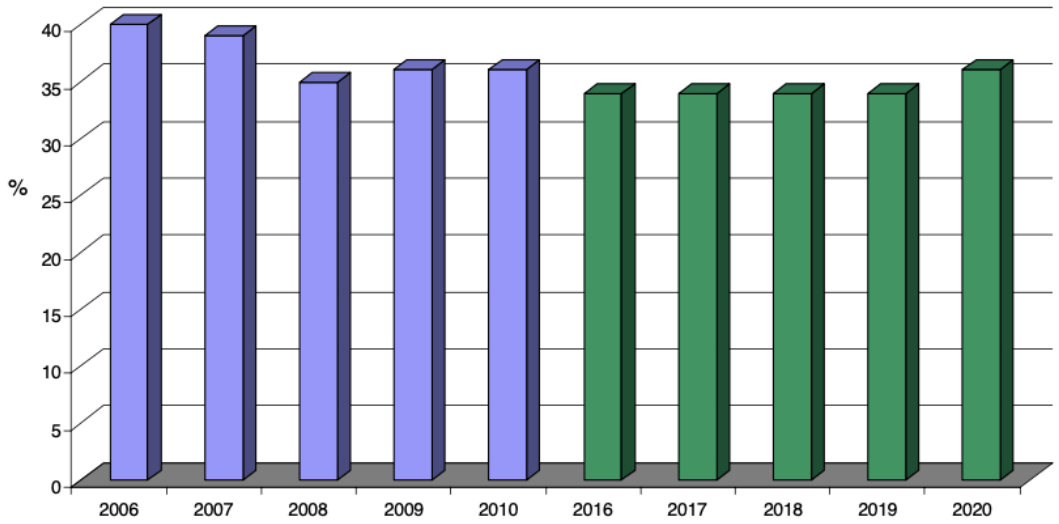
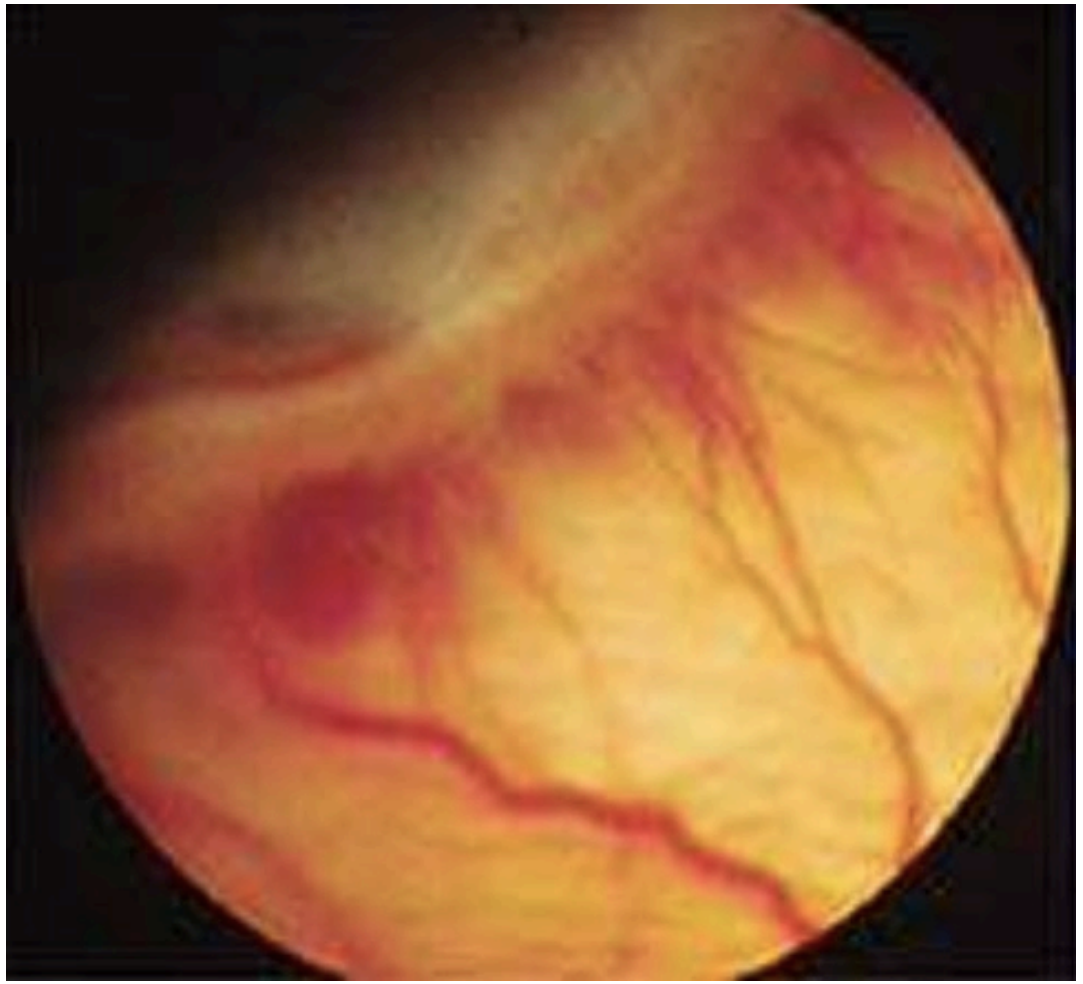


Cosa abbiamo imparato: *Retinopatia del prematuro* (ROP)

Incidenza ROP, qualunque stadio, in neonati sotto i 1500 gr (VON)

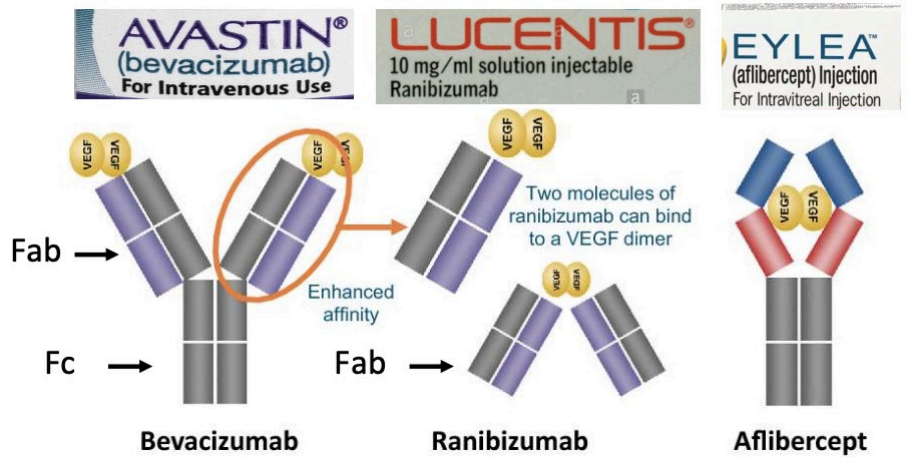




Cosa abbiamo imparato: Retinopatia del prematuro (ROP)

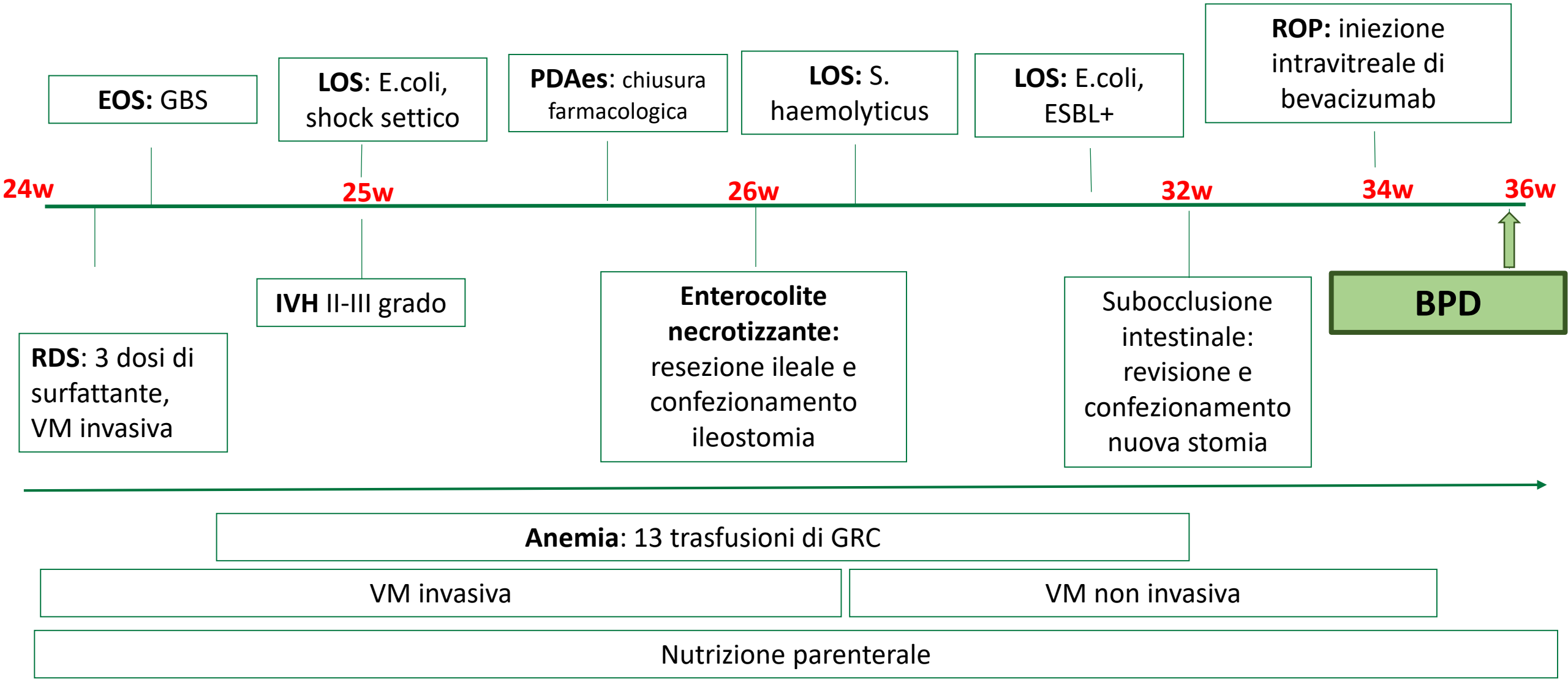
Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial

Stahl et al., *Lancet* 2019

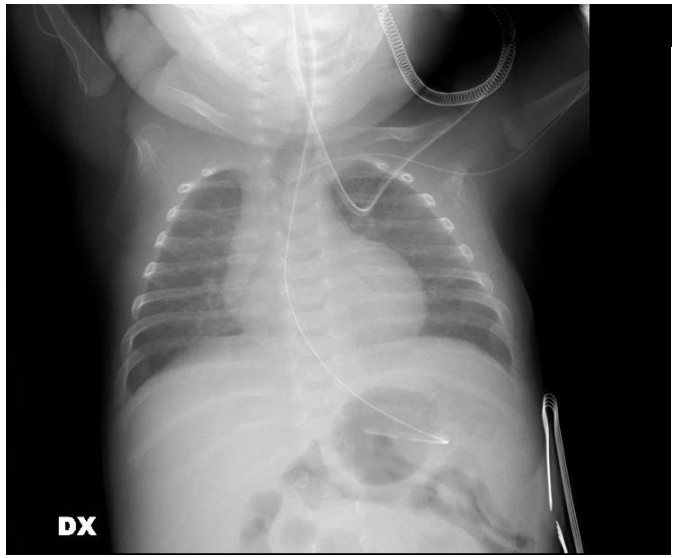


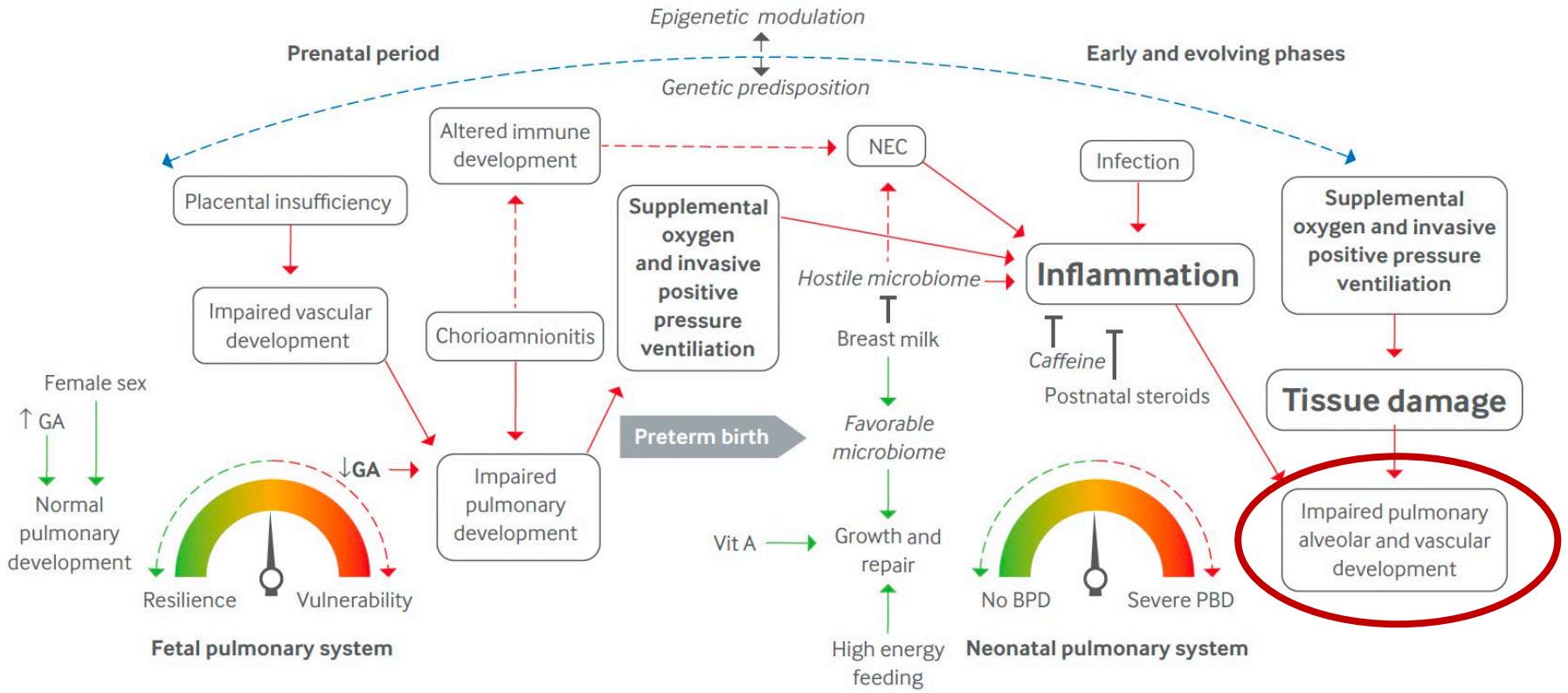
Findings In the treatment of ROP, ranibizumab 0·2 mg might be superior to laser therapy, with fewer unfavourable ocular outcomes than laser therapy and with an acceptable 24-week safety profile.

Decorso Clinico



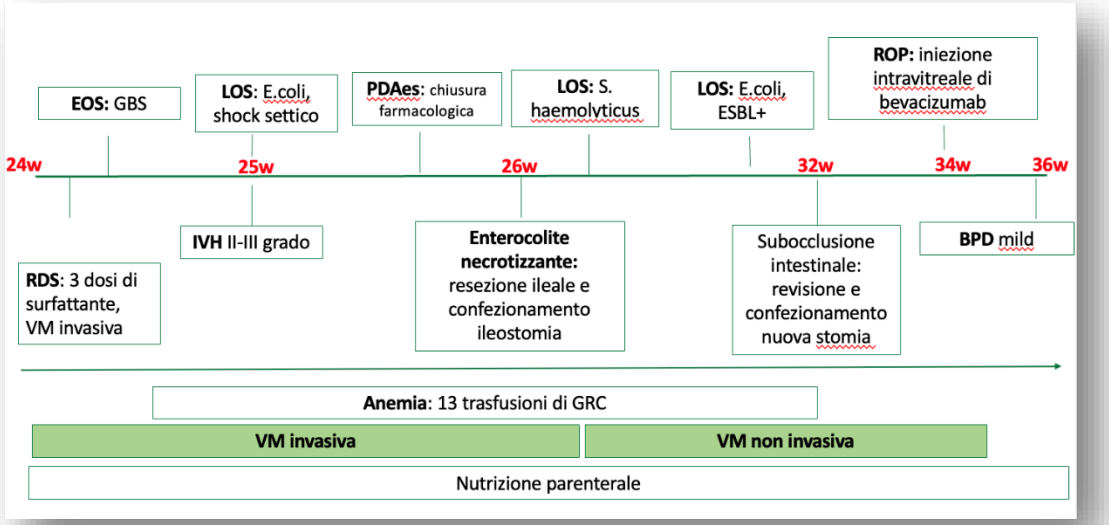
Cosa abbiamo imparato: *BPD*

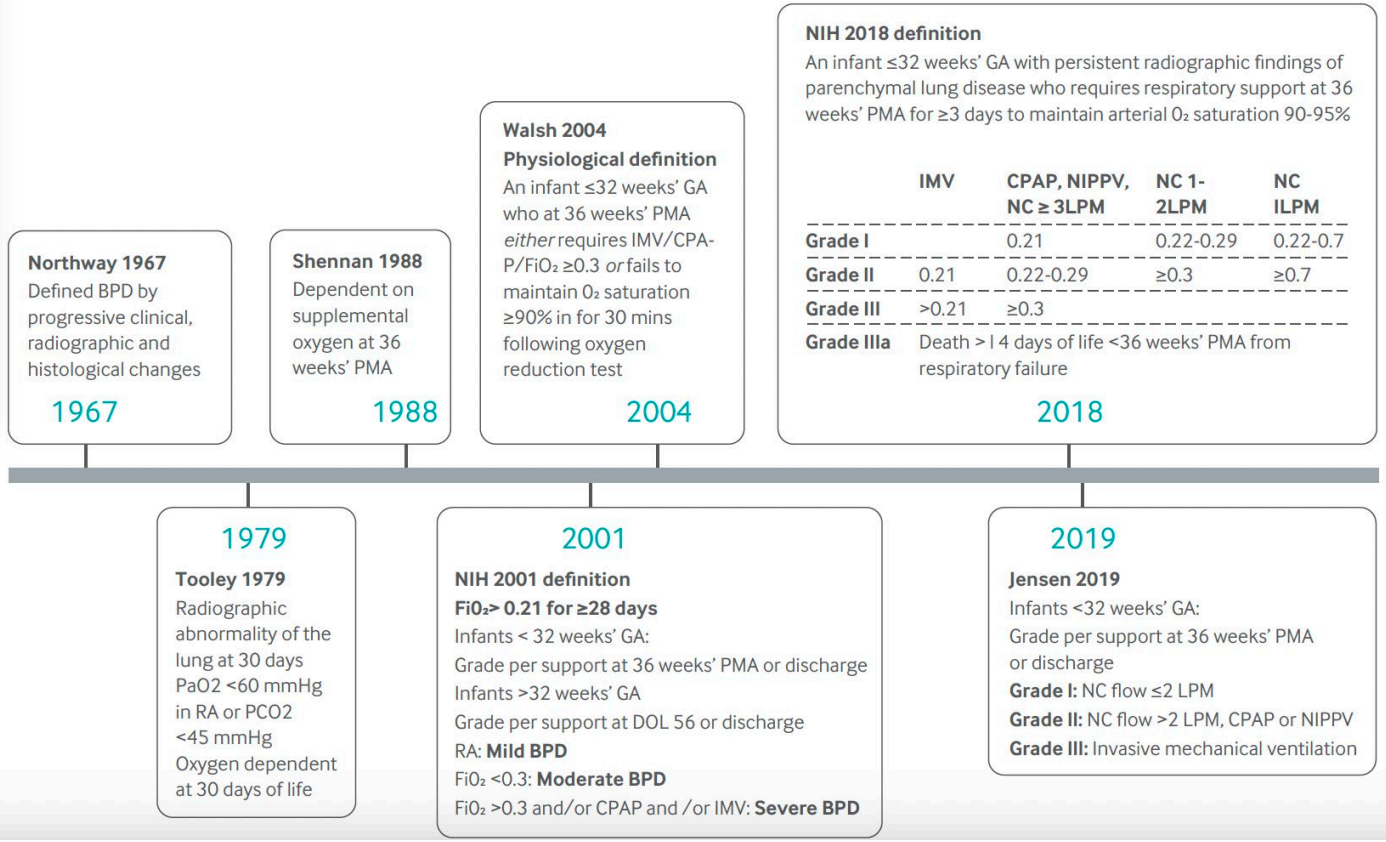




Gilfillan M, Diagnosis and management of bronchopulmonary dysplasia. BMJ. 2021 Oct

Cosa abbiamo imparato: *BPD, definizioni*





Gilfillan M, Diagnosis and management of bronchopulmonary dysplasia. BMJ. 2021 Oct

Cosa abbiamo imparato: *BPD, non solo patologia respiratoria*

Outcome*	No BPD (N = 876)	Mild BPD (N = 1186)	Moderate BPD (N = 1143)	Severe BPD (N = 643)
% CP	8.1	11.3	17.0	26.8†
% MDI <70	21.0	25.6	35.1	49.8†
% PDI <70	12.2	16.4	26.1	41.7†
Blind†				
% Unilateral	0.23	0.17	1.1	1.6
% Bilateral	0.11	0.68	1.2	2.2
% Hearing impairment	0.82	2.7	3.7	6.0†
% Hearing aids	0.35	1.7	2.0	3.9†
% Neurodevelopmental impairment	28.1	34.4	44.6	61.9†
Weight‡, kg	10.3 (1.5)	10.4 (1.5)	10.2 (1.5)	10.0 (1.5)†
Length‡, cm	80.4 (4.5)	80.6 (4.3)	80.1 (4.4)	79.1 (4.4)†
Head circumference‡, cm	46.8 (1.7)	46.9 (1.8)	46.7 (1.9)	46.3 (2.1)†
% Weight <10th percentile	48.8	49.8	55.2	62.6†
% Length <10th percentile	30.6	28.9	37.9	46.2†
% Head circumference <10th percentile	21.8	21.7	27.3	39.4†
Home oxygen prescribed, n (%)	23 (2.7)	88 (7.5)	656 (57.8)	395† (62.1)
Age home oxygen stopped, mo (SD; n)	7.3 (3.8; 19)	7.2 (4.4; 81)	7.6 (4.1; 601)	9.7† (4.8; 311)

ARTICLES | DECEMBER 01 2005

Validation of the National Institutes of Health Consensus Definition of Bronchopulmonary Dysplasia

Richard A. Ehrenkranz, MD; Michele C. Walsh, MD; Betty R. Vohr, MD; Alan H. Jobe, MD, PhD; Linda L. Wright, MD; Avroy A. Fanaroff, MB, BCh; Lisa A. Wrage, MPH; Kenneth Poole, PhD; for the National Institutes of Child Health and Human Development Neonatal Research Network

PEDIATRICS®

*«BPD is not merely a lung disease, but a **systemic condition** with **lifelong implications for adult health and quality of life**»*

Cosa abbiamo imparato: *BPD, la sfida inizia sin da subito*

Therapeutic intervention	Current status	Evidence level	Recommendation leve
Early phase (up to 1 postnatal week)			
Oxygen supplementation	Resuscitation:		
	Titrate supplemental oxygen to obtain preductal oxygen saturation >80% by 5 minutes of life[93]	I	B
	Maintain oxygen saturations 90-95%[96]	I	A
Ventilatory strategy	Trial of CPAP for spontaneously breathing infants	I	A
	Consider surfactant administration if FiO_2 remains consistently >0.4 on PEEP +6 cm H_2O	I	B
	Use InSURE/LISA technique to administer surfactant	I	B
	Consider volume targeted ventilation strategies: TV 4-6 mL/kg[119]	I	A
	Use short inspiratory times (0.3-0.4 s),[177] rapid rates (40-60 per min) and low PIP on pressure	III	B
	control settings (14-20 cm H_2O), moderate PEEP (4-6		
	:45-55 mm Hg[179]		
	Trial of extubation to NIPPV/SNIPPV prior to 7 days in i		
	settings[180]		
Methylxanthines	Administration of caffeine within first 3 days of life dec		
Intratracheal administration of budesonide and surfactant	Associated with an increase in BPD free survival (NNT		
	Studies to date not adequately powered to assess long		
Vitamin A	Improves BPD free survival with reported NNT 14-15[18]		
	times a week for 4 weeks		
Low dose hydrocortisone	Low dose hydrocortisone (total dose 8.5 mg over 10 d		
	free survival		
	Increased risk of late onset sepsis in infants <26 weeks		
	Increased risk of SIP in infants who receive indometha		
Fluids	Restrictive fluid intake may decrease BPD[183]		
Nutrition	Exclusive human milk feeding reduces the risk for BPD		
Evolving BPD (> 1 postnatal week to 36 weeks' PMA)			
Dexamethasone	Low dose dexamethasone (0.89 mg/kg over 10 days) facilitates extubation but does not reduce BPD[142]	I	C
	High dose dexamethasone (0.5 mg/kg-1 mg/kg) reduces BPD but may increase the risk of NDI and CP[184]	I	C
	Greatest global benefit is for infants with risk of BPD >66%—ie, those who remain intubated at 3-4 weeks postnatal age[141 185]		
Ventilatory strategy	Avoid endotracheal tube ventilation, encourage non-invasive support strategies (NIPPV, SNIPPV, nCPAP)[18]0	I	A
	Blood gas targets: pH 7.25-7.35; PaO_2 50-70 mm Hg; PCO_2 50-60 mm Hg[179]	I	A
	No advantage to allowing higher CO_2 limit[186]		
Diuretics	May improve respiratory mechanics and facilitate weaning of support. Do not prevent BPD. Continue use only if clear response demonstrated[37]	I	B
Nutrition	Same as for early phase	I	A
Methylxanthines	Same as for early phase	I	A
Established phase (>36 weeks' PMA)			
Echocardiographic screening for BPD PH	25% of infants with moderate or severe BPD have echocardiographic evidence of pulmonary hypertension[40]	III	A
Bronchodilators	May improve symptoms in subpopulations of affected infants[57]	II-3	B
Inhaled steroids	Later use may improve symptoms in subpopulations of infants[57]	III	B
Diuretics	Chronic therapy as for the evolving phase[37]	I	B
	Consider allowing infant to outgrow dose[57]	III	B
Nutrition	Same as for early and evolving phase. Avoid excessive weight gain	II-2	A
Immunization	Prophylaxis against RSV and influenza decreases re-hospitalization and morbidity	I	A
	RSV prophylaxis is cost effective[187]		

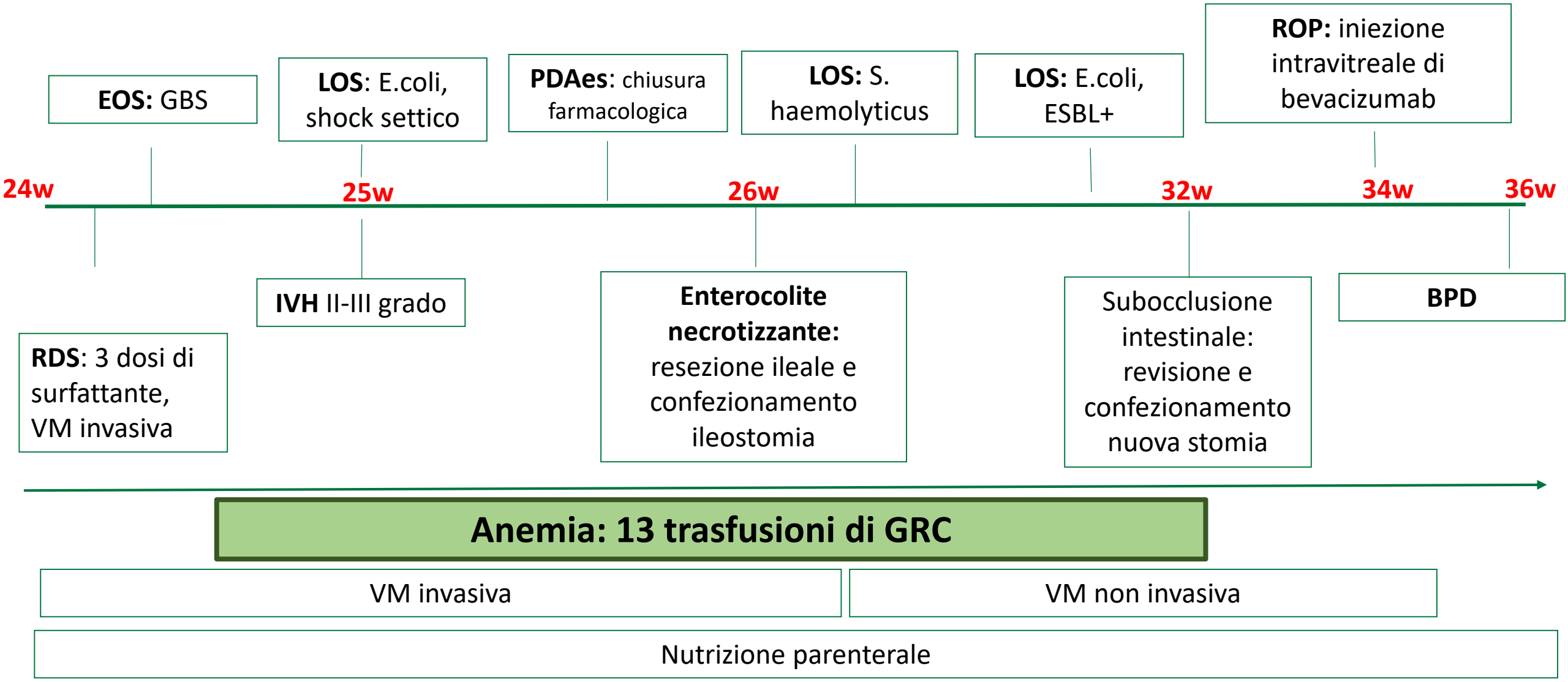
ARTICLES | DECEMBER 01 2005

Validation of the National Institutes of Health Consensus Definition of Bronchopulmonary Dysplasia

Richard A. Ehrenkranz, MD; Michele C. Walsh, MD; Betty R. Vohr, MD; Alan H. Jobe, MD, PhD; Linda L. Wright, MD; Avroy A. Fanaroff, MB, BCh; Lisa A. Wrage, MPH; Kenneth Poole, PhD; for the National Institutes of Child Health and Human Development Neonatal Research Network

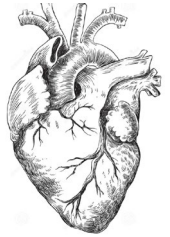
PEDIATRICS®

Decorso Clinico



Cosa abbiamo imparato: *trasfusioni di GRC*

Complicanze a breve termine 50-80% dei neonati < 28 EG riceve almeno una trasfusione di GRC



cardiac overload (TACO)

GRC

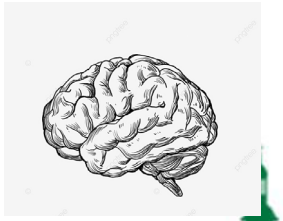
Transfusion-related immunomodulation (TRIM)

Mercurio
Piombo
Cadmio

Citochine proinfiammatorie
Ferro libero

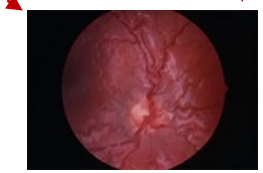
Incremento del rilascio di O2 ai tessuti
*ruolo protettivo di HbF

IVH
ND



Stress ossidativo

ROP



TRALI

Apoptosi delle cellule alveolari
Inibizione VEGF

TA-NEC

Cosa abbiamo imparato: *trasfusioni di GRC*

Complicanze a lungo termine

Red blood cell transfusions in preterm newborns and neurodevelopmental outcomes at 2 and 5 years of age

Camilla Fontana[1], Genny Raffaeli[1,2], Nicola Pesenti[2,3], Tiziana Boggini[2], Valeria Cortesi[1,2], Francesca Manzoni[1,2], Odoardo Picciolini[4], Monica Fumagalli[1,2], Fabio Mosca[1,2], Stefano Ghirardello[2]

Neurodevelopmental outcome	Transfusions within the first 28 days of life							
	24 months CA				5 years of age			
	Overall n=360		Without brain lesions n=342		Overall n=360		Without brain lesions n=342	
	Estimate	p	Estimate	p	Estimate	p	Estimate	p
General Quotient	−1.44	0.020	−2.12	0.001	−0.85	0.069	−1.31	0.006
Locomotor	−0.90	0.223	−1.68	0.031	−0.59	0.237	−1.14	0.023
Personal-social	−1.72	0.021	−2.09	0.009	−0.96	0.051	−1.23	0.015
Hearing and speech	−1.55	0.047	−2.51	0.003	−0.83	0.156	−1.45	0.022
Eye and hand co-ordination	−0.58	0.385	−1.21	0.089	−1.01	0.062	−1.53	0.008
Performance	−0.77	0.239	−1.62	0.019	−0.48	0.323	−0.97	0.056
Practical reasoning					−0.76	0.162	−1.47	0.011

CLINICAL RESEARCH ARTICLE

Transfusions and neurodevelopmental outcomes in extremely low gestation neonates enrolled in the PENUT Trial: a randomized clinical trial

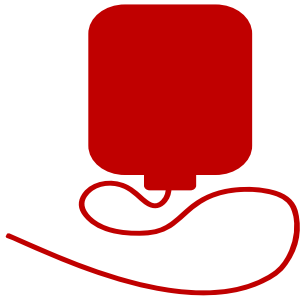
RESULTS: Each transfusion was associated with a decrease in mean cognitive score of 0.96 (95% CI of [−1.34, −0.57]), a decrease in mean motor score of 1.51 (−1.91, −1.12), and a decrease in mean language score of 1.10 (−1.54, −0.66). Significant negative

Cosa abbiamo imparato: *trasfusioni di GRC*

Trasfondere meno…e meglio!

Ritardato clampaggio del cordone ombelicale
Eritropoietina fino a 32-34 settimane

Evitare esami ematici non necessari
Utilizzare micrometodi
Utilizzare campioni placentari



Abbassare le soglie trasfusionali
GRC da cordone ombelicale

Katheria 2015, Ghirardello 2021, Juul 2020, Andersson 2011, Raffaeli 2020, Carroll 2015

Cosa abbiamo imparato: *trasfusioni di GRC*

Trasfondere meno.. E meglio!

The NEW ENGLAND JOURNAL of MEDICINE

JAMA | Original Investigation

Effects of Liberal vs Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infant

The ETTNO Randomized Clinical Trial

ORIGINAL ARTICLE

Higher or Lower Hemoglobin Transfusion Thresholds for Preterm Infants

Table 2 Haemoglobin transfusion thresholds and primary outcome for ETTNO and TOP trials

Study	ETTNO trial[24]				TOP trial[25]			
Transfusion threshold group	Higher		Lower		Higher		Lower	
Severity stratum	Critical	Non-critical	Critical	Non-critical	Respiratory support	No respiratory support	Respiratory support	No respiratory support
Haemoglobin threshold,* g/dL								
Week 1	13.7	11.7	11.3	9.3	13.0	12.0	11.0	10.0
Weeks 2–3 (ETTNO) or 2 (TOP)	12.3	10.3	10.0	8.0	12.5	11.0	10.0	8.5
Week >3 (ETTNO) or ≥3 (TOP)	11.3	9.3	9.0	7.0	11.0	10.0	8.5	7.0
Primary outcome	Neurodevelopmental impairment† at 2 years' corrected age or death before assessment				Neurodevelopmental impairment‡ at 2 years' corrected age or death before assessment			
Primary outcome, % – OR[24] or adjusted relative risk[25] (95% CI)					44.4	42.9	50.1	49.8
					1.05 (0.80 to 1.39)		1.00 (0.92 to 1.10)	
Death, % – OR[24] or adjusted relative risk[25] (95% CI)					8.3	9.0	16.2	15.0
					0.91 (0.58 to 1.45)		1.07 (0.87 to 1.32)	
Neurodevelomental impairment, % – OR[24] or adjusted relative risk[25] (95% CI)					37.6	35.9	39.6	40.3
					1.12 (0.83 to 1.51)		1.00 (0.88 to 1.13)	

Kirpalani 2020, Franz 2020, Bell 2022

Kirpalani 2020, Franz 2020, Bell 2022

Cosa abbiamo imparato: *trasfusioni di GRC*

Il futuro: trasfusioni da sangue cordonale

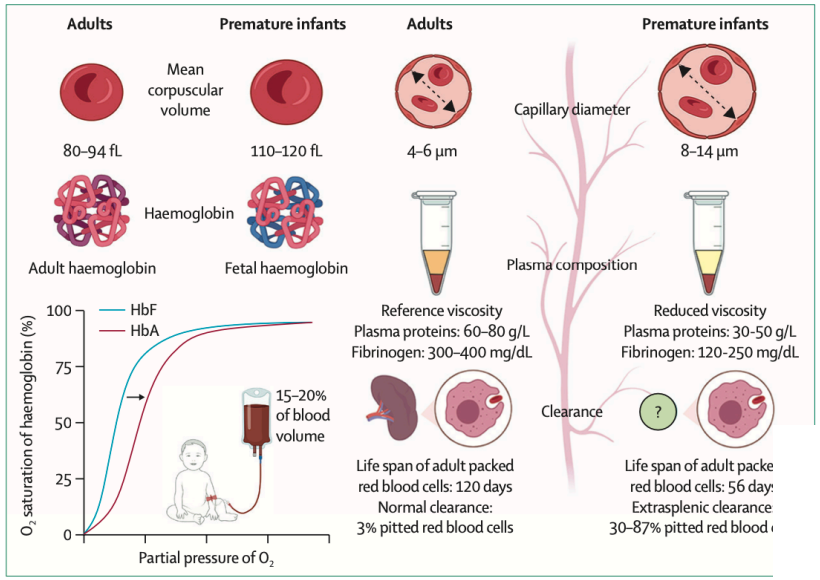


Figure: **Adult erythrocytes in an immature body**
Adult red blood cells differ substantially from the red blood cells of premature infants.

Cord blood transfusions in extremely low gestational age neonates to reduce severe retinopathy of prematurity: results of a prespecified interim analysis of the randomized BORN trial

Luciana Teofili[1,2*†], Patrizia Papacci[1,2†], Carlo Dani[3], Francesco Cresi[4,5], Giulia Remaschi[3], Claudio Pellegrino[1,2], Maria Bianchi[1], Giulia Ansaldi[4], Maria Francesca Campagnoli[5], Barbara Vania[4], Domenico Lepore[1,2], Fabrizio Gaetano Saverio Franco[3], Marco Fabbri[6], Roberta Penta de Vera d'Aragona[7], Anna Molisso[8], Enrico Beccastrini[3], Antonella Dragonetti[4], Lorenzo Orazi[9], Tina Pasciuto[1], Iolanda Mozzetta[1], Antonio Baldascino[1], Emanuela Locatelli[4], Caterina Giovanna Valentini[1], Carmen Giannantonio[1], Brigida Carducci[1], Sabrina Gabbriellini[6], Roberto Albiani[4], Elena Ciabatti[6], Nicola Nicolotti[1], Silvia Baroni[1,2], Alessandro Mazzoni[6], Federico Genzano Besso[4], Francesca Serrao[1], Velia Purcaro[1], Alessandra Coscia[4,5], Roberta Pizzolo[4], Genny Raffaeli[10,11], Stefania Villa[10], Isabella Mondello[12], Alfonso Trimarchi[12], Flavia Beccia[1,2], Stefano Ghirardello[13] and Giovanni Vento[1,2]

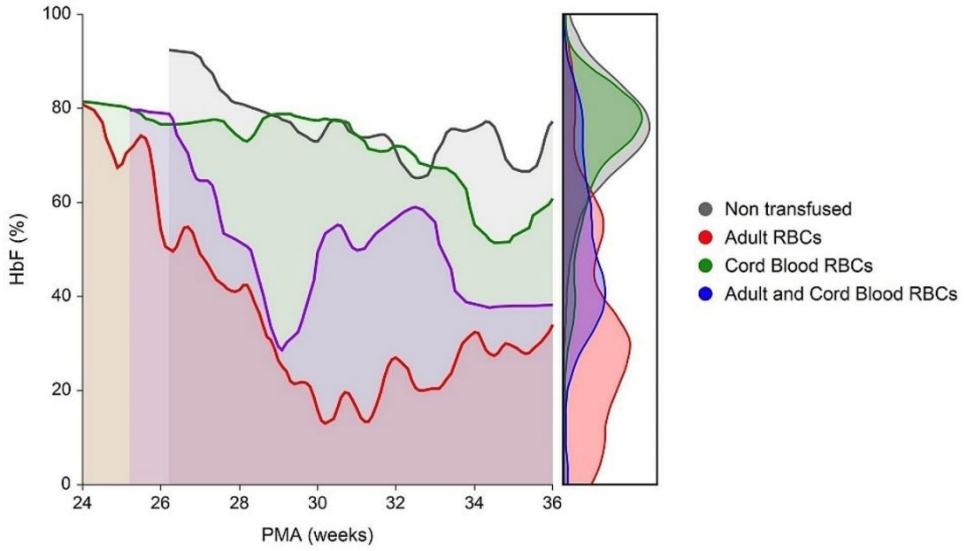


Fig. 2 Area under the curve (AUC) of HbF and post-menstrual age (PMA). The lines represent median values of HbF. (**A**) HbF AUC of patients grouped according to the occurrence of severe ROP. (**B**) HbF AUC of patients grouped according to the types of RBC products received before 30 weeks of PMA

Bellach 2022, Teofili 2024

Grazie

Ai medici e infermieri terapia intensiva neonatale per il loro lavoro quotidiano