Neonatal sepsis: Management in the NICU

Paolo Manzoni,MD, PhD

Neonatology and NICU - S. Anna Hospital - Torino, Italy
Fondazione "Crescere insieme al S.Anna-ONLUS"

Clinical Trial Center , OPBG - Roma, Italy

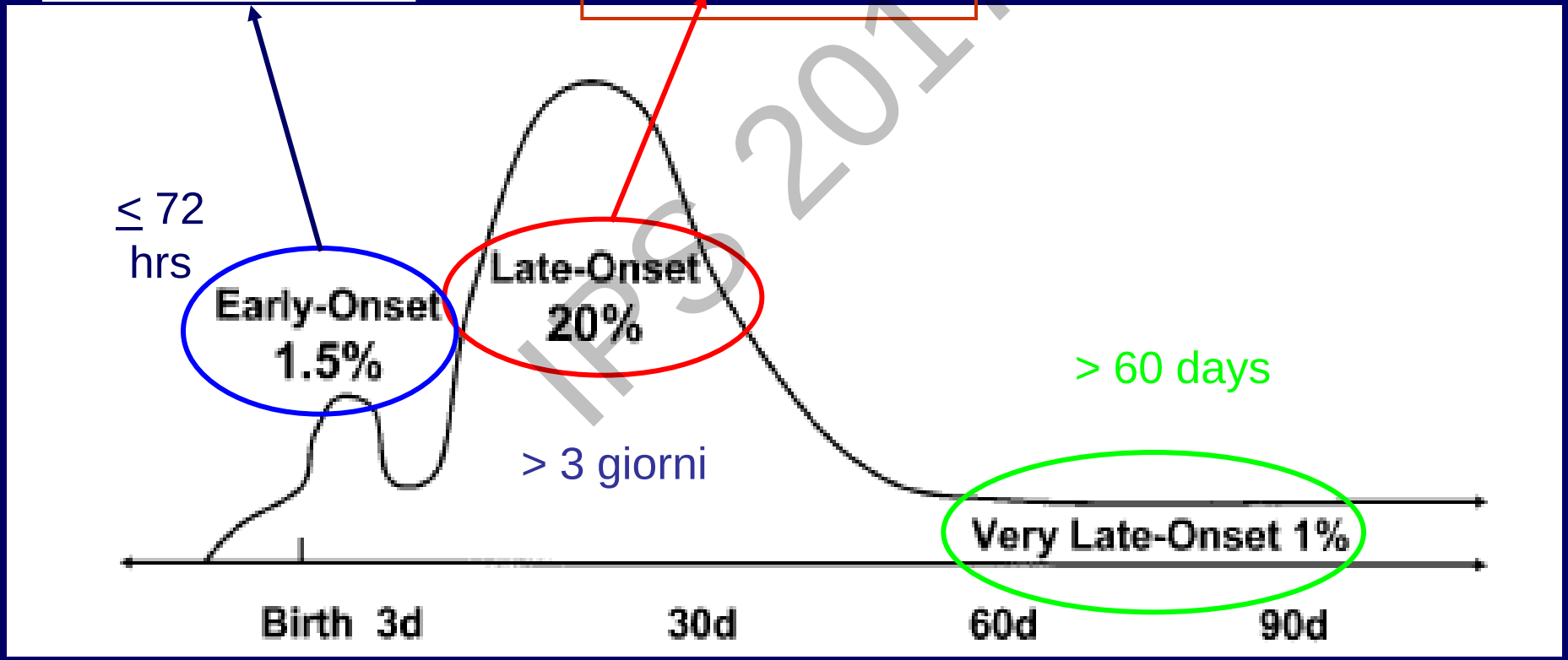
- Burden of disease: incidence, outcomes
- Classification: late-onset sepsis
- EOS → GBS
- LOS → pathogens, characteristics
- Risk factors
- Diagnosis
- Prevention
- Management : use of antibiotics; CVC management; nutritional management

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)



Kaufman, Clin Microbiol Rev 2004

Use of antibiotics in USA nei preterm VLBW neonates

National Institute of Child Health and Human Development Neonatal Research Network

	Numbers	Incidence rates
Sepsis late-onset	1313/6215	21%
Antibiotic treatment	3459/6215	56%
Sepsis early-onset	147/7606	1,9%
Antibiotic treatment	3652/7606	48%

Stoll, 2002

Stoll, 1996

Kaguelidou F, Turner MA, Choonara I, van den Anker J, Manzoni P, Alberti C, Langhendries JP, Jacqz-Aigrain E.

Randomized controlled trials of antibiotics for neonatal infections: a systematic review

Br J Clin Pharmacol. 2013 Jul;76(1):21-9. doi: 10.1111/bcp.12113.

BJCP British Journal of Clinical Pharmacology — BPS British Pharmacological Society

Many antibiotics used,
Poor evidence from RCTs !

Table 2. Tested antibiotics and context of evaluation in the 35 relevant randomized controlled trials in neonates

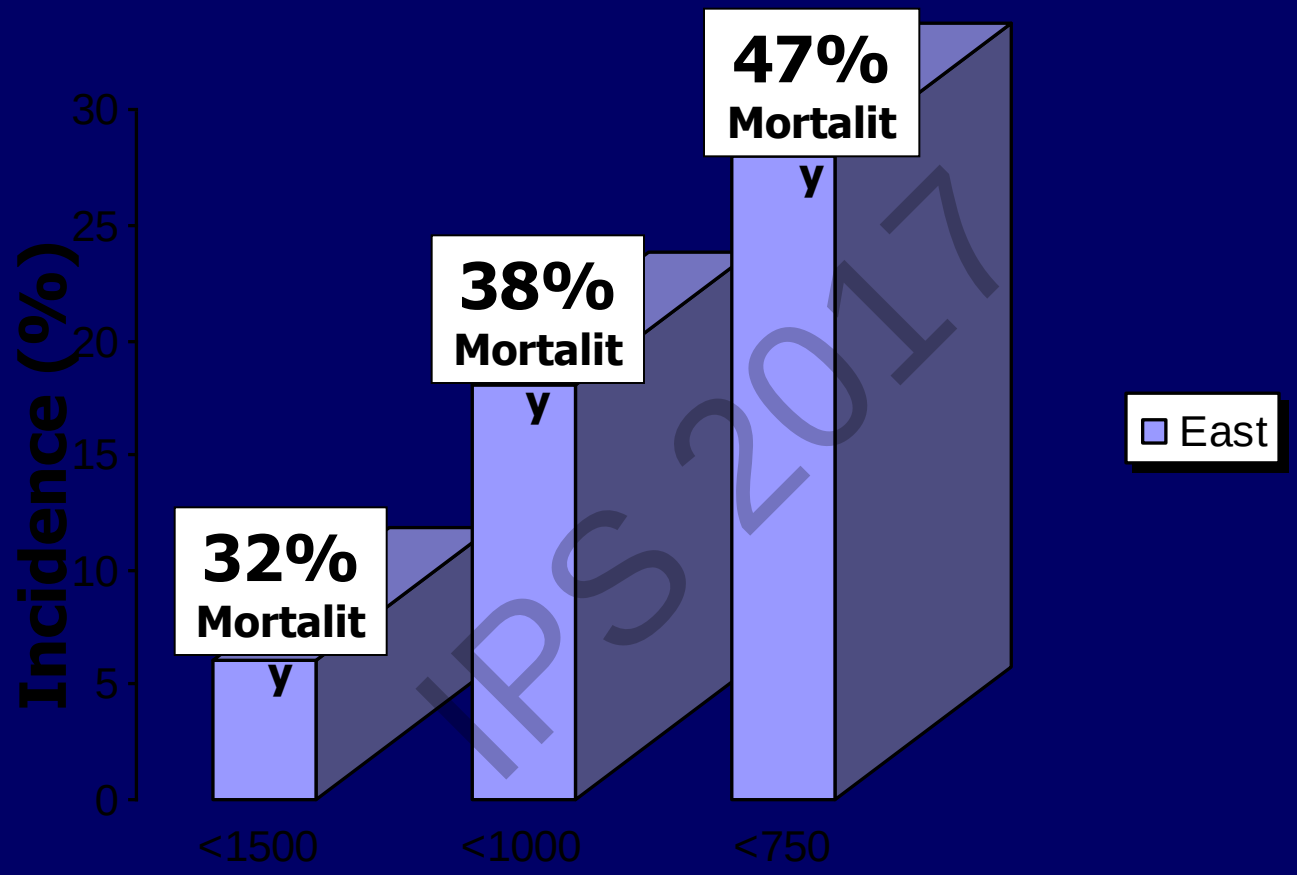
Antibiotics	Infection/Disease	Number of RCTs (%)	
		Therapeutic use	Prophylactic use
Gentamicin		**12 (34%)**	
	Suspected or proven bacterial sepsis or focal infection	8*	
	Meconium aspiration syndrom		1
	Type of infection not stated	3*	
Ampicillin + aminoglycosides		**5 (14%)**	
	Neonatal pneumoniae (+ gentamicin)	2	
	Meconium aspiration syndrom (+ gentamicin/amikacin)		2
	Bacterial infection in high risk infants (+ netilmicin)		1
Vancomycin		**4 (11%)**	
	Nosocomial coagulase-negative staphylococci infections		2
	Necrotising enterocolitis		1
	Catheter-related bloodstream infections (+ heparin lock)		1
Erythromycin		**4 (11%)**	
	Chronic lung disease with/without Ureaplasma Urealyticum colonisation		3
	Infectious conjonctivitis		1
Fucidic acid		**2 (6%)**	
	Catheter-related bloodstream infections (+ heparin lock)		1
	Infectious conjonctivitis	1	
Amoxicillin		**1 (3%)**	
	Catheter-related bloodstream infections		1
Benzathine penicillin		**1 (3%)**	
	Congenital syphilis		1
Linezolid		**1 (3%)**	
	Sepsis due to resistant Gram + bacteria	1	
Teicoplanin		**1 (3%)**	
	Coagulase-negative staphylococci infections		1
Amikacin		**1 (3%)**	
	Suspected or proven bacterial infection	1*	
Azithromycin		**1 (3%)**	
	Chronic lung disease		1
Ceftazidim		**1 (3%)***	
	Suspected or proven sepsis	1*	
Various antibiotics		**1 (3%)**	
	Suspected or proven sepsis	1	

* Antibiotic efficacy was evaluated upon pharmacokinetic parameters

Early-Onset vs. Late-Onset Sepsis : whcih are the differnces ?

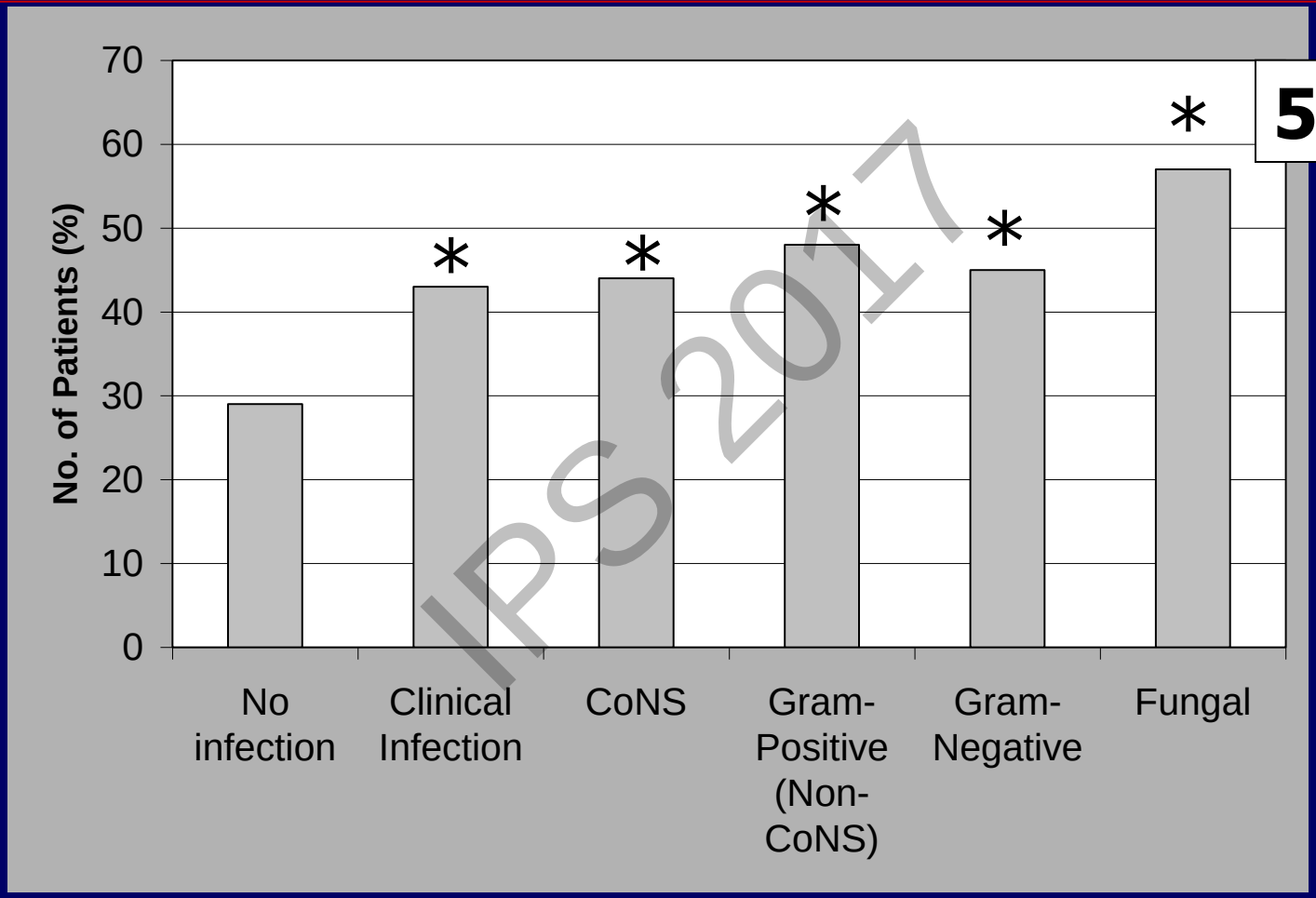
	Early	*Late*
Timing	<72 -96 hrs	>72 -96 hrs
Causative agents	>Gram neg	>Gram pos
Origin	>maternal	>nosocomial
Diagnostic Markers	Reliability +/-	Reliability ++/-
Mortality	high	medium
Prevention	maternal	in the nursery

Mortality and birth weight



NICHD Neonatal Network Data, Sept 1, 1998-Aug 31, 2000
Stoll et al. *Pediatrics* 2002 110:285 (n=6215)
Benjamin et al. *Pediatrics* 2006;117:84-92. (n=3991)

Neurodevelopmental Impairment and Bloodstream Infection in Infants <1000 g



*P≤0.001 vs. no infection

Stoll, JAMA 2004

- Burden of disease: incidence, outcomes
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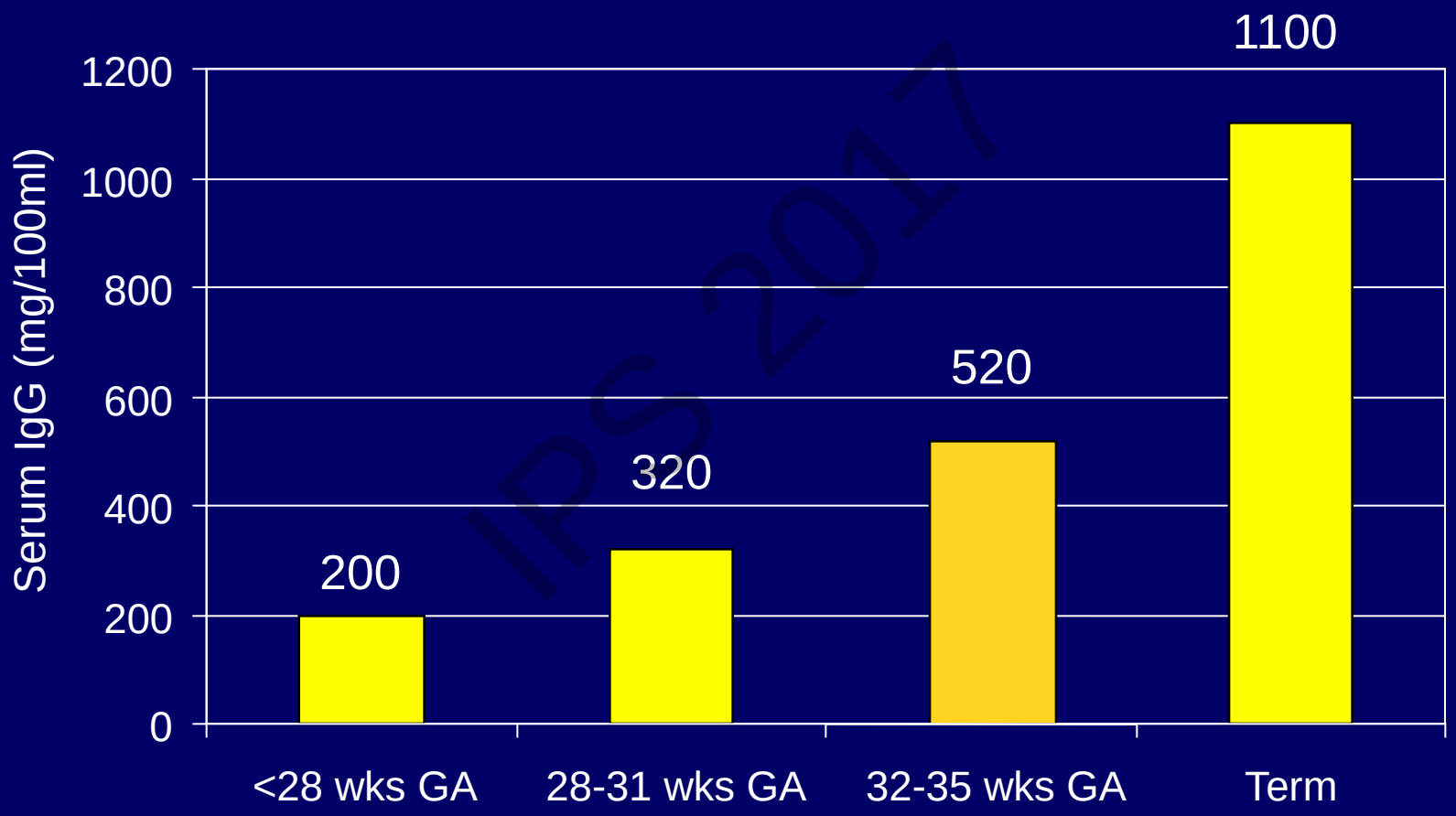
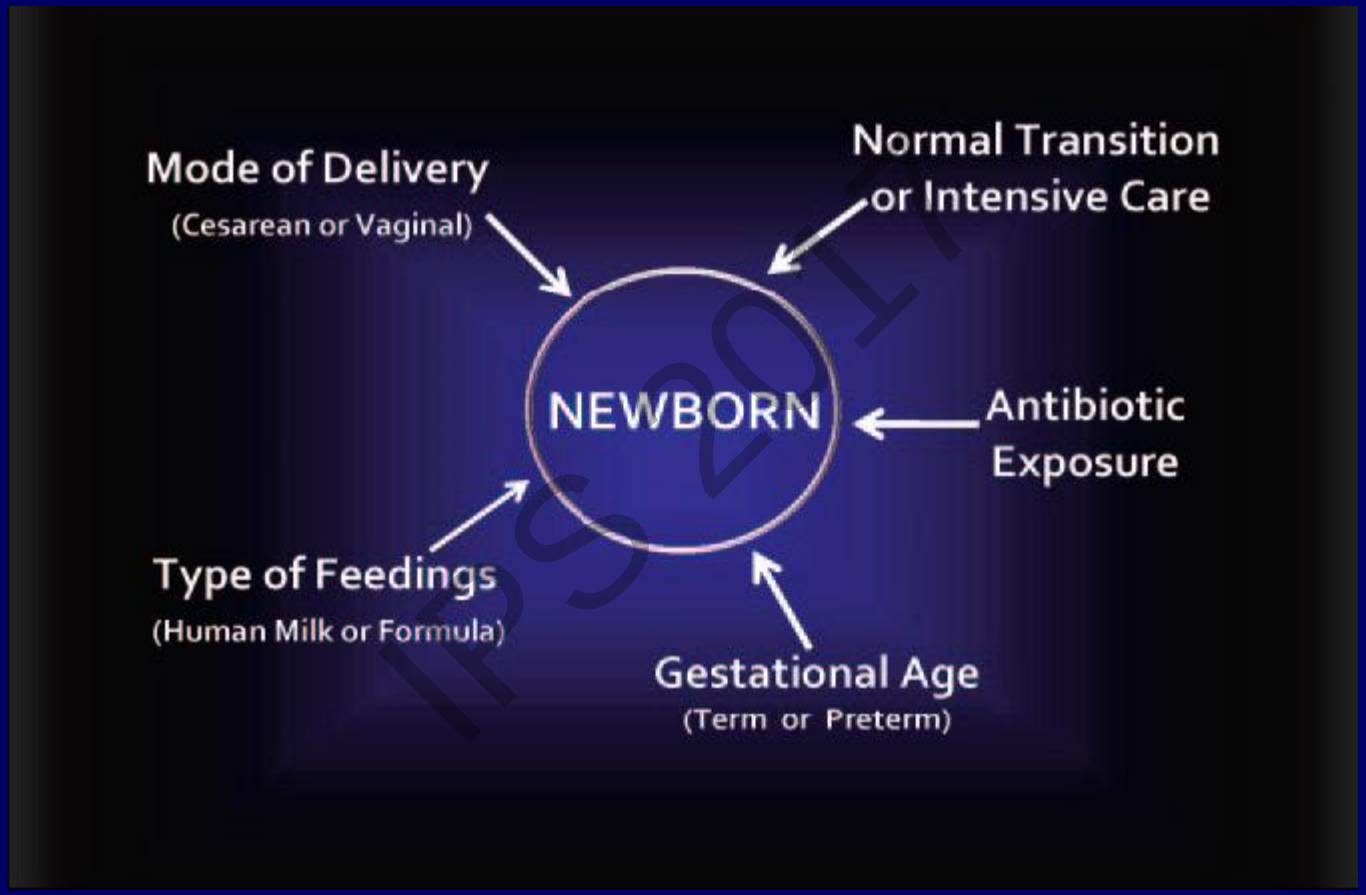
Prematurity Interrupts Optimal Transfer of Maternal IgG



Adapted from data and formulas as published by Yeung CY, Hobbs, JR. *Lancet.* 1968;7553:1167-70

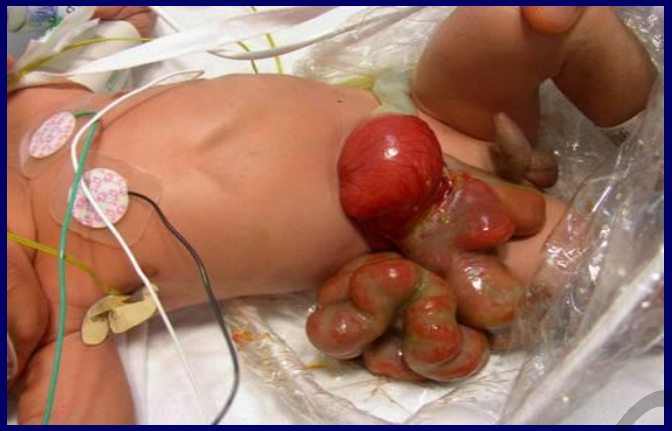
Factors affecting the Enteric Microflora composition in neonates



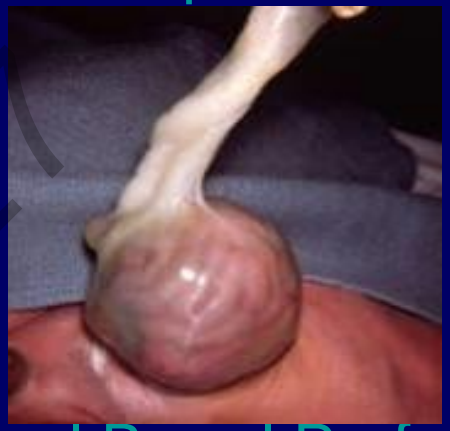
Adapted from Sharma R et al, NeoReviews 2009

Surgical Population in NICU is at highest risk: Complicated Gastrointestinal Disease

Gastroschisis



Omphalocele

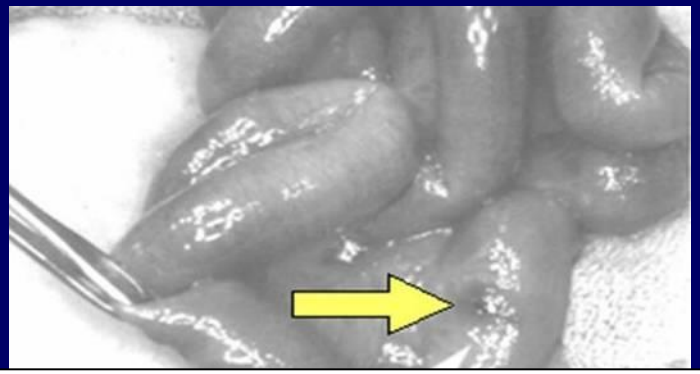


Necrotizing Enterocolitis

16.5% Candidemia

Chapman 2000, Noyola 2000.

Focal Bowel Perforation



44% *Candida* Peritonitis

Coates, 2005

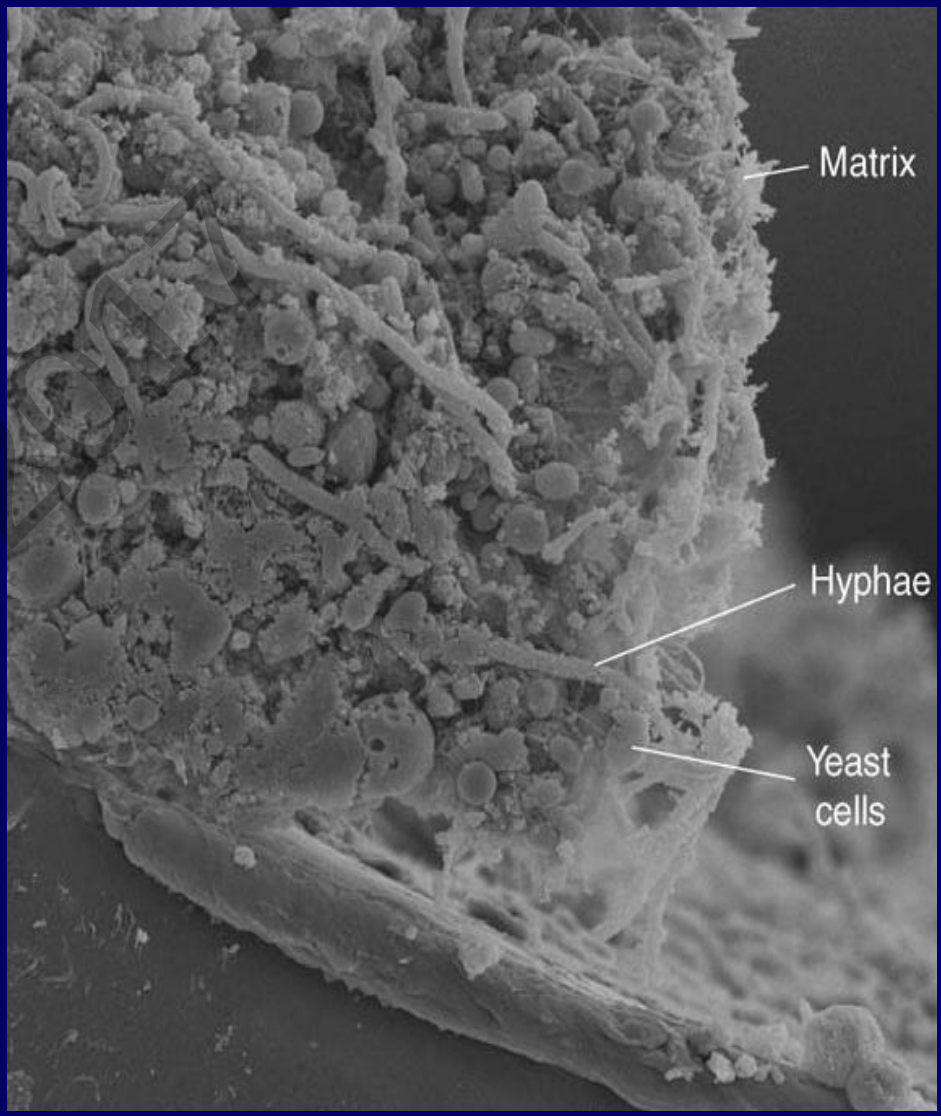
Risk of CVC-related sepsis

OR= 2,0 (95% CI 1,1-3,9)
(Avila-Figueroa, 1998)

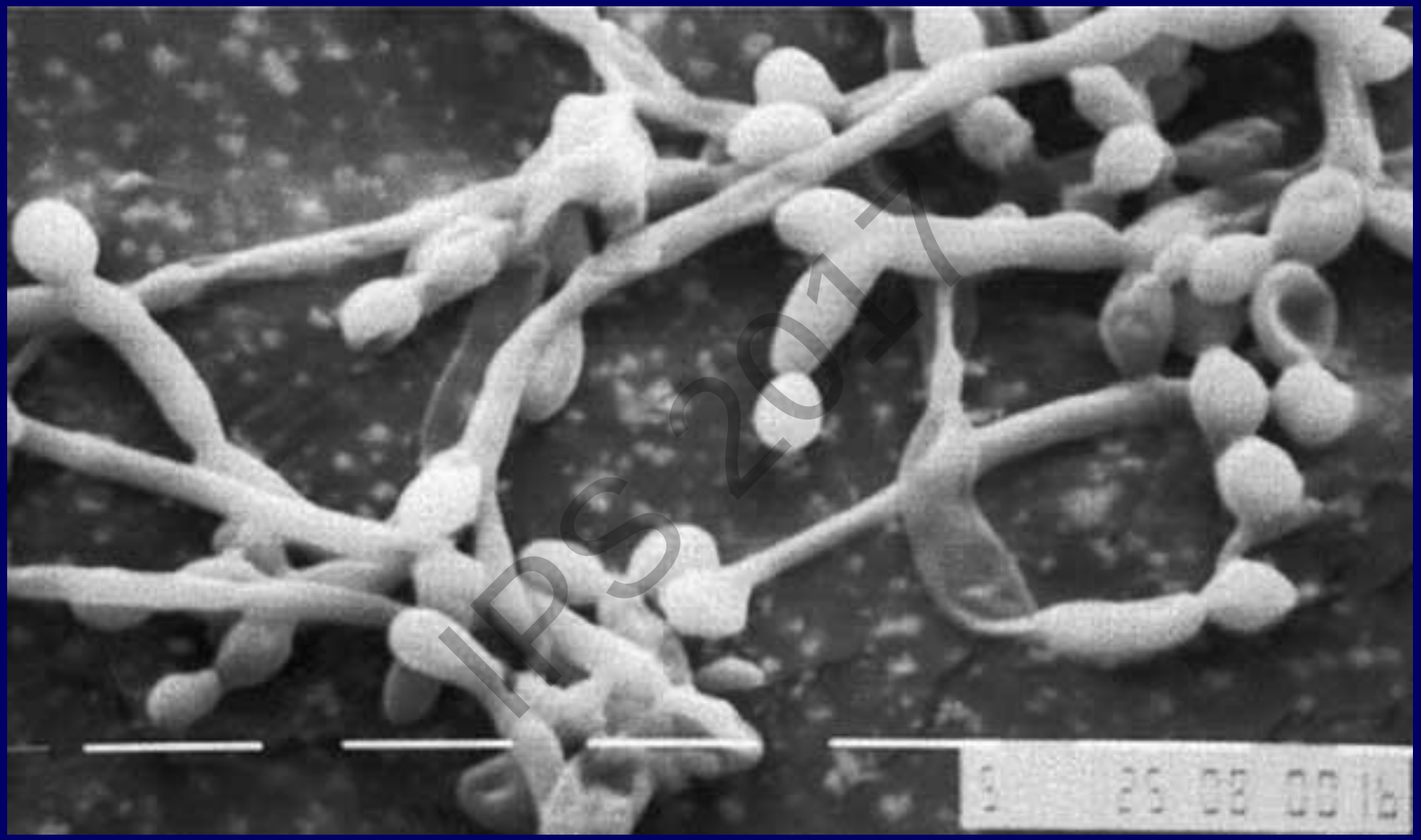
RR= 3,81(P < 0,001)
(*Pediatric Prevention Network, 2001)*

RR= 5,87 (P = 0,001)
(Auriti, 2003)

OR= 13,6 (p= 0.01)
(Rojas, 2005)



Fungal Biofilms



- Electron micrograph of biofilm formed by *C. albicans* on catheter material

Jabra-Rizk MA et al (Baltimore), Emerg Infect Dis 2004;10:14-9

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The role of Neonatologists

1. timely diagnosis
2. timely treatment

To do this, neonatologists need to have :

- Accurate knowledge of the of maternal history with regard to occurrence of infectious diseases and/or colonization
- Careful adherence to the neonatal GBS prevention protocols
- Full knowledge of what you can expect from the laboratory markers and the microbiology -culture evaluations

Diagnosis of Sepsis : sensitivity and specificity of various diagnostic markers

Table 3. Sensitivity, specificity, and positive and negative predictive value of some laboratory tests used in the diagnosis of infection in the newborn (Ref. 4)

Test	Sensitivity	Specificity	PPV	NPV
Blood culture	11–38	68–100	90–100	72–100
WBC <5000 >30,000	17–90	31–100	50–86	60–89
I/T ratio >0.02	81	45	23	92
CRP >10 mg/L	37	95	63	87
IL-8 >70 pg/mL	77	76	42	94
I/T ratio >0.02 + CRP > 10 mg/L	89	41	24	94
IL-8 > 70 pg/mL + CRP >10 mg/L	91	74	43	98
16 S PCR[a]	96.0	99.4	88.9	99.8

PPV, positive predictive value; NPV, negative predictive value; WBC, white blood cell count; I/T, immature/total neutrophil ratio; CRP, C-reactive protein; IL, interleukin; PCR, polymerase chain reaction.

[a]From Ref. 35. All values are percentages.

Khalid, 2005

The Limits of blood cultures in the diagnosis of infections

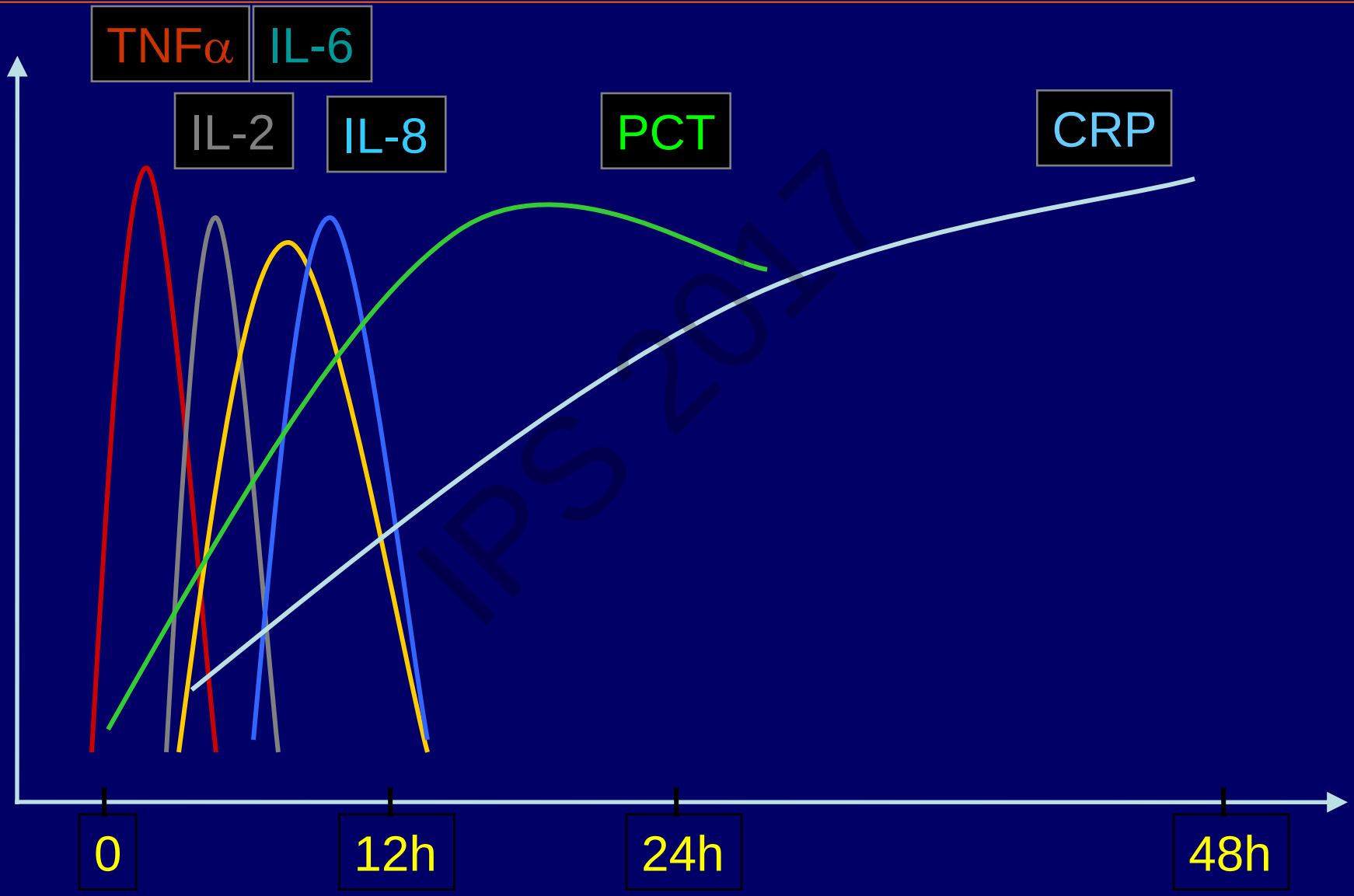
- Failure to identify the various species of pathogens (eg., up to 15% of the microbilogical samples can be actually contaminated with Candida spp,).

- 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 "peripheral" vs. blood "central"

Issues related to the Timing of the sepsis markers



Possible laboratory “markers” that are suggestive for causative pathogens of neonatal infections

- **Hyperglycaemia** ***(Manzoni et al, Acta Paediatr 2006)***
- **Glycosuria** ***(Bekhof et al, BMC Pediatr 2015)***
- **Thrombocytopenia** ***(Guida et al, Pediatrics 2003; Benjamin et al, Pediatrics 2003***
- **CRP increase** ***(Makhoul IR, Pediatrics 2002)***

Table 1
Summary of hematologic changes in neonatal sepsis

Pathogen or Group of Pathogens	RBC Count	WBC Count	Neutrophils Count	Lymphocytes Count	Platelets Count
Gram positives	[a]	↑ or ↓	[a] (rarely ↓)	[a]	↓↓
Gram negatives	[a]	↑or ↓	↓	[a]	↓
Fungi	[a]	↑or ↓	↓↓	[a]	↓↓↓

(from Manzoni P, Clin Perinatol 2015)

Clinical Signs of Sepsis: 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, >= .25 cutoff	45%	84%	6%	98%
I:T ratio, >= .30 cutoff	35%	89%	7%	98%

Escobar, et al. Pediatrics 2000;106:256-263

- Burden of disease: incidence, outcomes
- Classification: Early and late-onset sepsis
- EOS → GBS
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- Risk factors
- Diagnosis
- Key points for appropriate management

List of Key points for appropriate management of infections in the NICU (1)

1. it is appropriate to consider any premature infant with microbiological or clinical evidence of infection as having disseminated disease:
   - → perform all measures to screen out end-organ involvements
   - → perform careful follow-up to capture/intercept late NDI sequelae associated with infection

2. two antibiotic treatment strategies are possible:
   - ❑ targeted therapy
   - ❑ empirical/pre-emptive treatment.
     - → This last option is the most frequent one, given the rarity of cases in which the causative pathogen s known since the beginning.

List of Key points for appropriate management of infections in the NICU (2)

3. Rules about the choice of antibiotics when instituting antibiotic treatment:
   - ✓ a combination of agents active on both Gram-negative and –positive is strongly recommended
   - ✓ use narrow-spectrum antibiotics : start antibiotics with the most possible limited spectrum
   - ✓ Meropenem and Imipenem can select carbapenem-resistant strains
   - ✓ Broad-spectrum antibiotics are associated with increased risk of systemic fungal infections
   - ✓ when previous antibiotic exposure is reported, switch to a different antibiotic class
   - ✓ therapy adjustments based on the microbiology findings need to follow.

Antibiotics in Neonatal Intensive Care Unit: need to reinforce stewardship

"….judicious use of antibiotics is an important tool for limiting the emergence of resistant organisms, and appropriate antibiotic policies should be developed in every NICU in order to restrict the use of unnecessary broad spectrum antibiotic therapy…."

Stronati M et al. J Chemother 2007; 19(S2): 52-5.

General Recommendations :

- Don't use if not necessary
- If use, withdraw if not/nomore necessary
- Use the narrowest possible spectrum

Torino S. Anna NICU
Protocols for empiric antibiotic treatment in VLBW infants

Early-Onset: **Ampicillin+Aminoglicoside**

Late-Onset : **Vancomycin + Aminoglicoside**

→ **2nd line Teicoplanin + add Piperacillin tazobactam**

→ **3rd line add Meropenem , consider Micafungin**

List of Key points for appropriate management of infections in the NICU (3)

4. Microbiology is Pivotal !

- ✓ Always perform blood /deep cultures when starting antibiotics
- ✓ Even though many episodes of sepsis are caused by a breakthrough, pathogenic microorganism, in many other cases peripheral colonization usually precede systemic infection
- ✓ Be guided by local ecology and epidemiology (information from surveillance cultures is useful)
- ✓ Treat sepsis, not colonization
- ✓ Be aware of maternal infectious disease
- ✓ Consider the central venous catheter status and the possibility/probability that biofilms have formed
- ✓ Start Empirical , but switch as soon as you can to targeted

List of Key points for appropriate management of infections in the NICU (4)

5. Role of laboratory markers:
   - Limited value in diagnosis
   - Good confirmatory value of diagnosis
   - Good guidance for assessing response to therapy

6. Be ready to withdraw as much as you are ready to institute antibiotics :
   - ✓ discontinue antibiotics as soon as possible if clinical-diagnostics allows
   - ✓ There is a general consensus on discontinuation of therapy after 48 - 72 hours if negativity of blood cultures and in absence of clinical signs suggestive of suspected sepsis

Should Antibiotics be Discontinued at 48 Hours for Negative Late-Onset Sepsis Evaluations in the Neonatal Intensive Care Unit?

Jeffrey R. Kaiser, MD, MA
James E. Cassat, BS
Mary Jo Lewno, MT (ASCP)

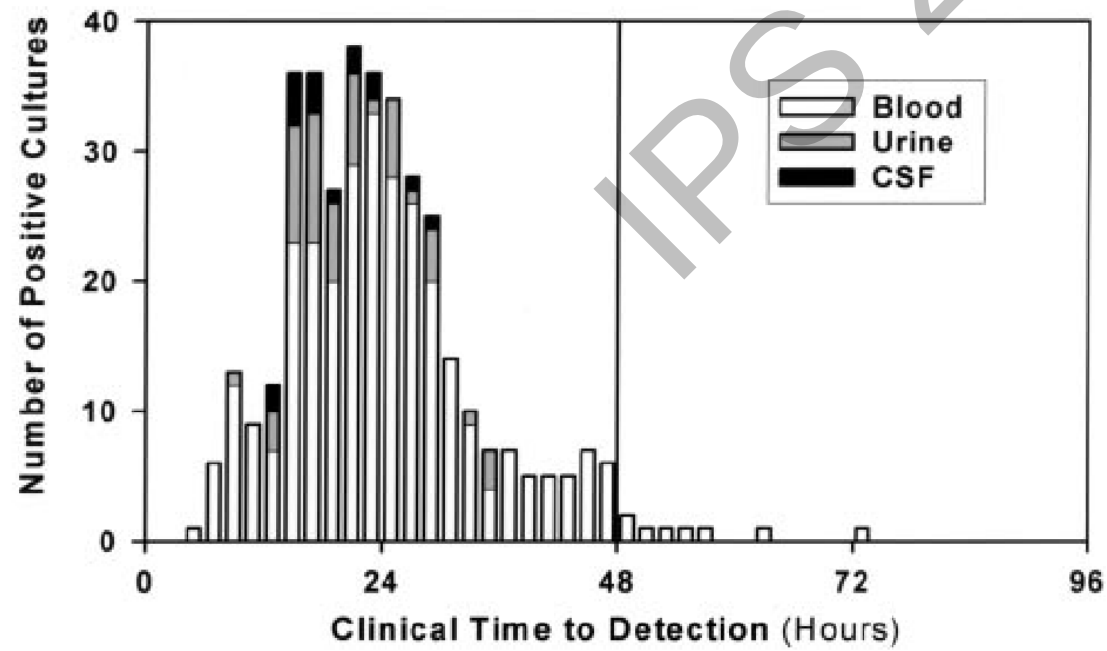
Journal of Perinatology (2002) **22,** 445–447

98% (97% blood; 100% Urine e CSF)

8 pos >48 hrs

2783 Cultures

283 Pos (10,2%)



Withdraw antibiotics if not – nomore necessary

"….Antibiotic should be started empirically whenever a neonatal severe infection is suspected and suspended after 48-72 h, if cultures and clinical signs exclude infection…."

Borghesi a et al. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. J Hosp Infect. 2008 Apr;68(4):293-300.

List of Key points for appropriate management of infections in the NICU (5)

7. Duration of antibiotic treatment :

- At least 2 weeks in bloodstream infections
- At least 3-4 weeks in end-organ localizations
- At least 4 weeks in meningitis :
  - meningitis due to Gram positive → 2 weeks after sterilization
  - meningitis due to Gram negative → 3 weeks after sterilization
- In any case, recommended duration is 7-10 days AFTER the first negative blood culture

Isaacs. "Rationing antibiotic use in neonatal units". Arch Dis Child Fetal Neonatal ed 2000;82:F1
Kaiser. "Should antibiotics be discontinued at 48 hours for negative late-onset-sepsis evaluations in NICU J. Perinatology 2002;22:445-447

How can we prevent Antibiotic resistance ?

"….Judicious use of antibiotics is an important tool for limiting the emergence of resistant organism and appropriate antibiotic policies should be developed in every NICU in order to restrict the use of unnecessary broad spectrum antibiotic therapy…."

Antibiotics in Neonatal Intensive Care Unit

J Chemother. 2007 Oct; 19 Suppl 2:52-5.

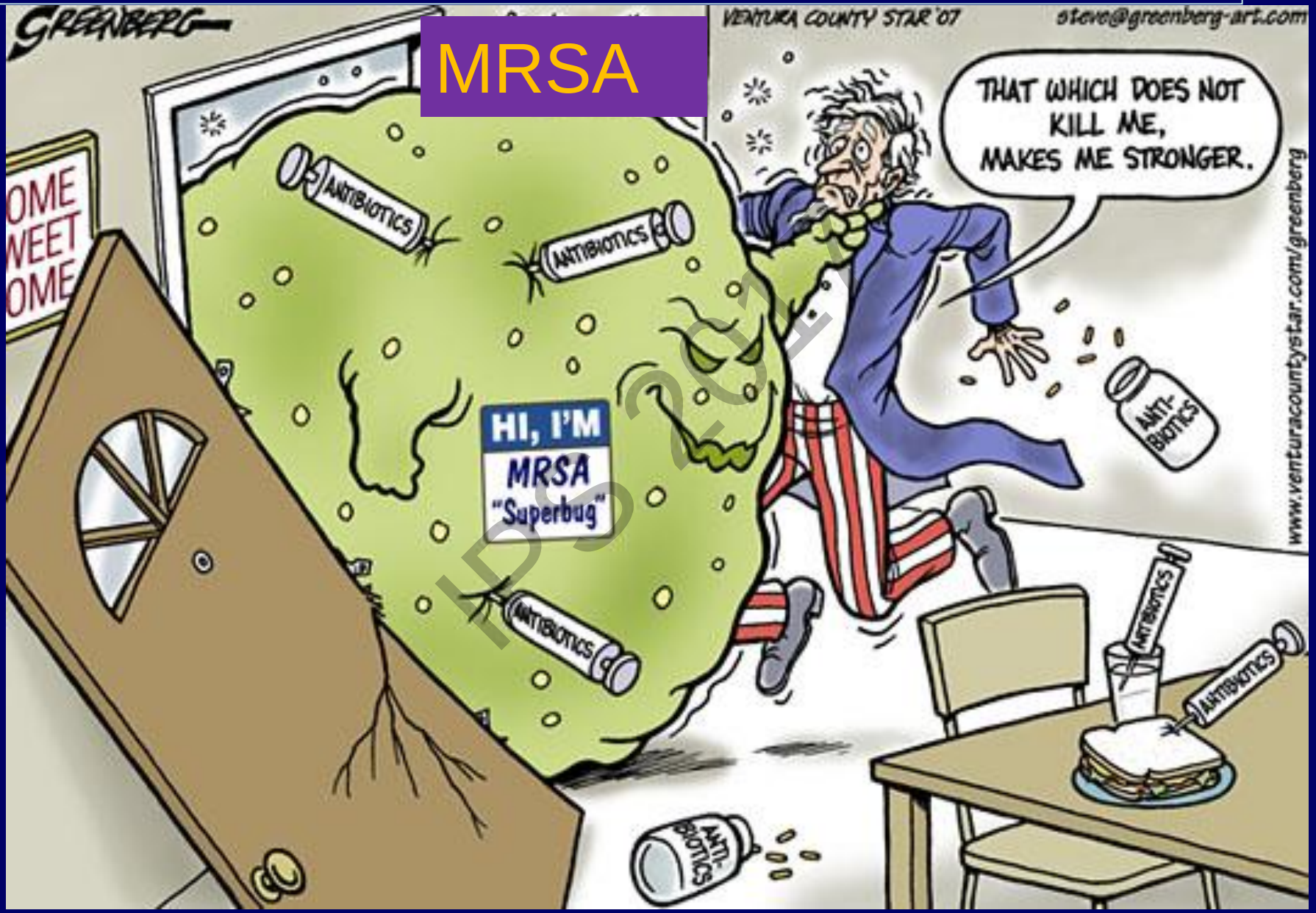
Bundles of prescription and of discontinuation for use of antibiotics in the NICU

JB Cantey, PS Wozniak,JE Pruszynski,PJ Sánchez
Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study
Lancet Infect Dis 2016. 16 (10), 1178–1184

Joseph B Cantey, , et al
Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study
Lancet Infect Dis 2016. 16 (10), 1178–1184

- Observational study in the level 3 NICU at Parkland Hospital, Dallas, TX, USA.
- All antibiotic use in infants admitted to the NICU during 9 months was monitored and analysed. Continuation of empirical antibiotic therapy for ruled-out sepsis courses beyond 48 h, pneumonia, and “culture-negative” sepsis were selected as targets for antibiotic stewardship interventions.
- During the 9-month intervention period, (1) empirical antibiotic therapy was set to discontinue after 48 h in the electronic medical record and (2) the duration of therapy for pneumonia and culture-negative sepsis was limited to 5 days.
- Changes in Antibiotic use, defined as days of therapy per 1000 patient-days, were compared between the baseline and intervention periods (primary outcome)
- Antibiotic use declined from 343 days of therapy/1000 patient-days during the baseline period to 252 days of therapy/1000 patient-days in the intervention period ($p<0.0001$), representing an overall decrease of 27%.
- No difference in safety outcomes was observed between the intervention and baseline periods.

Why is it necessary to target antibiotic use?
Risk for selection of resistances



Most frequent Gram-positive and Gram-negative resistant organisms in the NICU

Pathogen	Resistance
CONS	**oxacillin/methicillin**
MRSA	**oxacillin/methicillin**
Enterococci VRE	**vamcomycin**
ESBLs (extended spectrum β lactamase) ➢*Klebsiella* ➢*E. coli*	**piperacillin-tazobactam, ceftazidime, and/or gentamicin, 3rd generation cephalosporins, including cefotaxime, ceftriaxone, and ceftazidime**
Klebsiella pneumoniae carbapenemases producers (KPCs)	**imipenem and meropenem**

Antibiotic exposure increases the risks of development of resistances

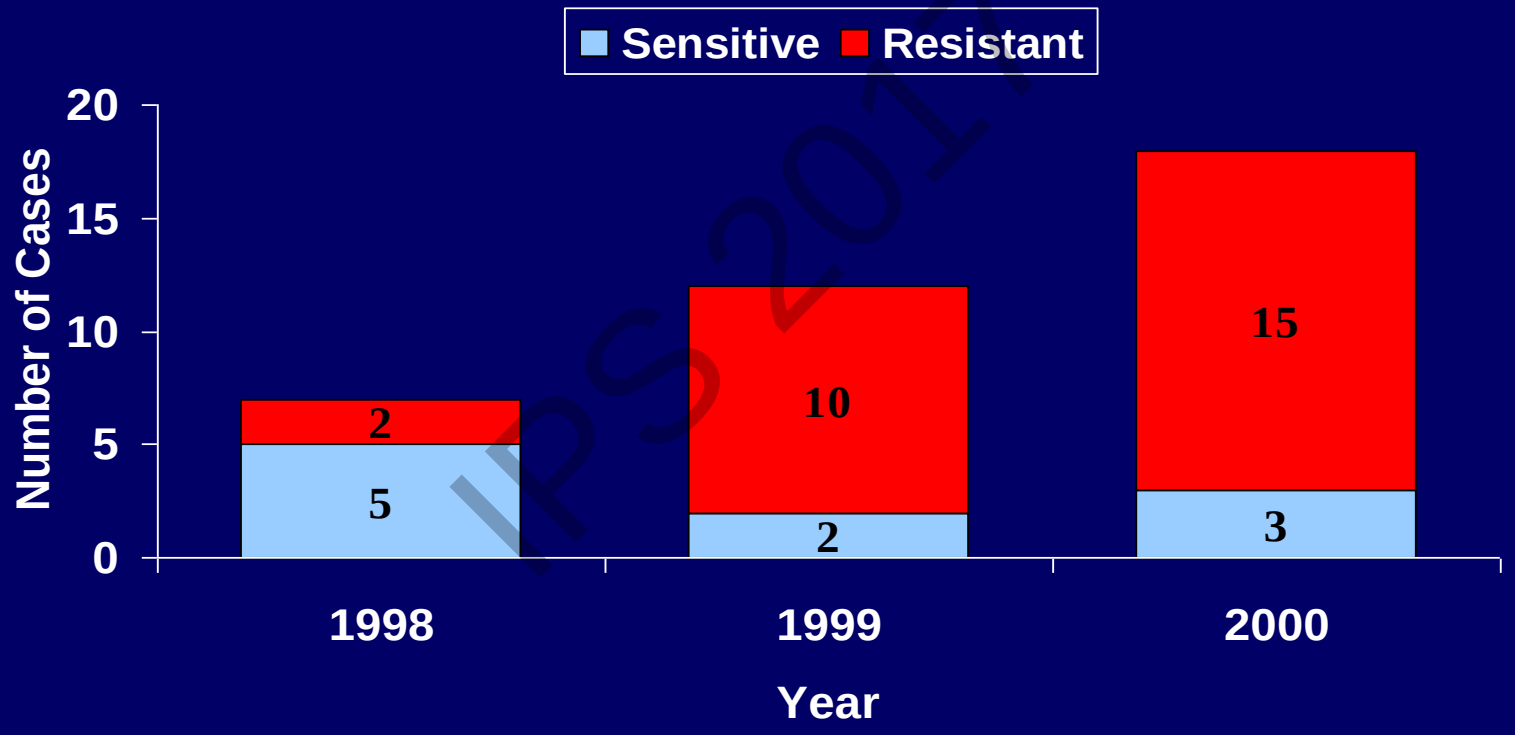
Pathogen and Antibiotic Exposure	Increased Risk
Carbapenem Resistant Enterobacteriaceae and Carbapenems	**15 fold**
ESBL producing organisms and Cephalosporins	**6- 29 fold**

Patel G et al. Infect Control Hosp Epidemiol 2008;29:1099-1106

Zaoutis TE et al. Pediatrics 2005;114:942-9

Talon D et al. Clin Microbiol Infect 2000;6:376-84

Trend of Ampicillin Susceptibility of *E. coli* from Early-Onset Sepsis Cases Preterm Infants, Selected Counties CA and GA, 1998-2000



N=37, p=0.02, linear trend

Hyde, Pediatrics, 2001; 110(4):690-95

AJIC American Journal of Infection Control

Surveillance of multidrug-resistent gram-negative bacilli in NICU: prominent role of cross transmission

Neonates n= 210	Colonized ny multi- resistent Bacilli N= 116	Colonized by susceptible Bacteria N= 39	Not colonized N=55	P
Total time of exposure to antibiotics	8 days	2.3 days	5.5 days	< 0,01

Mammina, 2007

“New” Antibiotics : their use in neonates should always be, at the moment, only “targeted” and “rescue”

1. Linezolid
2. Daptomyin
3. Tygecicline

Mainly active on Gram-pos

1. Colystin
2. Ertapenem
3. Doripenem

Mainly active on Gram-neg

And what about antibiotic management of the Central Line ?

Don’t use if not necessary: No evidence to support any PROPHYLACTIC use of Antibiotics in the NICU (1)

Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical venous catheters (Review)

Inglis GDT, Davies MW

Authors’ conclusions

There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when UVCs are inserted in newborn infants. There is no evidence to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with UVCs.

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database of Systematic Reviews 2005

Don’t use if not necessary: No evidence to support any PROPHYLACTIC use of Antibiotics in the NICU (2)

Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters (Review)

Inglis GDT, Jardine LA, Davies MW

Authors’ conclusions

There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when umbilical artery catheters are inserted in newborn infants, and no evidence to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with umbilical artery catheters.

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database of Systematic Reviews 2007

Don’t use if not necessary: No evidence to support any PROPHYLACTIC use of Antibiotics in the NICU (3)

Prophylactic systemic antibiotics to reduce morbidity and mortality in neonates with central venous catheters (Review)

Jardine LA, Inglis GDT, Davies MW

Authors’ conclusions

Prophylactic systemic antibiotics in neonates with a central venous catheter reduces the rate of proven or suspected septicaemia. However, this may not be clinically important in the face of no significant difference in overall mortality and the lack of data on long-term neurodevelopmental outcome. Furthermore, there is a lack of data pertaining to the potentially significant disadvantages of this approach such as the selection of resistant organisms. The routine use of prophylactic antibiotics in infants with central venous catheters in neonatal units cannot currently be recommended.

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database of Systematic Reviews 2008

No evidence to support any PROPHYLACTIC use of Antibiotics in the NICU: the CDC policy statements

Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011

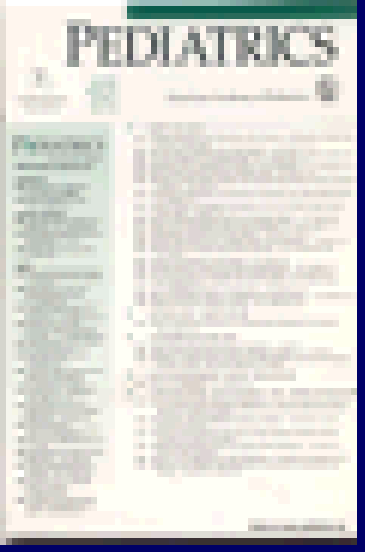
Systemic Antibiotic Prophylaxis

Do not administer systemic antimicrobial prophylaxis routinely before insertion or during use of an intravascular catheter to prevent catheter colonization or CRBSI [114].

Category IB

Umbilical Catheters

No recommendation can be made regarding attempts to salvage an umbilical catheter by administering antibiotic treatment through the catheter. Unresolved issue



Bacteremia, central catheters and neonates: when to pull the line

Complications:

- End-organ localization
- Persistent bacteriemia
- Death

Early catheter removal	Complicated Sepsis
YES	2/25 (8%)
NO	59/128 (46%)
OR (95% CI)	9.8 (2.2- 43.4)

Benjamin, Pediatrics 2001

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)

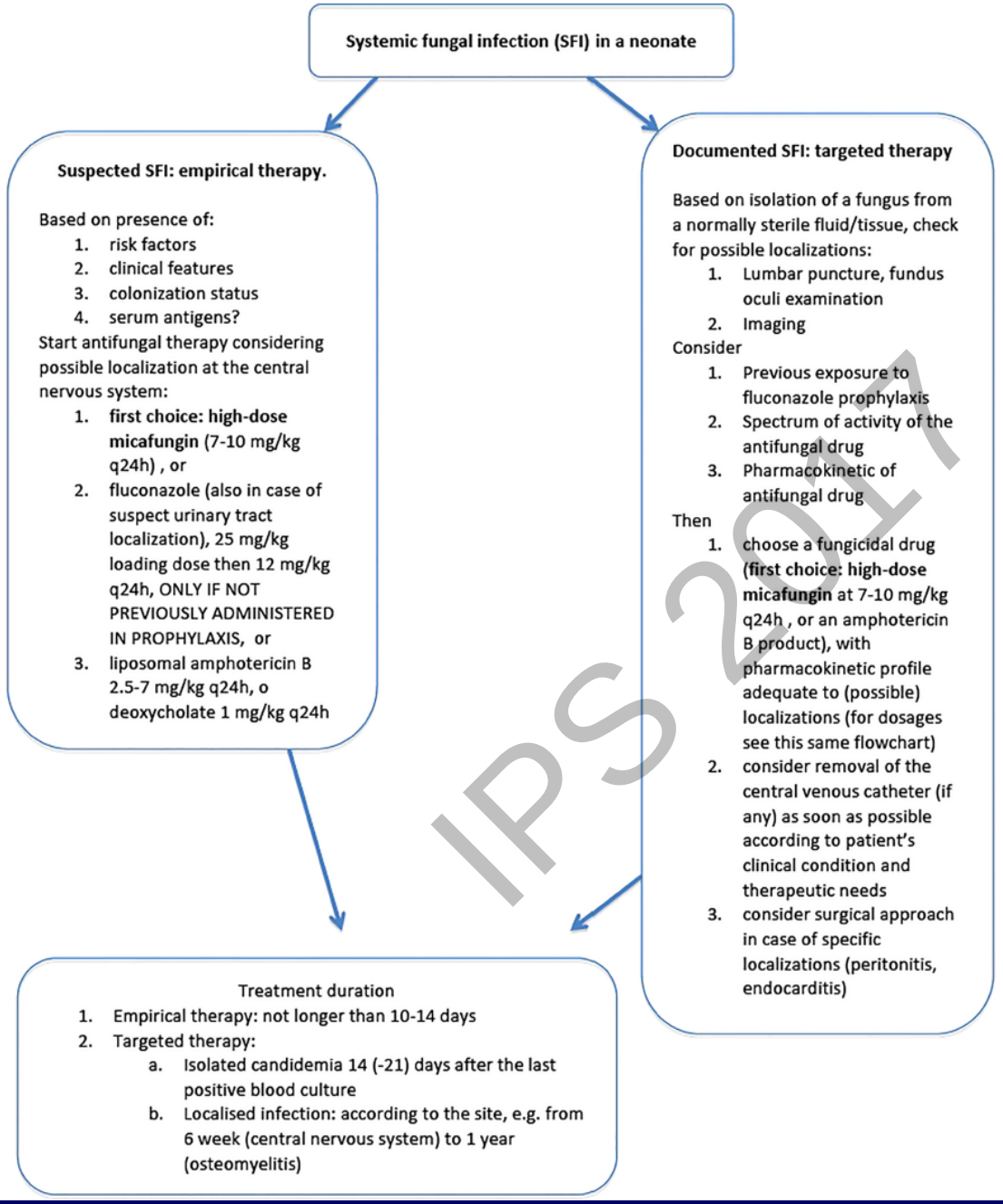
THE LANCET
Volume 376 · Number 9734 · Pages 1–68 · July 3–9, 2010 www.thelancet.com

In summary: the main take-home messages

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

Manzoni P, Dall'Agnola A. Lancet Infect Dis 2016

And what about fungal infections ?



Manzoni P, et al. Update on the management of Candida infections in preterm infants

Arch Dis Child Fetal Neonatal Ed 2015;0:F1–F6.

Optimal rescue strategy

→ to perform treatment with the most potent antifungal available to minimise the risk that septic foci may escape treatment and disseminate

- Ideal antifungal drugs for neonates **must have:**
  - **significant activity against biofilms**
  - **significant activity against *C. glabrata*, *C. tropicalis* and *C. krusei* (because they may survive prophylactic fluconazole)**
  - **ability to be used in mono-therapy**
  - **good tolerability**
  - **no pharmacological interactions**

HIT FAST, HIT HARD !!

- The Echinocandins are the most appropriate class of antifungal agents to date available to address the specific neonatal needs
- Micafungin is the only antifungal agent to date approved for neonatal use in Europe

	Micafungin[1]	Caspofungin[2]	Anidulafungin[3]
Invasive candidiasis	**Yes**	Yes	Yes
Neutropenic patients	**Yes**	Yes	No
Paediatric patients	**Yes**	≥ 12 months	No
Neonates	**Yes**	**Limited data**	**No**
Prophylaxis in HSCT patients or expected neutropenic patients			
Adults	**Yes**	No	No
Paediatric patients	**Yes**	No	No
Neonates	**Yes**	No	No

Manzoni et al, EHD 2012

KARLOWICZ, MG et al

Should Central Venous Catheters Be Removed as Soon as Candidemia Is Detected in Neonates?

Pediatrics 2000;106(5).

104 IFI:

- 50 infants had early-removal CVC (ERCVC) within 3 days
- 54 infants had late-removal CVC (LR-CVC) >3 days after the first positive blood culture for *Candida spp*.
- All infants were treated with amphotericin B.
- The ER-CVC group had significantly shorter duration of candidemia (3 days) than the LR-CVC group (6 days) (*P*=0.002)
- The case fatality rate of *Candida albicans* candidemia was significantly affected by the timing of CVC removal:
  0 of 21 infants died in the ER-CVC group in contrast to 9 of 23 (39%) in the LR-CVC group.

Conclusions

Failure to remove CVC as soon as candidemia is detected in preterm neonates is associated with significantly increased mortality in *C albicans candidemia* and prolonged duration of candidemia regardless of *Candida spp.*

Thank you !

paolomanzoni@hotmail.com

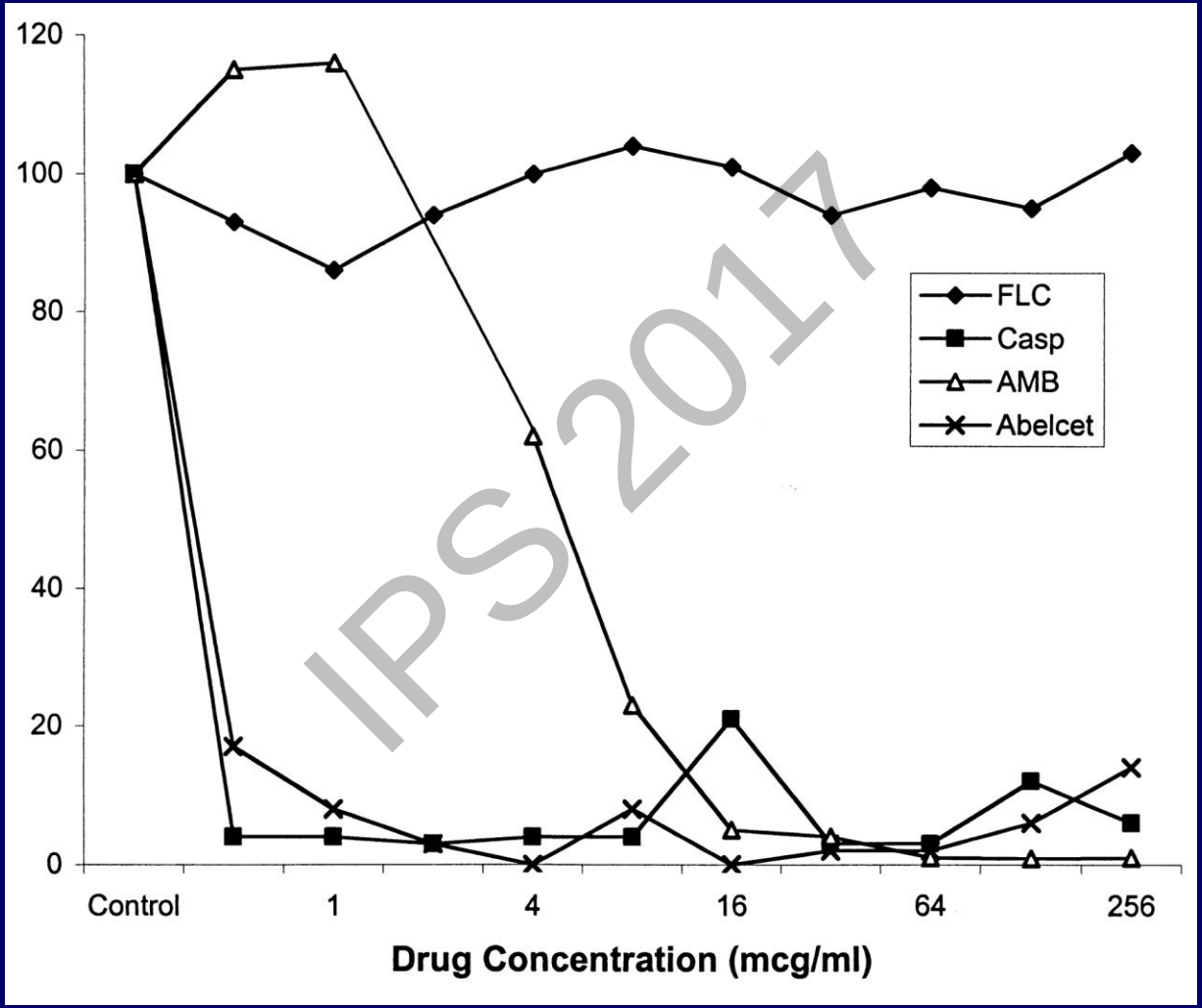
Risk factors for fungal infection in neonates

- **In preterm infants:**
  1. Extreme prematurity: lowest gestational ages
  2. Candida colonisation
  3. Risk for biofilms
  4. Antibiotic and medication practices
  5. Central venous catheter
  6. Prior bacterial bloodstream infection
  7. Lack of enteral feeding
  8. Skin immaturity / burns
  9. Hyperglycaemia
  10. Use of H2-blockers
  11. Duration of mech. ventilation
      (Chronic lung disease ± postnatal steroids)

- **In any gestational age neonate:**
  – Complicated gastrointestinal (GI) disease

Saiman L, et al. *Pediatr Infect Dis J* 2000;19:319–24; Linder N, et al. *J Hosp Infect* 2004;57:321–4; Feja KN, et al. *J Pediatr* 2005;147:156–61; Benjamin DK, et al. *Pediatrics* 2003;112:543–7; Benjamin DK, et al. *Pediatrics* 2006;117:84–9; Cotton CM, et al. *Pediatrics* 2006;118:717–22; Makhoul IR, et al. *J Hosp Infect* 2007;65:237–43.

Activity of *Candida* spp. in Biofilms (48h)



Kuhn DM et al (Cleveland), Antimicrob Agents Chemother 2002;46:1773-80