Postgraduate Education Course
Infectious Diseases in Pregnant Women, Fetuses and Newborns

Bertinoro, 29 September-3 October 2013

Group B Streptococcus Infection

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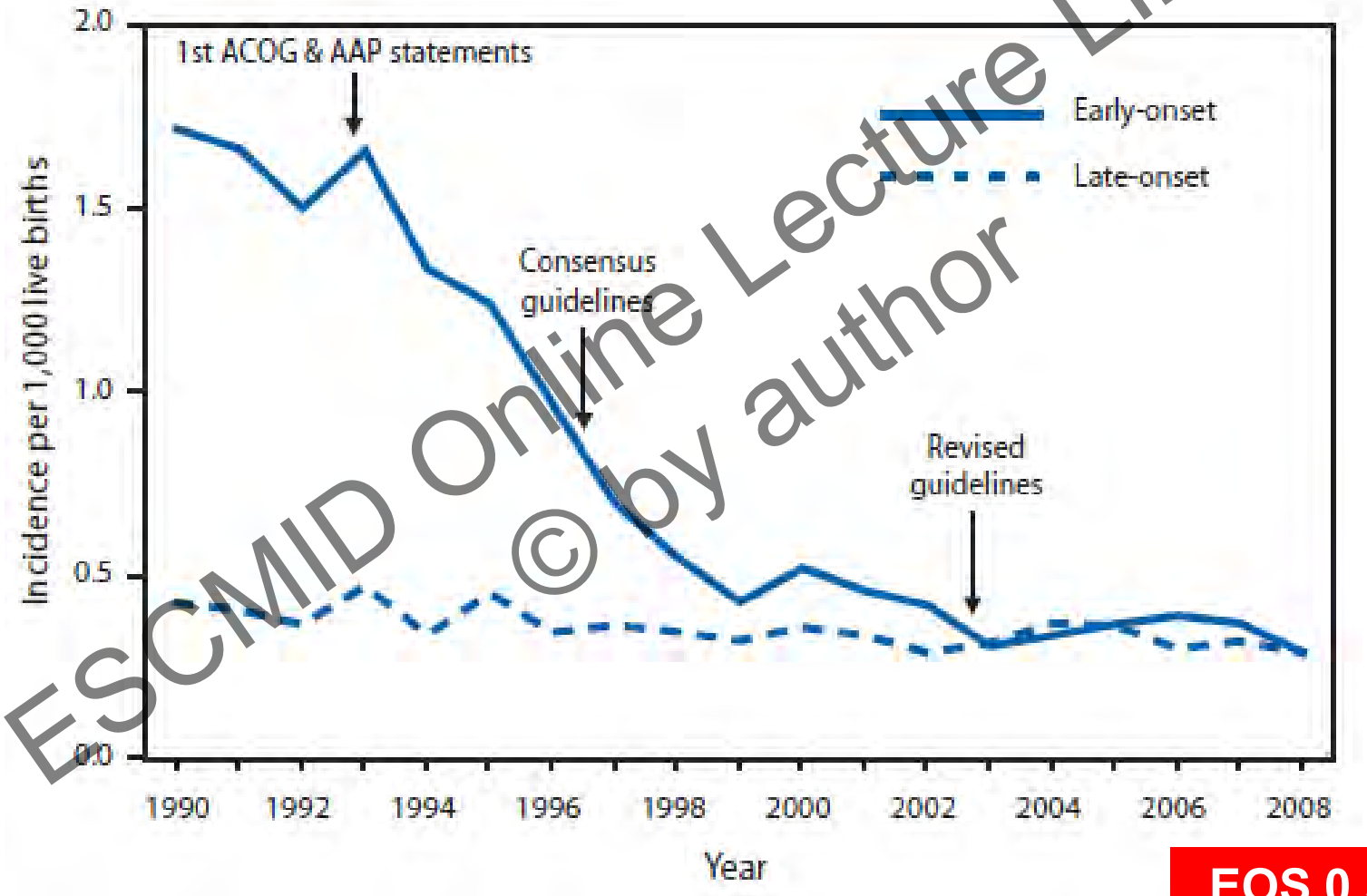
Burden of disease



EOS 0.3/1000 LB

Jordan, Pediatr Infect Dis J 2008

Burden of disease

Pathogen	EOS[a]		EOM[b]	
	n	%	*n*	%
Gram-positive	231	62	8	50
GBS	159	43	3	19
Viridans group streptococci	20	5	2	13
S aureus[c]	9	2	1	6
Enterococci	10	3	1	6
Group A streptococci	9	2	—	—
Coagulase-negative staphylococci[d]	3	<1	—	—
Other Gram-positive[e]	21	6	1	6
Gram-negative	137	37	8	50
E coli	107	29	7	44
Haemophili	11	3	—	—
Other Gram-negative[f]	19	5	1	6
Fungi	2	<1	—	—
Candida albicans	2	<1	—	—
Total	370	100	16	100

TABLE 2 Rates of EO Infections per 1000 LBs According to Birth Weight

	BW, g			
	401–1500[a]	1501–2500	>2500	All
All	10.96	1.38	0.57	0.98
GBS	2.08	0.38	0.35	0.41
E coli	5.09	0.54	0.07	0.28

395586 LBs (2006-2009)

16 centers NRN

611 newborns EOS and/or EOM

Stoll, Pediatrics 2011

MMWR
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

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FROM THE AMERICAN ACADEMY OF PEDIATRICS

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

Policy Statement—Recommendations for the Prevention of Perinatal Group B Streptococcal (GBS) Disease

Continuing Education Examination available at http://www.cdc.gov/mmwr/cme/contad.html

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Prenatal Management:

the obstetrician

Vaginal-rectal GBS screening

TIMING	
	35-37 weeks of gestation **No more than 5 weeks before delivery (NPV 95-98%)**
COLLECTION AND PROCESSING	
	Swab of lower third of vagina and rectum **Specimen cultured with selective enrichment broth (Todd-Hewitt broth+gentamicin/nalidixic acid or colistin/nalidixic acid)→ subculture to blood agar plates→ SGB identification with CAMP test or latex agglutination with antisera or chromogenic methods (or genomic methods)**
ANTIMICROBIAL SUSCEPTIBILITY TESTING	
	Clindamycin and erythromycin susceptibility test in penicillin-allergic women
POPULATION	
	Universal **Exceptions: GBS bacteriuria (current pregnancy)** **previous infant with GBS disease**

Candidates for intrapartum antibiotic prophylaxis

1. PREVIOUS INFANT WITH INVASIVE GBS DISEASE

(any kind of delivery, any VRS result)

2. GBS BACTERIURIA-CURRENT PREGNANCY

(any VRS result, except CS performed before the onset of labor with intact amniotic membranes)

3. POSITIVE GBS VRS-CURRENT PREGNANCY

(except CS performed before the onset of labor with intact amniotic membranes)

4. UNKNOWN GBS STATUS AND ANY OF THE FOLLOWING:

- GA < 37 weeks at delivery
- PROM ≥ 18 hrs
- Intrapartum temperature ≥ 38°C (≥ 100.4°F)
- (Intrapartum NAAT positive for GBS)

IAP: the right choice

ALLERGY TO PENICILLIN?

NO

PENICILLIN G, IV
5 milion units initial dose,
then 2.5-3 milion units every 4hrs until delivery

OR

AMPICILLIN, IV
2 initial dose,
then 1 g every 4 hrs until delivery

COMPLETE IAP
If started at least 4 hrs before delivery

YES

HISTORY OF SEVERE SYMPTOMS?

- Anaphylaxis
- Angioedema
- Respiratory distress
- Urticaria

YES

Susceptibility to clindamycin and erythromycin?

NO

VANCOMYCIN, IV
1 g every 12 hrs until delivery

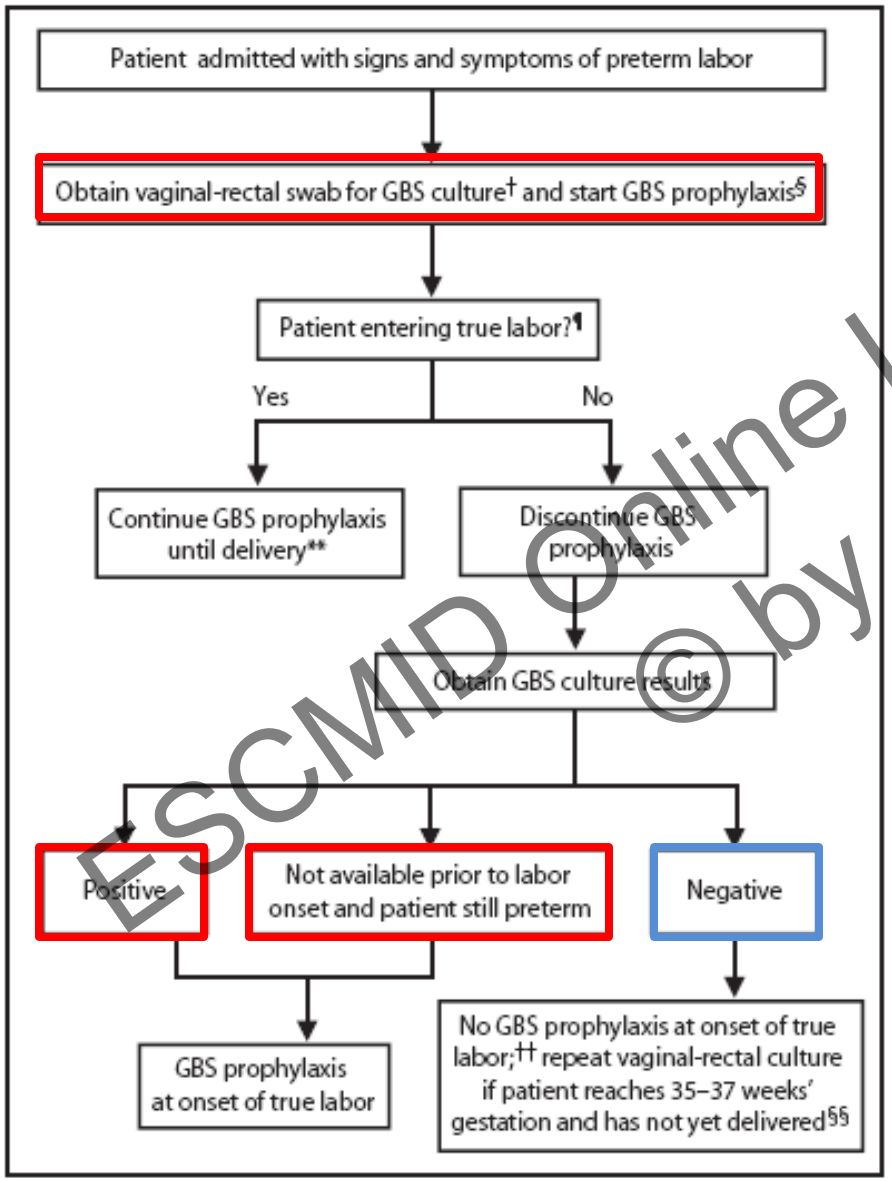
YES

CLINDAMYCIN, IV
900 mg every 8 hrs until delivery

NO

CEFAZOLIN, IV
2 g initial dose,
then 1 g every 8 hrs until delivery

Preterm labor



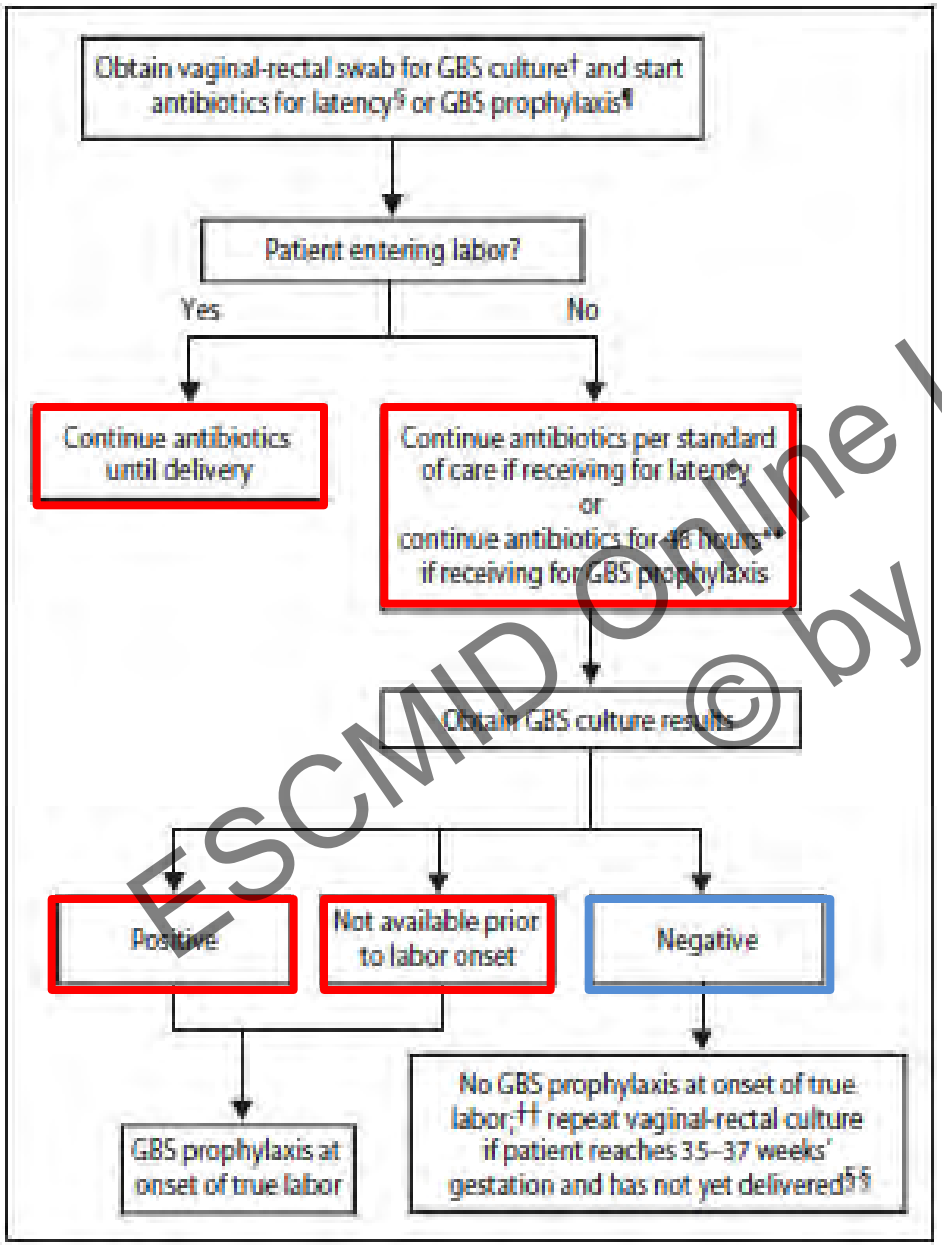
NEGATIVE GBS VRS VALIDITY: 5 WEEKS!!!!

PATIENT WITH HISTORY OF PTL RE-ADMITTED FOR PTL WITH PREVOIUS NEGATIVE VRS

VRS PERFORMED ≤ 5 WEEKS PRIOR → **OK**

VRS PERFORMED > 5 WEEKS PRIOR → **REPEAT VRS AT ADMISSION**

pPROM

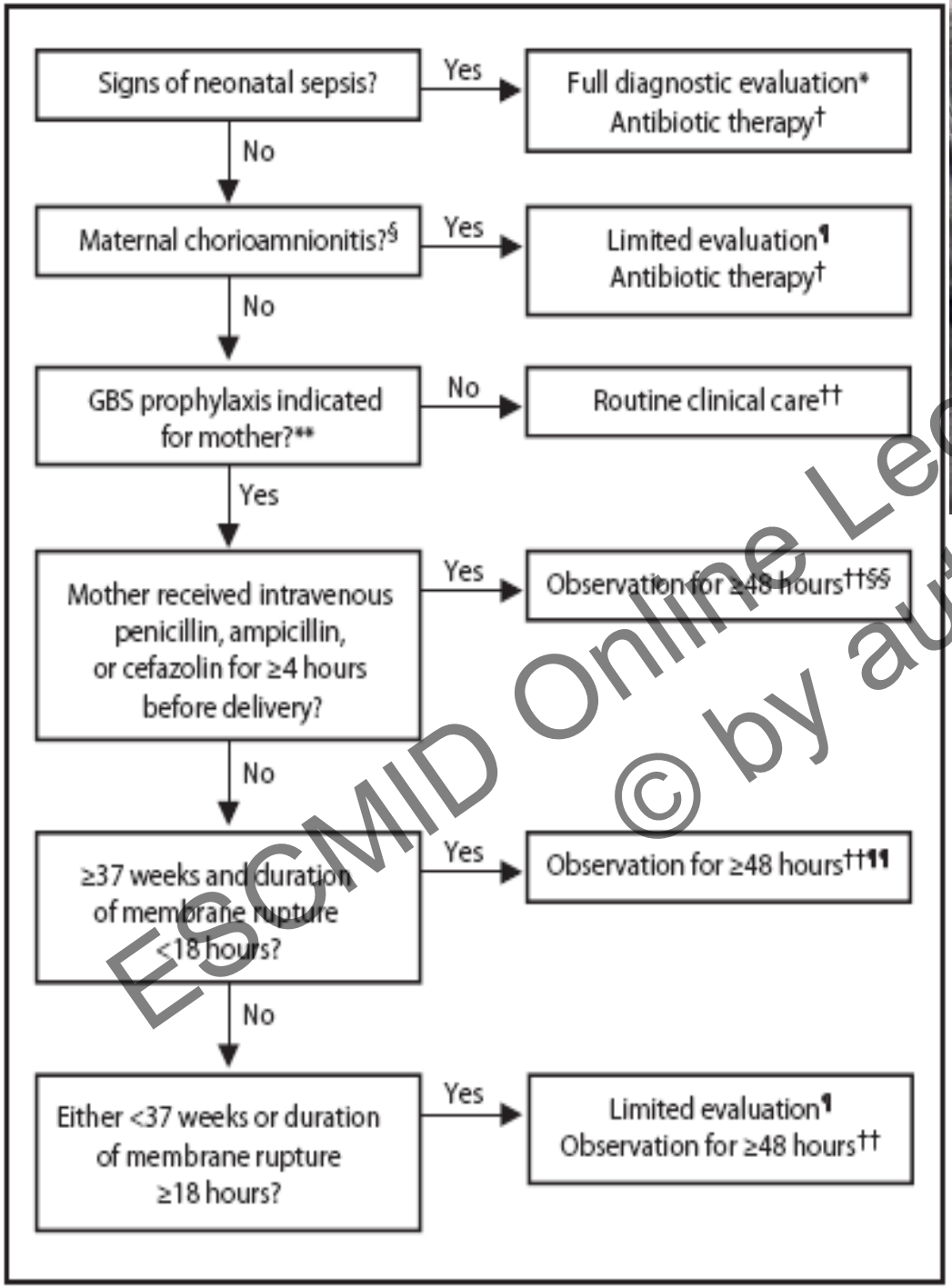


LATENCY ANTIBIOTIC REGIMEN

- **AMPICILLIN, IV: 2 g initial dose, then 1 g every 6 hrs for at least 48 hrs;**
- **If different regimens are used GBS prophylaxis should be added;**
- **STOP AFTER 48 HRS IF NOT IN LABOR.**

Postnatal Management:

the neonatologist



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

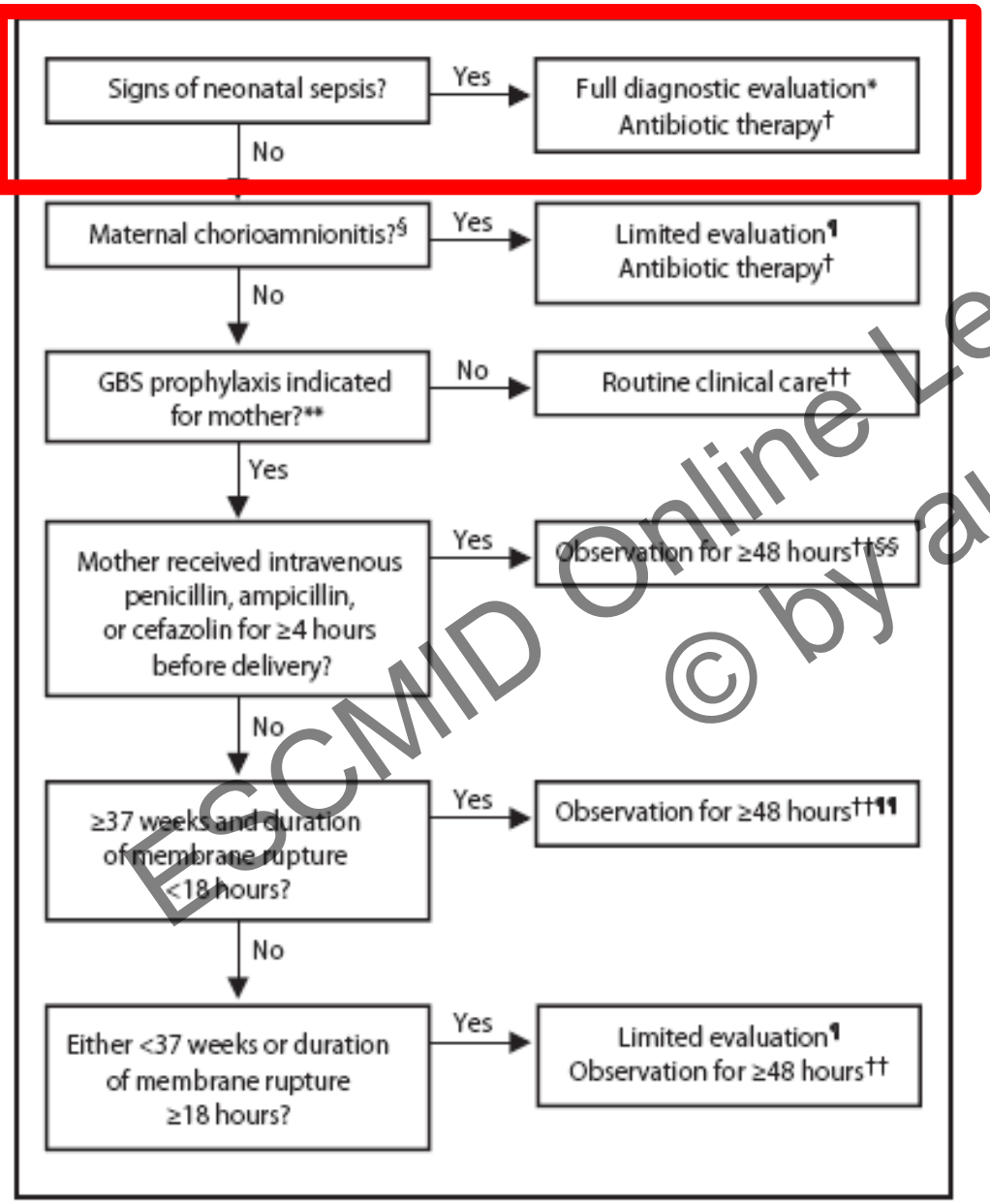
** See table 3 for indications for intrapartum GBS prophylaxis.

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

Newborn with signs of sepsis



FULL DIAGNOSTIC EVALUATION:

1. **BLOOD CULTURE**
2. **CBC (+ WBC differential count)**
3. **CHEST X-RAY (distress)**
4. **LUMBAR PUNCTURE**

Further exams: CRP, PCT, PCR, coagulation tests, LKFT

COVER: GBS + E. COLI and other Gram negative pathogens

- **AMPICILLIN IV**
  100 mg/Kg x 2 at term
- **GENTAMICIN/NETILMICIN IV**
  4 mg/Kg x 1 at term

“To tap or not to tap?”

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Guidance for the Clinician in Rendering Pediatric Care

CLINICAL REPORT

Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis

Lumbar Puncture

The decision to perform a lumbar puncture in a neonate with suspected early-onset sepsis remains controversial. In

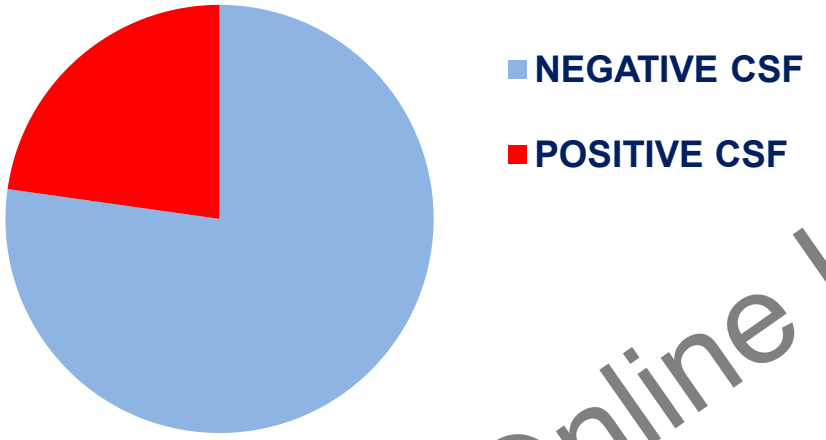
“LOW RISK” POPULATION:

- **Well appearing newborn with risk factors for EOS;**
- **Newborn with symptoms likely attributable to non infectious diseases (TTN, RDS, IEM…)**

Polin, Pediatrics 2012

“To tap or not to tap?”

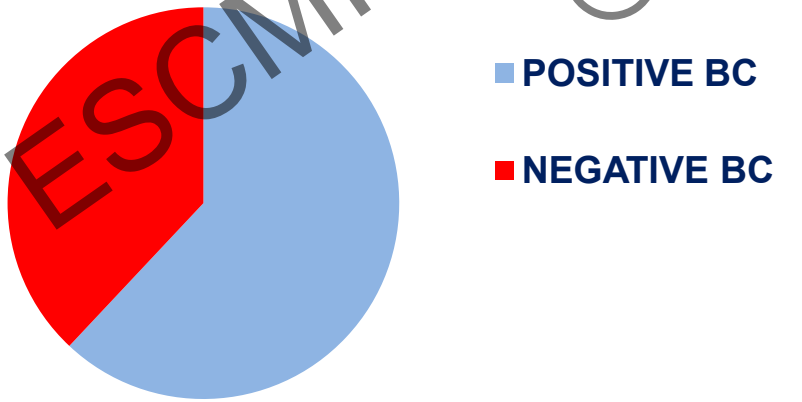
NEWBORNS WITH POSITIVE BC



NEWBORNS WITH EOS:
EOM UP TO 23%

EOM under-estimated because of LP performed during antibiotic treatment

NEWBORNS WITH POSITIVE CSF



NEWBORN WITH EOM:
NEGATIVE BC UP TO 38%

Missed diagnosis if LP not performed (GBS>E.Coli)

Garges, Pediatrics 2006
Stoll, Pediatrics 2011

INDICATIONS TO LP

1. **POSITIVE BC**
2. **SUGGESTIVE CLINICAL SIGNS AND LABORATORY TEST**
   at the beginning of sepsis work-up
3. **NO RESPONSE TO ANTIBIOTICS**

For critically ill newborns with respiratory or cardiocirculatory instability the LP must be delayed until a reasonable stabilty is achieved.

Polin, Pediatrics 2012
Stoll, Pediatrics 2011

CSF VALUES

9111 LP in newborns >34 WGA

	POSITIVE CSF (n=95)			NEGATIVE CSF (n=8927)		
	Min	Max	Median	Min	Max	Median
WBCs (n/mm^3)	0	15900	477	0	90000	6
Proteins (mg/dL)	41	1964	273	3	4122	103
Glucose (mg/dL)	0	199	20	0	1089	49

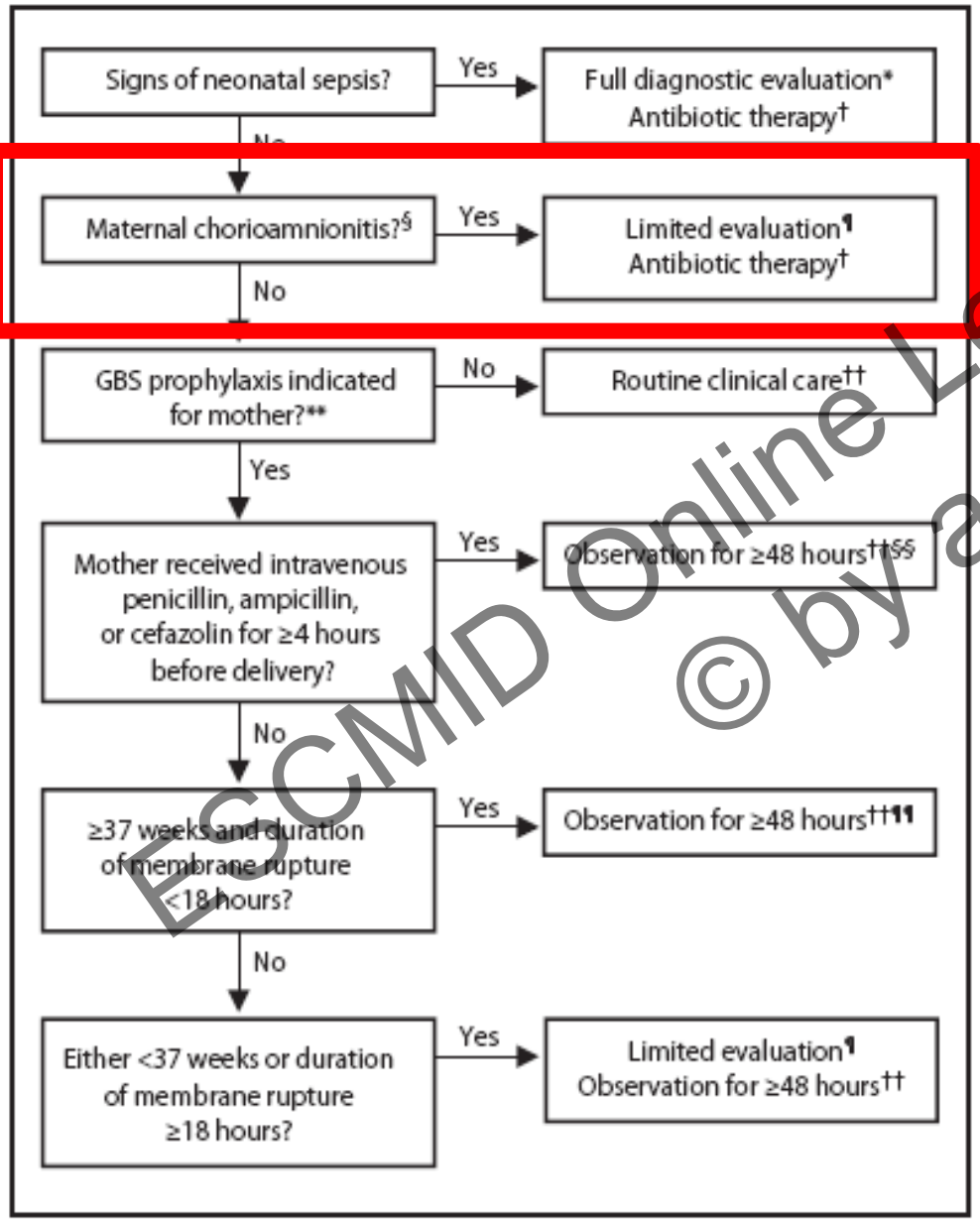
	Sensitivity	Specificity	PPV	NPV	+ LR	− LR
Elevated WBC	89.3	81.7	1.8	99.9	4.9	0.1
Elevated protein	92.6	75.7	1.5	100.0	3.8	0.1
Low glucose	60.7	95.7	5.4	99.8	14.0	0.4
Any abnormal value	96.7	67.2	1.1	100.0	3.0	0.1
All values abnormal	58.3	98.2	11.1	99.8	32.0	0.4

PPV (positive predictive value), NPV (negative predictive value), +LR (positive likelihood ratio), −LR (negative likelihood ratio).

- 13495 ≥ 31 WGA
- 46 newborns with GBS EOM

Garges, Pediatrics 2006

Well-appearing "at risk" newborn

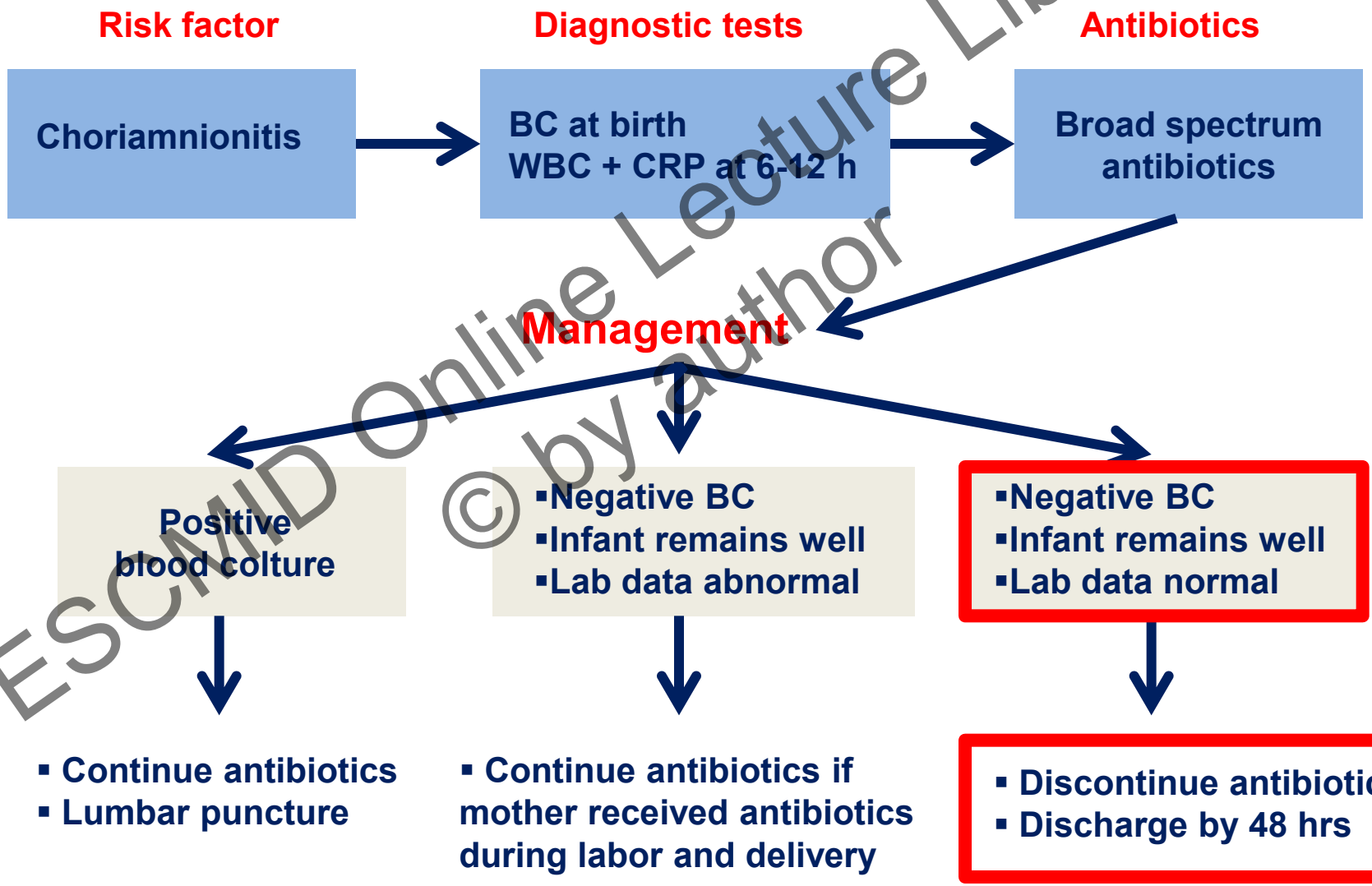


LIMITED EVALUATION:

1. **BC AT BIRTH**
2. **CBC (+ diff) AT BIRTH AND/OR AT 6-12 HRS OF LIFE**

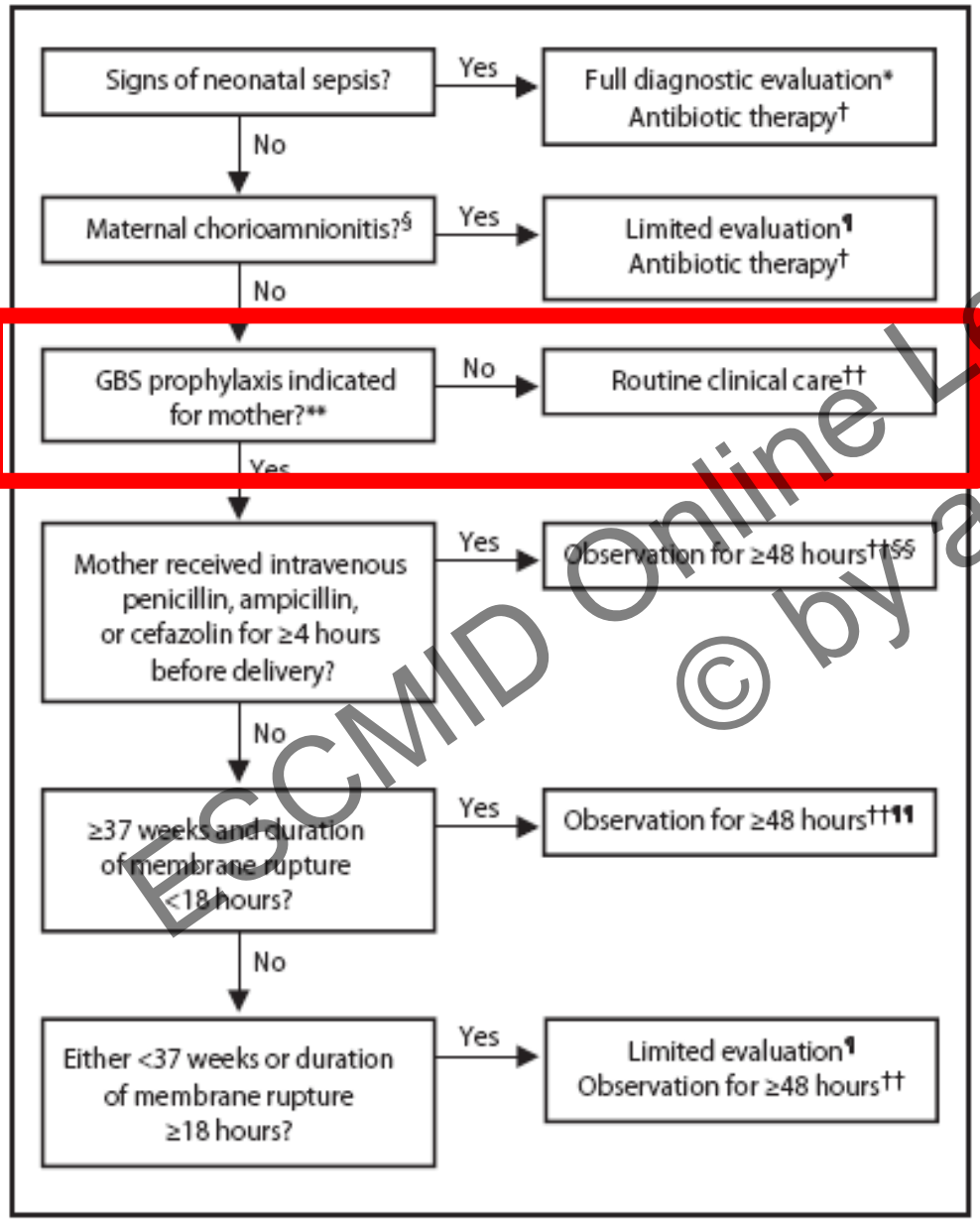
- **AMPICILLIN IV**
  100 mg/Kg x 2 at term
- **GENTAMICIN/NETILMICIN IV**
  4 mg/Kg x 1 at term

Chorioamnionitis

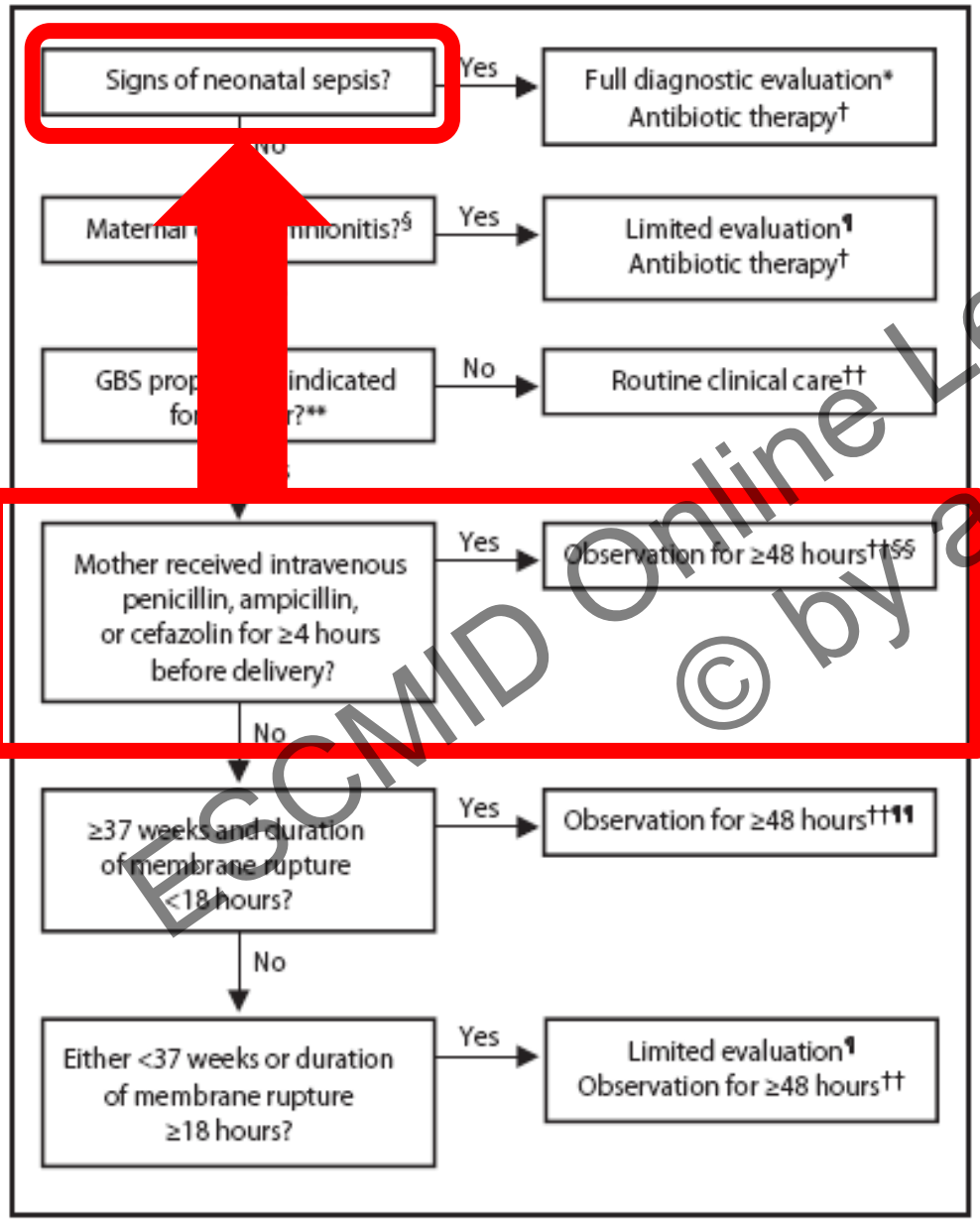


Polin, Pediatrics 2012

Well appearing “at risk” newborn

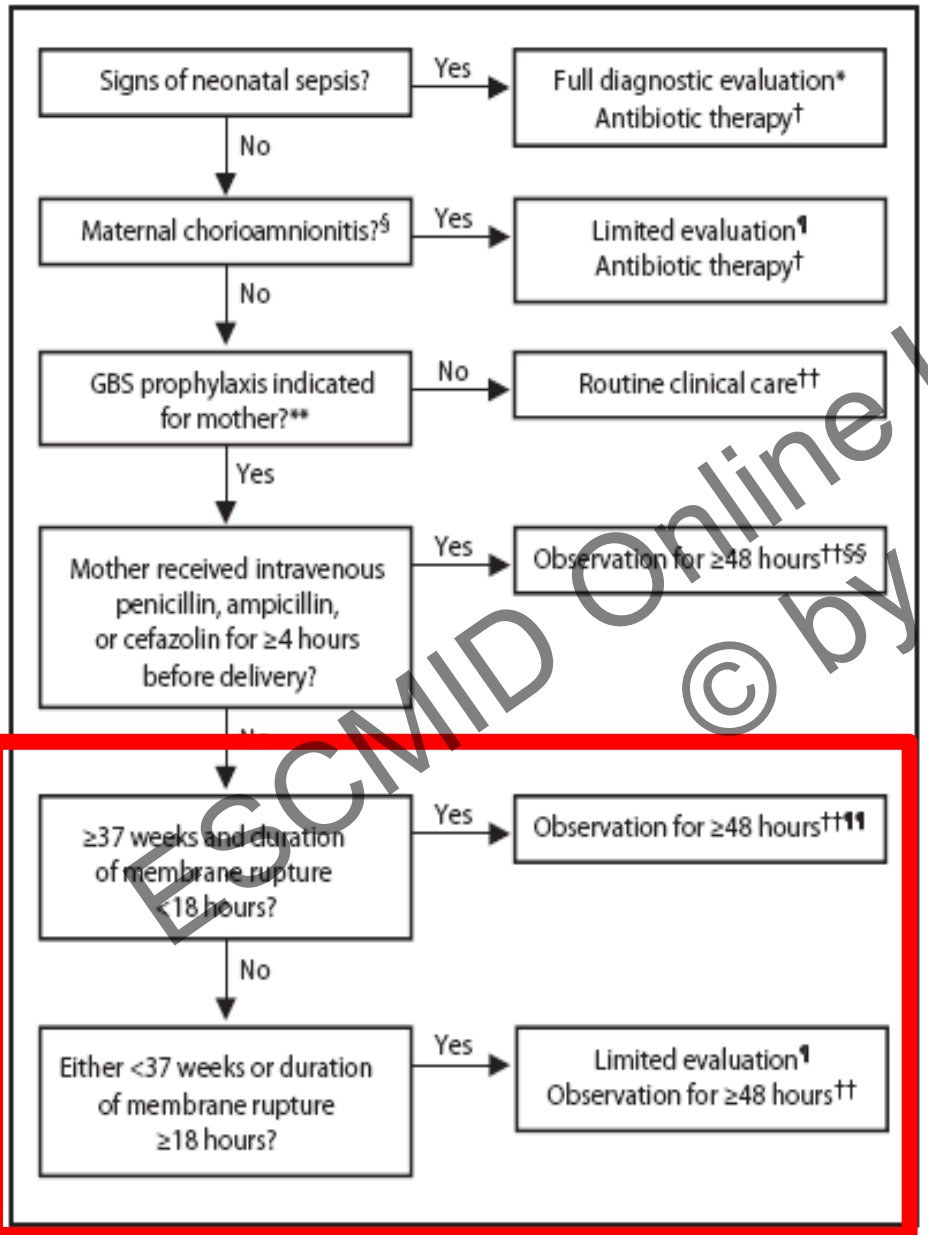


Well appearing “at risk” newborn



- **If signs of sepsis develop during the observation period perform full diagnostic evaluation and start antibiotics;**
- **In case of GA ≥ 37 weeks observation may occur at home if other discharge criteria have been met, access to medical care is readily available and a person who is able to comply fully with the instruction for home observation is present**

Well appearing "at risk" newborn



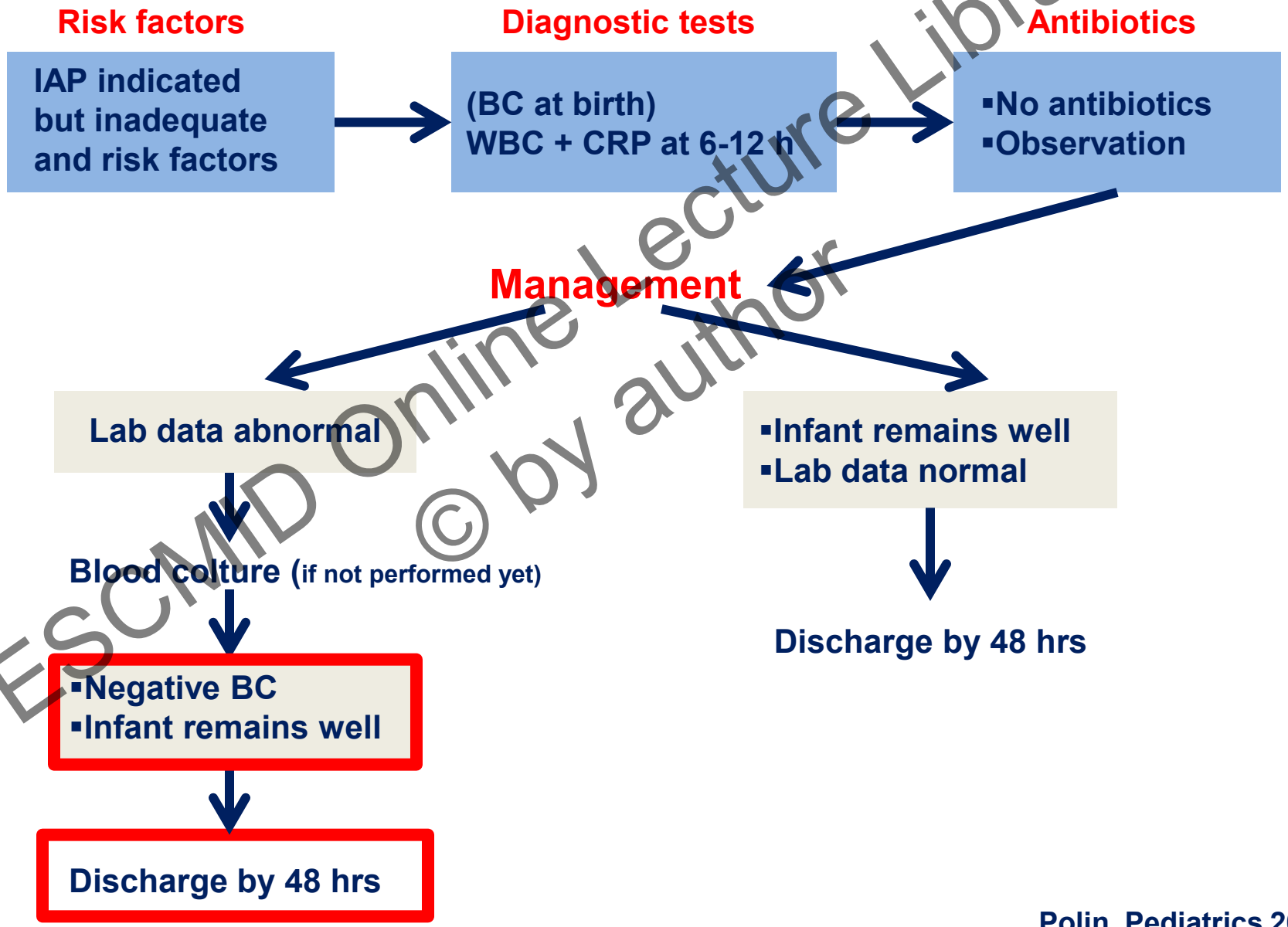
IAP INDICATED, NOT PERFORMED:

1. **INTRAPARTUM RISK FACTORS PRESENT:**
   - **LIMITED EVALUATION**
     (BC at birth, CBC +diff at birth and/or at 6-12 hrs);
   - **OBSERVATION ≥ 48 HRS.**

2. **INTRAPARTUM RISK FACTORS ABSENT:**
   - **OBSERVATION ≥ 48 HRS**
     (Some authors suggest CBC at 6-12 hrs)

- **IF THE NEWBORN BECOMES SYMPTOMATIC DURING THE OBSERVATION PERFORM FULL EVALUATION AND START ANTIBIOTICS**

Intrapartum risk factors



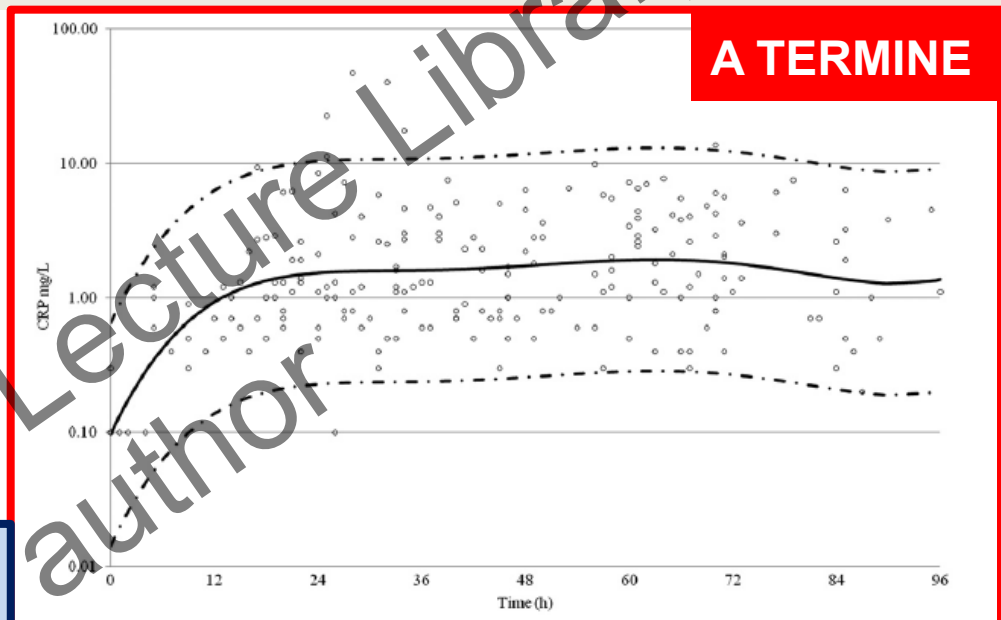
Polin, Pediatrics 2012

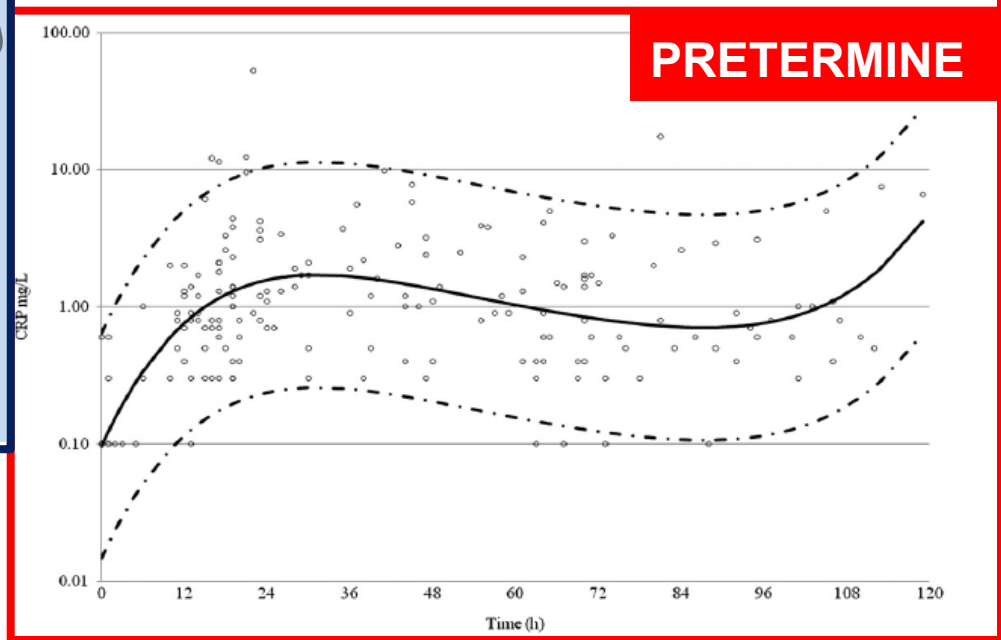
C-reactive protein

- 221 healthy term and 200 healthy preterm newborns;
- Physiological increase in the first DOLs (term>preterm).

POSITIVE RELATION WITH:

- vaginal delivery vs. CS;
- duration of labor;
- duration of ruptures of membranes;
- antenatal steroids;
- intrapartum antibiotics;
- fetal distress (borderline).

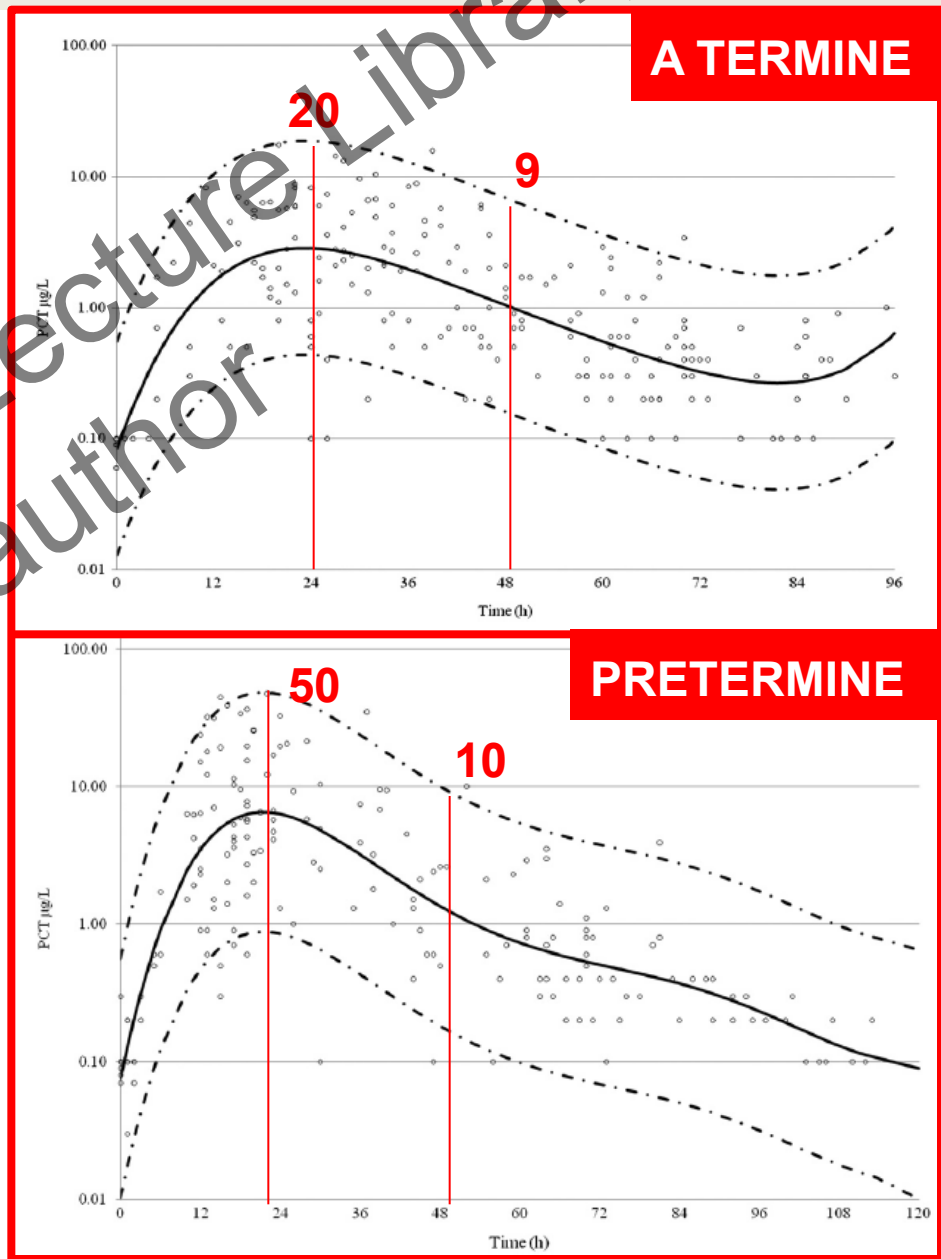




Chiesa, Clin Chim Acta 2011

Procalcitonin

- Physiological increase during the first DOLs (preterm>term)→ poor specificity;
- Poorly influenced by perinatal factors (duration of rupture of membranes and gestational diabetes borderline);
- Earlier peak values vs.CRP in septic patients (6-8 vs. 36-50 ore);
- Useful to monitor response to antibiotics (>48-72 h).

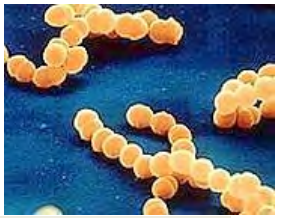


Chiesa, Clin Chim Acta 2011

Areas for improvement

EOS WITH GBS NEGATIVE VRS
(81% At term)

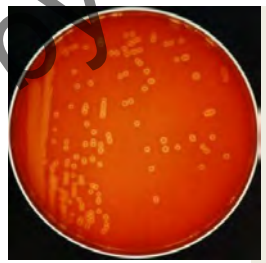
FALSE NEGATIVES



LATE GBS COLONIZATION

CONSIDER NOT VALID A NEGATIVE VRS OBTAINED ≥ 5 WEEKS PRIOR DELIVERY

UNPROPER SPECIMEN COLLECTION AND MANAGEMENT



Strict adherence is recommended to the guidelines for:

- **Collection and conservation**
- **Selective enrichment**
- **Chromogenic substrates use**

NAAT at present not recommended as a rotuine screening test.

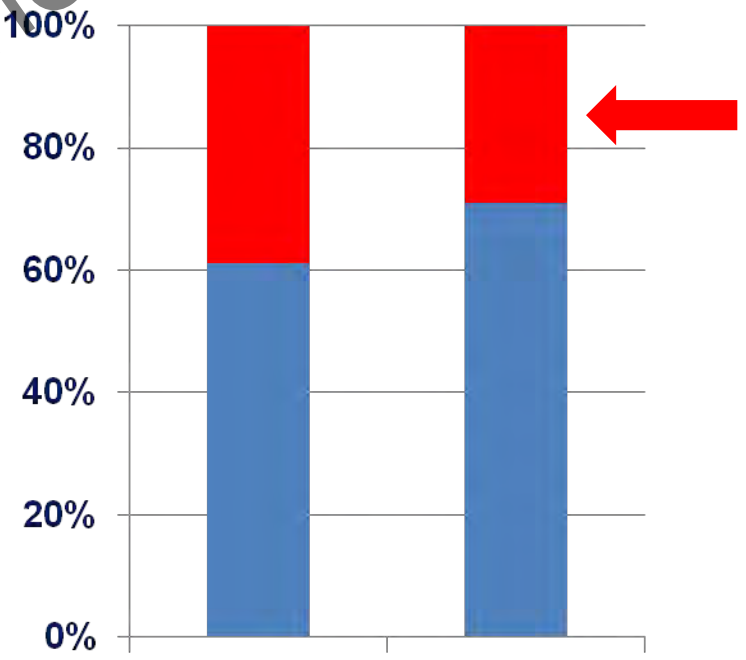
Randis, Pediatrics 2012
Stoll, Pediatrics 2011
Ansong; Early Hum Dev 2009

Areas for improvement

ADHERENCE TO GUIDELINES

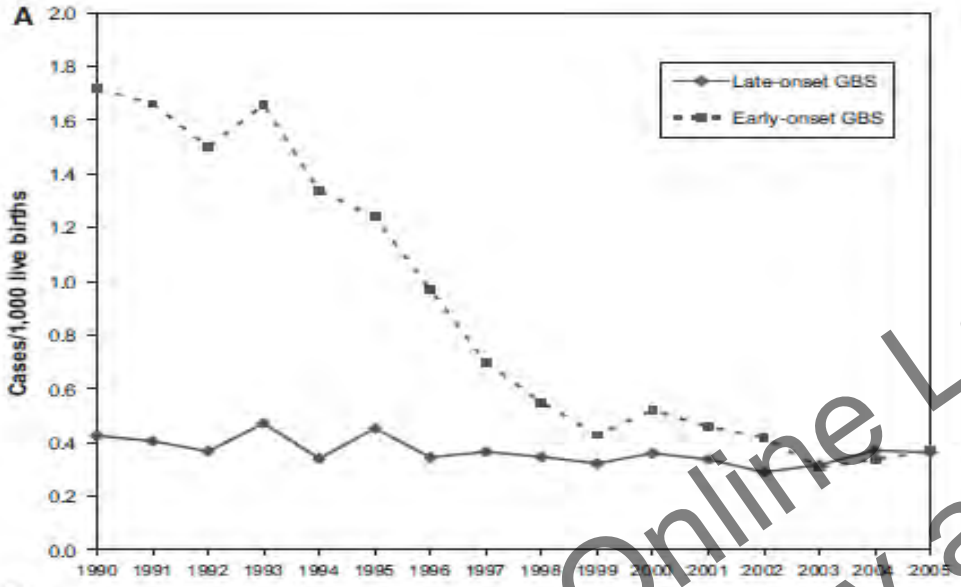
- VRS performed in 84% of pregnancies but not valid in 36% of cases;
- Valid VRS in 60% of mothers of newborns who developed GBS EOS.

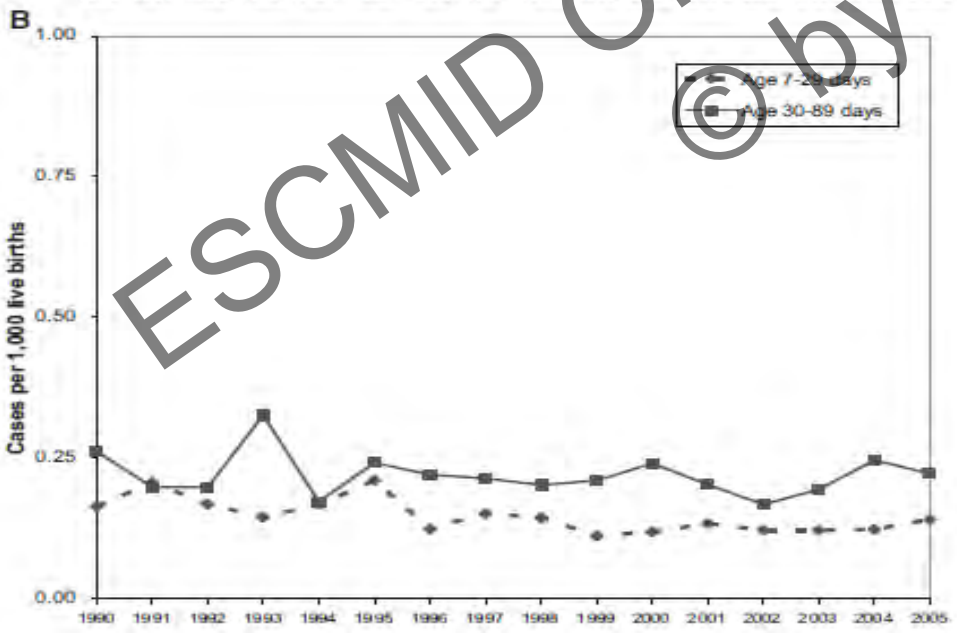
	IAP	NO IAP
GBS BACTERIURIA	76%	24%
GBS POSITIVE VRS	76%	24%
UNKNOWN GBS STATUS AND RISK FACTORS	66%	34%



Goins, Obstet Gynecol 2010
Stoll, Pediatrics 2011

GBS Vaccination





- 1726 GBS LOS;
- 26% meningitidis;
- Global case fatality ratio 4.3%;
- 1990-2005.

- 50% GBS positive VRS
- Breast milk
- Hands of health care workers

- IAP does not affect LOS incidence;
- IAP does not affect LOS incidence even in infants with onset of disease during the 1st month of life;
- IAP does not affect the timing of LOS onset (no delay).

Jordan, Pediatr Infect Dis J 2008

GBS vaccination

www.clinicaltrials.gov

STUDY TITLE	STATE	PHASE
Safety and Immunogenicity of a Group B Streptococcus Vaccine in Healthy Women	Completed	Ib
Immune Response Induced by a Vaccine Against Group B Streptococcus and Safety in Pregnant Women and Their Offsprings	Active, not recruiting	II
Safety and Immunogenicity of a Group B Streptococcus Vaccine in Non Pregnant and Pregnant Women 18-40 Years of Age	Completed	Ib/II
Extent of the Immune Response Induced by a Vaccine Against Group B Streptococcus and Safety in HIV Positive and HIV Negative Pregnant Women and Their Offsprings.	Completed	II
A Phase I, Randomized, Single-blind, Controlled, Single Center Study to Evaluate the Safety and Immunogenicity of a Dose Range of Glycoconjugate Antigen Vaccine of Group B Streptococcus in Healthy Women 18- 40 Years of Age	Completed	I
A Phase I, Randomized, Single-blind, Controlled, Single Center Study to Evaluate the Safety and Immunogenicity of a Dose Range of a Monovalent Glycoconjugate Antigen Vaccine of Group B Streptococcus in Healthy Women 18-40 Years of Age	Completed	I
A Study to Assess the Persistence of Two GBS Antibodies in Women Previously Immunized With a GBS Vaccine	Completed	I
A Study to Assess the Persistence of a GBS Antibody in Women Previously Immunized With a GBS Vaccine	Completed	I
Prevention of GBS Colonization Via Immunity	Completed	II
Antibody Levels Associated With Reduced Risk of Invasive Group B Streptococcus Disease in Infants Aged Less Than 90 Days	Not yet recruiting	--

Thank you!

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