

Neonatal Sepsis: Prevention of Group B Streptococcal Disease

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Potential Conflicts of Interest

Company	Relationship
Astellas Pharma	Research support, consulting
Cubist Pharmaceuticals	Research support, consulting
Pfizer	DSMB
Johnson and Johnson	Consulting

Outline

- Epidemiology of Early-onset Sepsis
- 2010 – GBS Guidelines
- Diagnosis
- Empirical Treatment for Early-onset Sepsis

Early-onset Sepsis

- 1st 3 days of life
- Vertical transmission
- Fulminant infection
- Pathogens
 - Group B *Streptococcus* (GBS) 30 - 50%
 - *E. coli* 10 - 20%
 - *Listeria*
 - Other Gram-negative bacteria
 - Other Gram-positive bacteria

Early-onset Sepsis – Premature Infants

- Very low birth weight infants (VLBW, <1500 g birth weight)

Organism	Incidence
<i>E. coli</i>	41%
GBS	12%
CoNS	15%

Group B *Streptococcus*

- Recognized as leading cause of infectious neonatal mortality and morbidity in 1970s
- GI/GU tract colonized in 10-30% of pregnant women
- 50% of infants born to colonized mothers are colonized
- 1-2% of colonized infants develop invasive disease

Group B *Streptococcus*

- Maternal colonization is typically transient
 - Colonization in early pregnancy is not predictive of neonatal sepsis
- Intrapartum antibiotic prophylaxis (IAP)
 - Decreased GBS sepsis by ~80% (1.7 to 0.34/1000 births)
- Mortality initially 50% now 4-6% due to improvements in neonatal care
 - Higher for preterm infants

GBS Bacteriuria

- 2-7% of pregnant women
- Marker for heavy colonization
- Antibiotic treatment does not eliminate GBS colonization

Group B *Streptococcus* Sepsis

- Risk factors
 - Maternal colonization
 - Preterm delivery
 - Fever
 - Chorioamnionitis
 - Prolonged rupture of membranes (PROM)
 - Young maternal age
 - Black race
 - Low levels of GBS-specific antibody
 - Previous infant with GBS disease

Early-onset Sepsis

	<u>Incidence of sepsis (/1000)</u>
■ Baseline	1-2
■ GBS (+) with prophylaxis	2-4
■ GBS (+) without prophylaxis	5-10
■ PROM	10
■ PROM + 5 min APGAR < 6	30-40
■ PROM + preterm	40-60
■ Chorioamnionitis	30-80
■ Chorioamnionitis + GBS (+)	60-200

Intrapartum Antibiotic Prophylaxis

- Effectiveness is 86-89% and maximal when given ≥ 4 hours prior to delivery

Agent	Controlled Trials	Reaches amniotic fluid/fetus
Penicillin	Yes	Yes
Ampicillin	Yes	Yes
Cefazolin	No	Yes
Clindamycin	No	No
Erythromycin	No	No
Vancomycin	No	Unknown

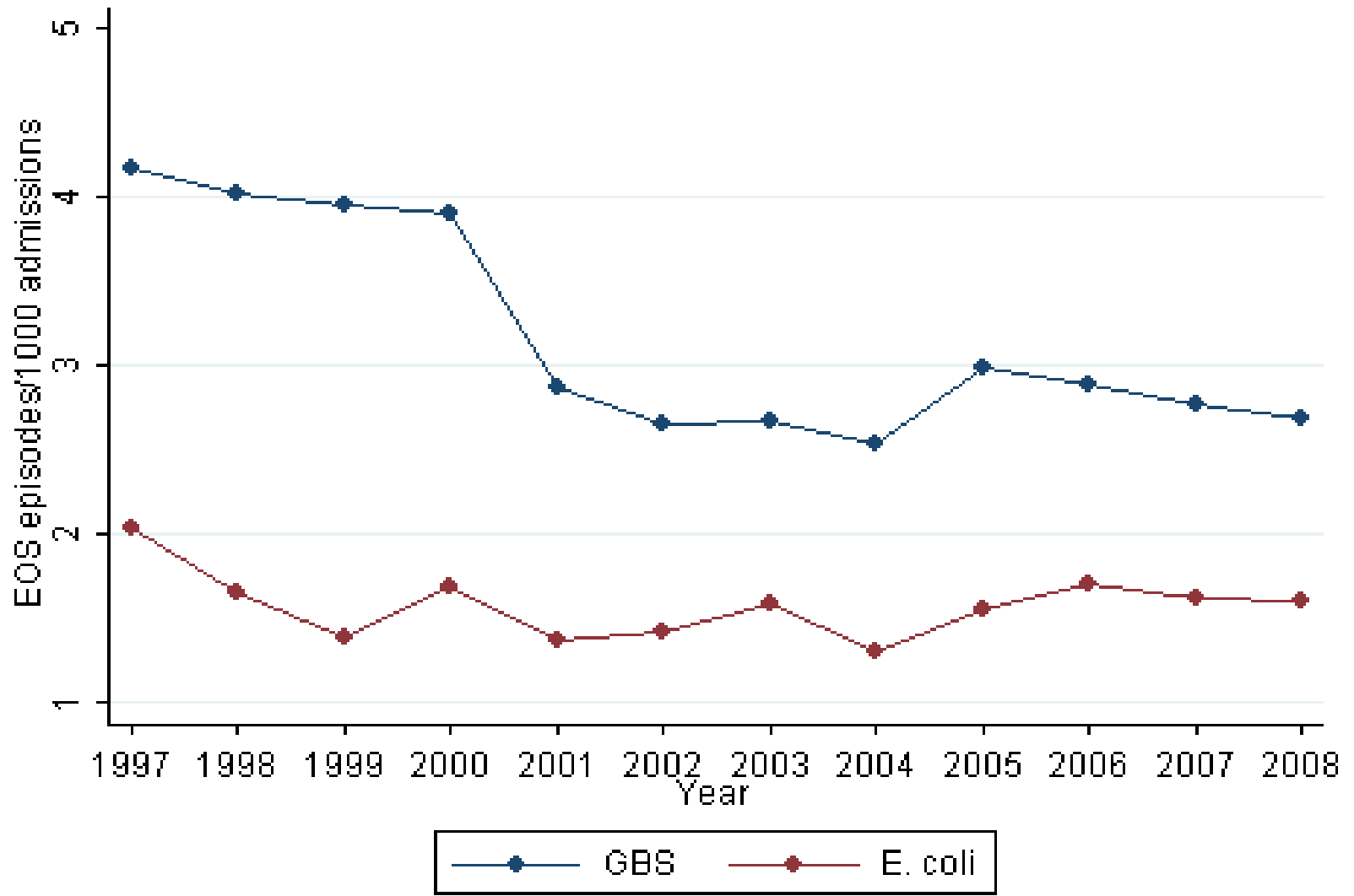
Intrapartum Antibiotic Prophylaxis - Safety

- Anaphylaxis
 - Rare maternal – no fatal cases
 - No risk in infant
- Antibiotic resistance
 - GBS with increasing MICs to penicillin/ampicillin reported
 - Increasing resistance to erythromycin (25-32%) and clindamycin (13-20%)
- Masking/delaying presentation
 - No difference in clinical presentation
 - 90% of GBS EOS cases manifest in 1st 24 hours.

Trends in *E. coli* infections

- Single center studies - increase in Gram-negative EOS after introduction of IAP
- Larger studies have not demonstrated increased incidence of EOS after introduction of IAP

Early-onset Sepsis



Late-onset Sepsis

- occurs after day of life 3
- vertical and horizontal transmission
- slower progressing course
- focal infection (meningitis)

Late-onset Sepsis - Pathogens

- Gram-positive
 - CoNS 48%
 - *S. aureus* 8%
 - *Enterococcus* 3%
 - GBS 2%
- Gram-negative
 - *E. coli* 5%
 - *Klebsiella* 4%
- *Candida* 6%

Guidelines for Prevention of Perinatal GBS Disease

- 1996 – Risk Based Screening
- 2002 – Universal Screening
- 2010 – Revised Guidelines

GBS Guidelines - Impact

- Prior to IAP
 - incidence GBS disease was 2-3/1000
- Risk based screening (1996)
 - 0.5/1000
- Universal screening (2002)
 - 0.3-0.4/1000
- Estimated that 4500 cases of neonatal GBS sepsis are prevented per year
 - 225 deaths

Impact of 2002 GBS Guidelines

- Screening increased from 48 to 85%
- IAP where indicated increased from 74% to 85%
- Limitations
 - Screening of preterm/unknown mothers only 18%
 - IAP provided to only 63% of preterm/unknown mothers
 - Only 77% of non-allergic mothers received penicillin or ampicillin
 - Only 14% of allergic (not high risk for anaphylaxis) received cefazolin
 - For mothers that received clindamycin or erythromycin, few isolates tested for susceptibility

2010 GBS Guidelines – Key Changes

- Updated algorithm for screening and IAP for women with preterm labor or PROM
- Erythromycin no longer an acceptable alternative for IAP in penicillin allergic women
- Do not have to draw screening CBC/culture for term infants with ROM <18 hours when IAP not given appropriately
- Do not have to draw screening CBC/culture for infants <35 weeks gestation when IAP given appropriately

2010 GBS Guidelines - Steps

Who gets screened?	Obstetrician
Who gets IAP?	Obstetrician/Pediatrician
Was IAP adequate?	Pediatrician
What work-up does the infant require?	Pediatrician

2010-GBS Guidelines - Screening

- Timing
 - 35-37 weeks gestation
 - NPV 95-98%
- Collection
 - Vagina, rectum
 - Processed within 24 hours

Who gets screened?

- All women at 35-37 weeks gestation
- Except
 - Women with previous infant with GBS disease
 - Women with GBS bacteriuria during pregnancy

Who gets IAP?

- GBS positive
 - Screen positive in late gestation (35-37 weeks)
 - GBS bacteriuria during pregnancy
 - Previous infant with invasive GBS disease

*Unless planned C/S in the absence of labor (at any gestation)
- Women who have unknown GBS status and one of the following:
 - Delivery at < 37 weeks
 - ROM > 18 hours
 - Maternal temp ≥ 100.4
 - Intrapartum nucleic acid amplification test positive for GBS

Who gets IAP?

- What is the preferred antibiotic?
 - Penicillin G
- In a nonallergic woman, what is an acceptable alternative?
 - Ampicillin
- In an allergic woman not at high risk for anaphylaxis?
 - Cefazolin
- In an allergic woman at high risk for anaphylaxis?
 - Susceptibilities to clindamycin and erythromycin should be determined
 - Clindamycin if the GBS is susceptible to both clindamycin and erythromycin or testing for inducible clindamycin resistance is negative
 - Vancomycin otherwise

IAP: Yes or No?

1. GBS status unknown, 36 weeks gestation.

Yes

2. GBS (-), 38 weeks gestation, ROM 24 hours.
Fever of 102.8

No

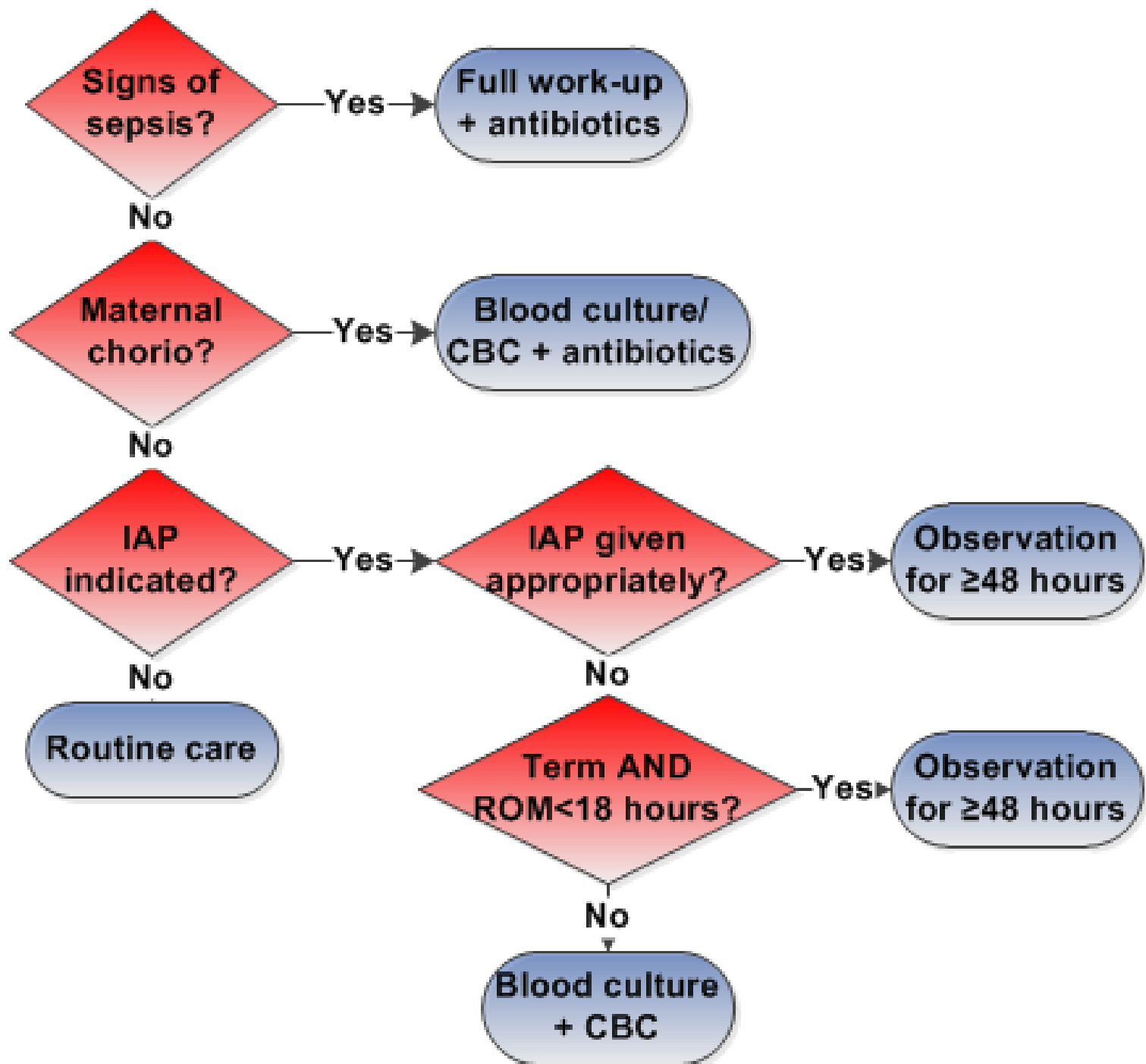
3. GBS (+), 38 weeks gestation, scheduled C-section with no labor or rupture of membranes.

No

Was IAP adequate?

- 1 dose of penicillin, ampicillin, or cefazolin
 - given ≥ 4 hours prior to delivery

What work-up does the infant require?



What is the correct work-up?

- Asymptomatic infant with no maternal indication for GBS IAP?
 - Routine care
- Asymptomatic infant with maternal chorio?
 - CBC, blood culture, antibiotics
- Asymptomatic 36 week infant whose mother received adequate IAP?
 - Observation for 48 hours

What is the correct work-up?

- Term infant whose mother received inadequate IAP and ROM < 18 hours?
 - Observation for 48 hours
- Preterm infant whose mothers dose not receive adequate IAP?
 - Screening CBC, blood culture
 - Observation for 48 hours

What is the correct work-up?

- GBS (+), 36 weeks, 3 doses of clindamycin due to penicillin allergy
 - CBC, blood culture
- GBS (+), 36 weeks, ROM 24 hours, febrile, 1 dose of cefazolin 4½ hours prior to delivery
 - Routine care
- GBS (-), chorio, term, asymptomatic
 - CBC, blood culture, antibiotics

Signs of Sepsis

- Nonspecific
 - irritability, lethargy, hypotonia, apnea, seizures
 - grunting, cyanosis, tachypnea
 - temperature instability
 - hypo/hyperglycemia
 - emesis, poor feeding
 - poor perfusion, hypotension
 - petechiae, jaundice

Lab Findings – Neonatal Sepsis

- High white blood cell count $>30,000$
- Low white blood cell count <5000
- Low absolute neutrophil count <1500
- Immature: total neutrophils > 0.2
- Blood culture
 - 50-80% sensitive
 - $<3\%$ of infants with clinical sepsis have (+) cultures

How to Interpret the Screening CBC

- CBC results examined on all asymptomatic “at risk children” ≥ 35 weeks
- CBC was abnormal if:
 - $WBC > 30K$, $WBC < 5K$, $ANC < 1500$, $I:T > 0.2$
- 1665 infants
 - 17 (1%) given discharge diagnosis of sepsis
 - 0 positive blood cultures
- 454 had an abnormal CBC
 - 7 (1.5%) given discharge diagnosis of sepsis

Diagnosis of “Sepsis”

- Sensitivity = 41%
- Specificity = 73%
- PPV = 1.5%
- NPV = 99%

	Septic	Not Septic
CBC Abnormal	7	447
CBC Normal	10	1201

CBC – Diagnostic Parameters

Marker	N (% positive)	Sens	PPV	NPV
WBC <5000	158,021 (1.3%)	18%	5.6%	98.9%
Male gender	158,021 (1.3%)	54%	1.2%	98.7%

C-reactive protein (CRP)

- Acute phase reactant
 - Synthesized in the liver in response to cytokines
- Useful to obtain serially 12-24 hours apart
- Upper limit of 1 mg/dL – high NPV
- Upper limit of 5 mg/dL – PPV of 10%

Lumbar Puncture – Diagnostic Parameters

	Sensitivity	PPV	NPV
WBC>25	69	8	99
glucose<24	32	14	98
protein >170	61	5	99
All Harriet Lane values abnormal	26	13	98
Any Harriet Lane value abnormal	78	5	99

When should I perform a lumbar puncture?

- Asymptomatic – No
 - 1000-2000 LPs to identify one episode of meningitis
- Symptomatic infants with respiratory distress – probably not
 - Incidence of meningitis <1%
- Symptoms of meningitis (apnea, seizure, lethargy, hypotonia, irritability) – Yes
- Positive blood culture – Yes
- Sepsis is only diagnosis - Yes

Remember

- Don't forget to do lumbar puncture
- Normal CBC very reassuring
 - Abnormal CBC almost as reassuring

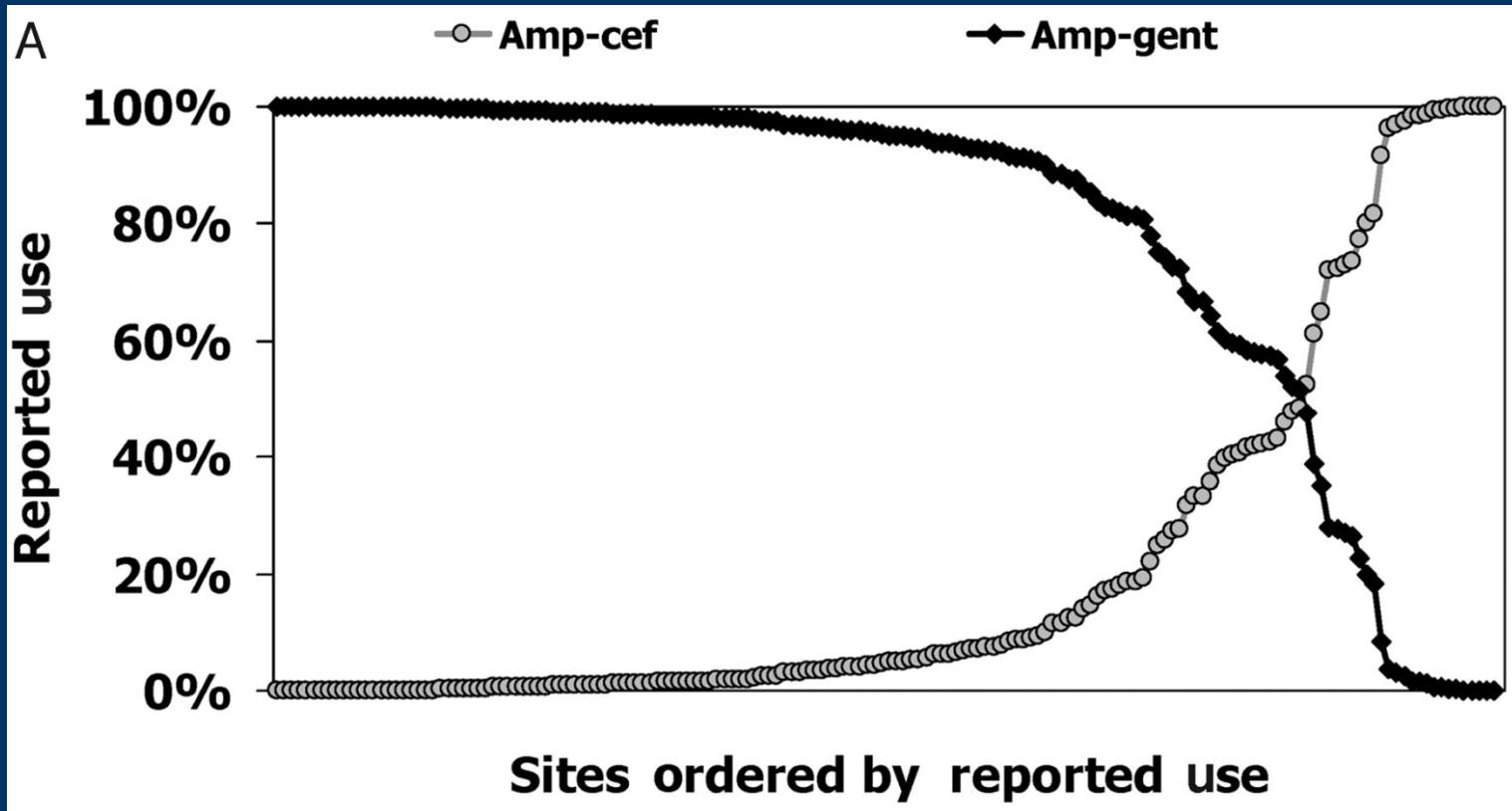
Empirical Antibiotics

- Majority of infants admitted to the NICU receive empirical antibiotics
- Antibiotics are the most commonly prescribed medicines in the NICU
 - #1 – ampicillin
 - #2 – gentamicin
 - #3 – cefotaxime
 - #6 – vancomycin
- 5447 VLBW infants with a culture at birth, only 84 (1.5%) had a positive culture

Empirical Antibiotics

- Use of prolonged courses (≥ 5 days) of empirical antibiotics in preterm infants
 - NEC, death, late-onset infection.
- Proportion exposed to prolonged courses
 - 27-85% in NICHD Neonatal Research Network

Antibiotic Selection: 1st 3 days of Life



- Cohort of 128,914 infants - cefotaxime exposure associated with increased mortality (OR = 1.5).

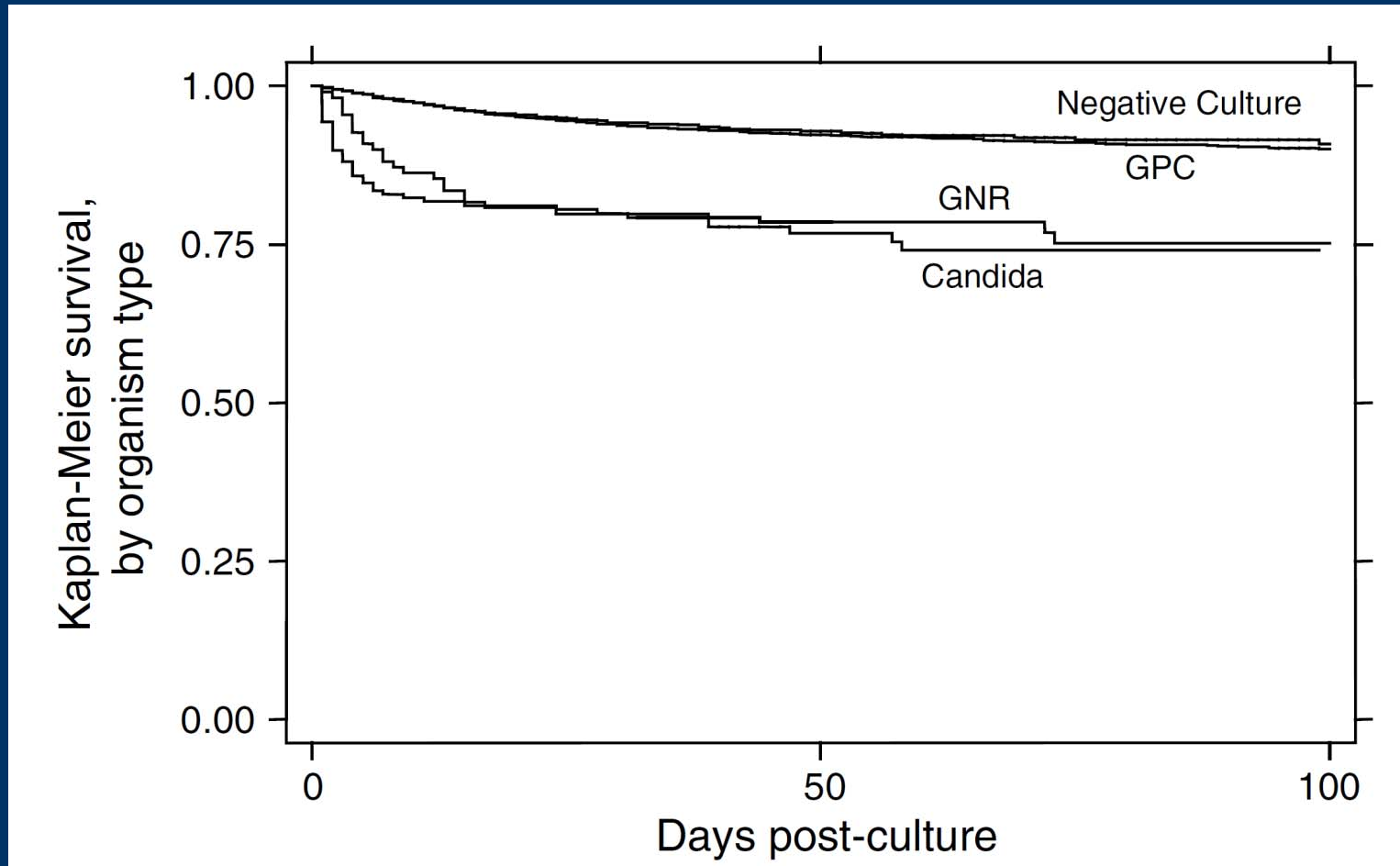
Broad Spectrum Antibiotics and Candidiasis

- 3702 ELBW infants
 - 3rd generation cephalosporin or carbapenem after day of life 3
 - OR for candidiasis = 2.16 [1.42, 3.27]

GBS treatment

- No resistance to penicillin or ampicillin observed
- Penicillin G
 - sepsis without focus – 10 days
 - meningitis – 14 days

Mortality Following Positive Blood Culture



Resistance Patterns

- Among isolates from 2006-2008 from NICUs in England and Wales
 - Early-onset pathogens (N=1516) – 94% sensitive to amoxicillin + gentamicin
 - Late-onset pathogens (N=3482) – 95% sensitive to amoxicillin + gentamicin

Rationale for Narrow Spectrum Empirical Coverage

- No well powered trial exists to guide therapy
- Antibiotics associated with harm
 - Candidiasis (broad spectrum)
 - Death (broad spectrum, long duration)
 - Necrotizing enterocolitis (long duration)
 - Late-onset infection (long duration)
- Gram-positives associated with low mortality
- Gram-negatives are typically sensitive
- Fungal pathogens - <2% of early-onset disease

Clark, Pediatrics, 2006. Cotten, Pediatrics, 2006.

Cotten, Pediatrics, 2009.

Antibiotic Therapy

- Clinician has to weigh consequences
 - Short-term – 24 hour mortality
 - Intermediate-term: school age neurodevelopment
 - Long-term – development of resistance and NICU public health