

# **NEONATAL SEPSIS**

**Clinical presentations, management and  
prevention strategies**

**RACP - May 2008**

# NEONATAL SEPSIS

Bimodal timing distribution -

**Early onset sepsis (EOS)** – onset of symptoms within the first 48 hours (majority from birth)

**Late onset sepsis (LOS)** – onset between 48 hrs and 28 days past term

# Neonatal host defences - limitations

## Opsonins

- Complement levels lower in newborn
- Fibronectin levels lower in prems
- IgA (mucosal immunoglobulin) absent at birth; poor rise in preterms
- IgG levels rise gradually until term (hence lower in prems); IgG - specificity critical for protection

# Neonatal host defences - limitations

## Neutrophils

- Low marginal pool
- Poor marrow response to acute infectious stress; hence neutropenia rather than neutrophilia is typical with infection in newborns
- Diminished chemotactic activity

# Neonatal Early Onset Sepsis

## Organisms

(ASGNI data 1991-1993; 4 perinatal centres)

	<u>No.</u>	<u>(%)</u>
GB Strep	53	(67)
E. Coli	14	(18)
H. flu	1	
S. Pneum	2	
L. Mono	2	
Other Strep	6	
Anaerobes	0	
S. Aureus	<u>1</u>	
Total	79	

**Overall Rate = 3.17 per 1000 livebirths (inborn)**

## GBS EOS – case profile

IOL at 36 weeks for PE; PGs x 2 then ARM  
24 hour labour, no maternal fever, no fetal distress  
SVD, minimal resuscitation; Apgars 6 and 8

Early onset respiratory distress - ? TTNB

CBP – neutrophils =  $0.45 \times 10^9$ ; I:T ratio = 54%

Hypotension and mixed acidosis – volume, inotropes,  
ventilation and antibiotics (**pen and gent**)

CXR – diffuse hazy opacities with air bronchograms

Blood cultures (+)ve for GBS

Subsequent CSF negative

Ventilated 6 days; hospitalisation 2 weeks

# Neonatal Early Onset Sepsis

## Epidemiology / Risk Factors - 1

- **rate 1- 4 / 1000 livebirths**
- **vertical (ascending) transmission ;  
intrapartum acquisition (exception  
– L monocytogenes)**
- **80-90% symptomatic at birth  
(usually with respiratory distress ;  
10% have meningitis)**
- **attack rate and mortality are gestational  
age dependent; 60% of cases < 37  
weeks gestation**
- **overall mortality 5-10%**

# Neonatal Early Onset Sepsis Epidemiology / Risk Factors - 2

## General Risk Factors

- **preterm labour**
- **prolonged ROM ( > 18 hrs)**
- **maternal temperature in labour ( > 37.5°C)**
- **multiple vaginal examinations in labour ( > 6)**
- **CHO intolerance**

Note – circa 60% of term EOS cases have no risk factors

# Neonatal Early Onset Sepsis

## Epidemiology / Risk Factors - 3

### GBStreptococcus

- **GBS colonisation rates**  
10 - 40 % (higher in lower socioeconomic groups)
- **1-2% of colonised women → babies with GBS sepsis**
- **Low maternal antibody to GBS subtype →**  
increased risk of neonatal sepsis  
thus, ↑ risk with co-twin of infected baby  
↑ risk with subsequent babies

# Neonatal Early Onset Sepsis

## Prevention Strategies - 1

Boyer and Gotoff - NEJM 1986; 34: 1665 - 1669

### Intrapartum Antibiotic Prophylaxis (IAP)

**Entry criterion** - GBS (+)ve mother (screened at < 32 wks)

- preterm labour or ROM >18 hrs
- if T >37.5°C, treat (withdraw from study)

**Treatment** - ampicillin 2gm i.v., then 1gm 4 hrly

- vs no treatment (ie no placebo); not blinded

**Results** - colonisation 8/85 vs 40/79 \*

- sepsis 0/85 vs 5/79 \*                      \* p < 0.05

# Neonatal Early Onset Sepsis

## Prevention Strategies - 2

### Cochrane Review

Smaill F (2000)

Intrapartum antibiotic prophylaxis - no GBS culture (+)ve

5 studies suitable

### Results

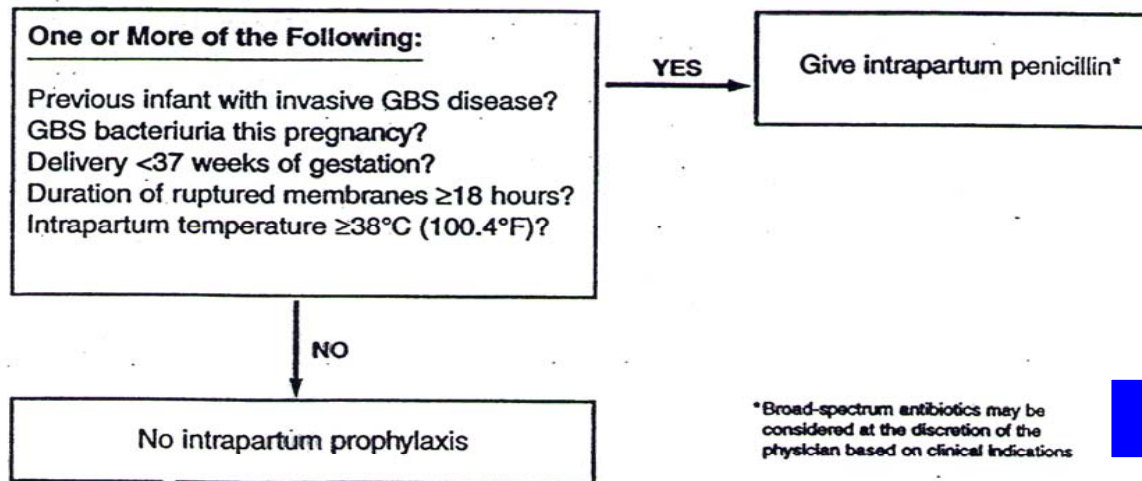
GBS colonisation	OR 0.10	95% CI 0.07 - 0.14
EO GBS sepsis	OR 0.17	95% CI 0.07 - 0.39
Neonatal death	OR 0.12	95% CI 0.01 - 2.00

Unlikely ever to generate adequate RCT

# Neonatal Early Onset Sepsis

## Prevention Strategies - EO GBStrep - 3a

### Risk factor strategy



Prevention strategy for early-onset GBS disease using risk factors without prenatal culture screening.

(Note - use lincomycin or erythromycin if allergic to penicillin)

AAP 1997 (ACOG 1996)

# Neonatal Early Onset Sepsis

## Prevention Strategies - EO GBStrep - 3b

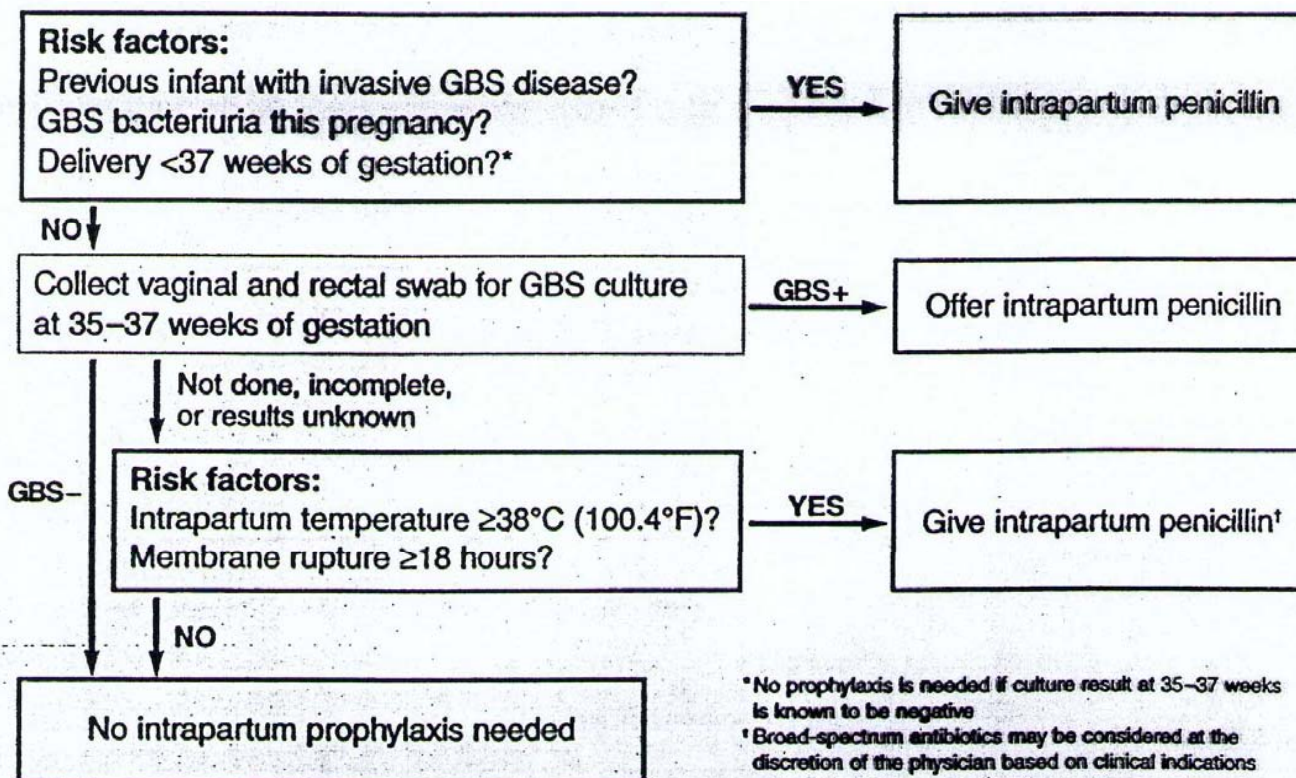
### Comments re risk factor approach

- covers 60-70% of cases of neonatal EOS
- only 7-10% of mothers exposed to antibiotics
- easy to apply
- no costs of screening / counselling

# Neonatal Early Onset Sepsis

## Prevention Strategies - EO GBStrep - 4a

### Combined risk factor and screening strategy



**NB**

Prevention strategy for early-onset GBS disease using prenatal culture screening at 35 to 37 weeks of gestation.

(Note - use lincomycin or erythromycin if allergic to penicillin)

AAP 1996 (CDC 1996)

## Maternal GBS screening

- **Introital or rectal swab (c.f. high vaginal swab)**
- **Suggested at > 35 weeks**
- **Selective culture medium improves detection rate**
- **Counselling re process and implications is important**
- **Timely availability of results; good records processes**

# Neonatal Early Onset Sepsis

## Prevention Strategies - EO GBStrep - 4b

### Comments re risk factor and screening approach

- covers 90-95% of neonatal EOGBS (population dependent)
- 15-20% of mothers exposed to antibiotics
- increased likelihood of anaphylaxis
- costs of screening and counselling
- requires access to antenatal care - highest risk groups may not be covered by this approach
- cumbersome; requires efficient laboratory and information infrastructures; inherent medico-legal issues
- issues re management of “GBS unknown” women

# EOS prevention strategies

**US multistate retrospective cohort study**

**1998-1999; 629,912 births**

**45 diverse US counties**

**Relative risk of early onset GBS lower for risk factor +  
screening vs risk factor only based approach**

**Adjusted relative risk =**

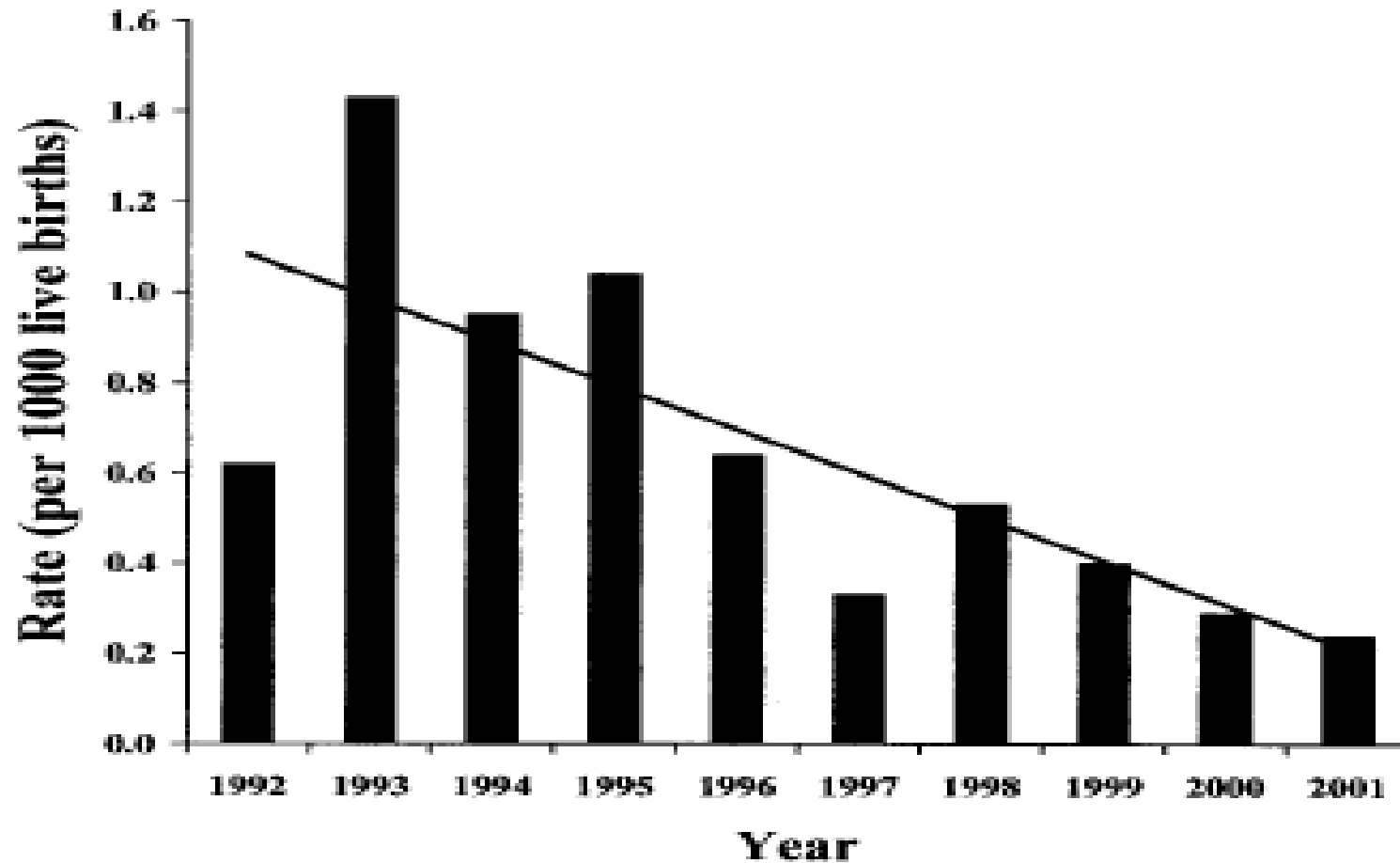
**0.46 (95% CI 0.36-0.60)**

**(NEJM 2002; 347: 233-9)**

## CDC Guidelines 2002

**Combined GBS screening + risk factor  
approach as recommended strategy**

# EOGBS – Aust 1992-2001

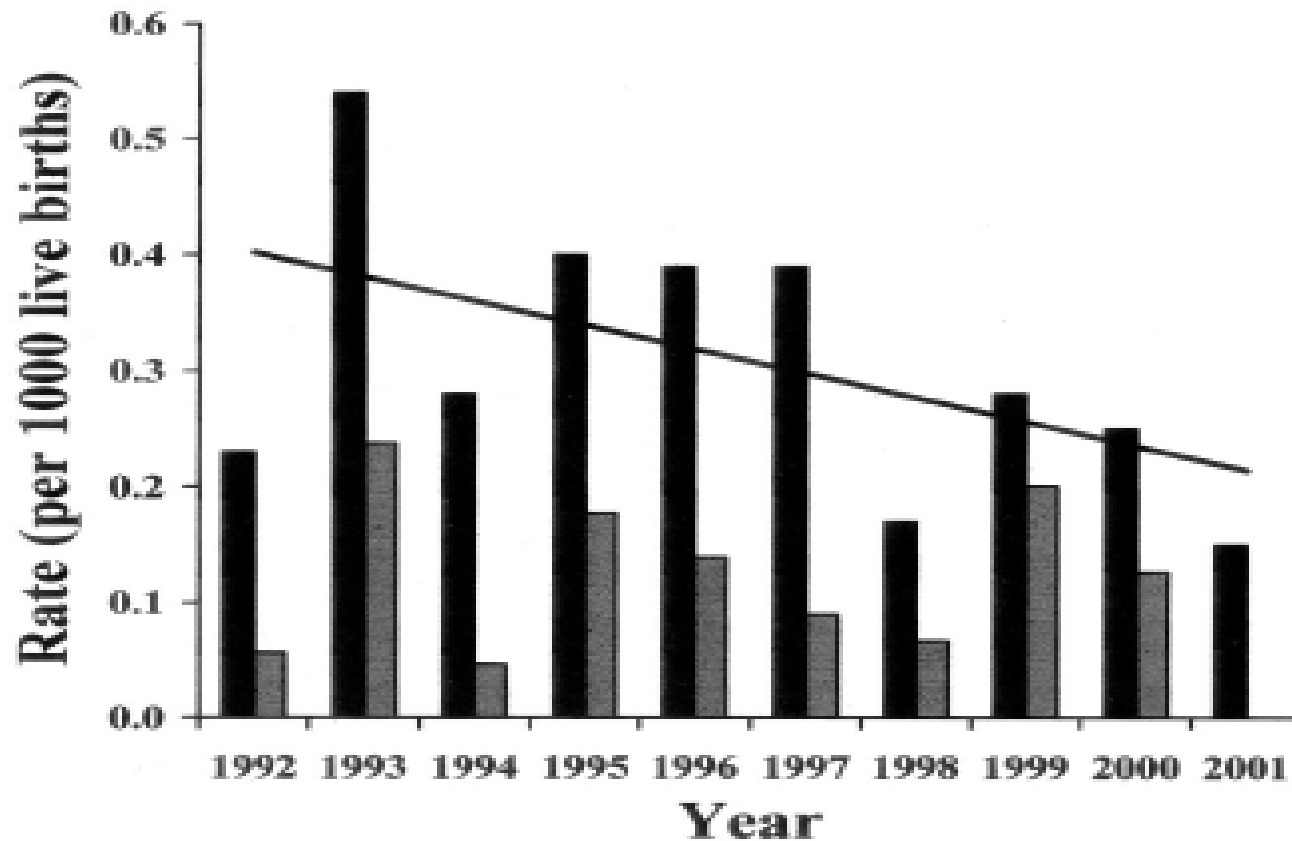


**FIGURE 1.** Early onset group B streptococcal sepsis rates in Australasia, 1992–2001. Diagonal line indicates trend line,  $P < 0.001$ .

## IAP for EOGBS caveats and cautionary notes

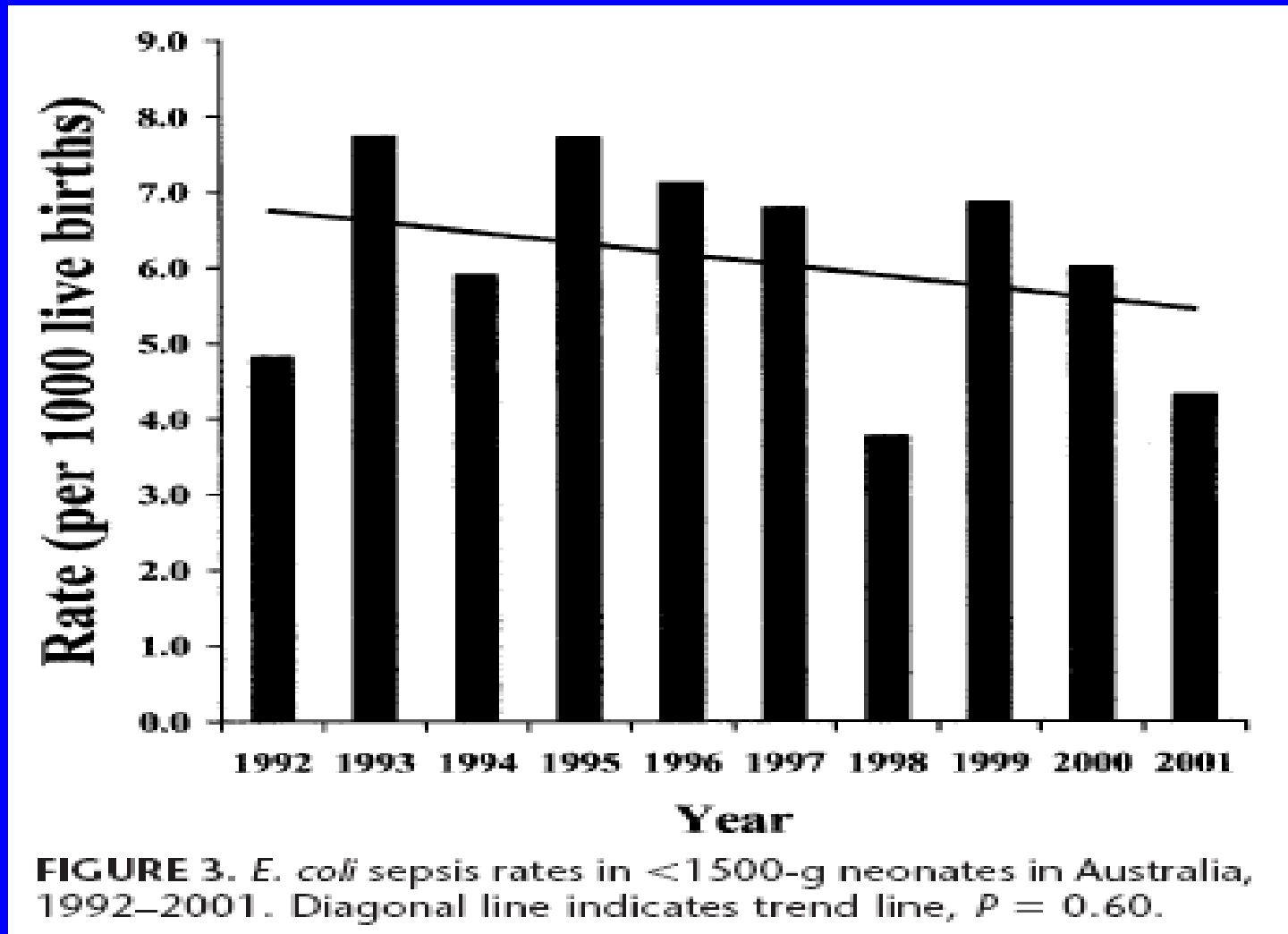
- Give early in labour (> 4 hrs before delivery)
- Reports of increasing rates of gram negative EOS  
eg Stoll et al. *Pediatr Inf Dis J* 2005; 24: 635-9  
bwgt < 1500 g; EOS – E Coli  
91-93 = 3.2/1000 vs 97-00 = 6.8/1000 \*
- Particularly linked to the use of ampicillin cf penicillin

## EOS – E coli. Aust 1992-2001



**FIGURE 2.** Early onset *E. coli* sepsis rate ■ and case fatality ratio ▒ in Australasia, 1992–2001. Diagonal line indicates trend line for *E. coli* sepsis,  $P = 0.07$ .

# EOS - E coli < 1500g. Aust 1992-2001



# Neonatal Early Onset Sepsis

## Future Directions / Strategies

**GBS vaccination**

**Rapid GBS detection in labour**

**Add gram (-) IAP cover in selected cases [eg  
PPROM with maternal cultures positive for  
gm (-) ve organism; eg pen and gent IAP]**

**Evolving resistance +/- changing organisms  
(importance of surveillance - ASGNI etc)**

# Neonatal Late Onset Sepsis Organisms

(Aust 1992-93; 12 months; perinatal setting)

<u>Organism</u>	<u>number (%)</u>	<u>died*</u>
CoNS	124 (56)	2
S aureus	25 (11)	3
E coli	20 (10)	3
Klebsiella	9 (4)	3^
Pseudomonas	8 (4)	4^
Enterobacter	5 (2)	3^
Group B strep	5 (2)	-
Candida	7 (3)	2
Other	17 (8)	2
Total	220	22

\* Death definitely or possibly attributable to infection

# Neonatal Late Onset Sepsis Organisms

(Aust 1992-93; 12 months; perinatal settings)

## Rate of LOS by birthweight

< 999g -  $70/310 = 22.6\%$

1000-1499g -  $59/563 = 10.5\%$

1500-1999g -  $15/876 = 1.7\%$

2000-2499g -  $6/1075 = 0.6\%$

>2499g -  $17/2899 = 0.6\%$

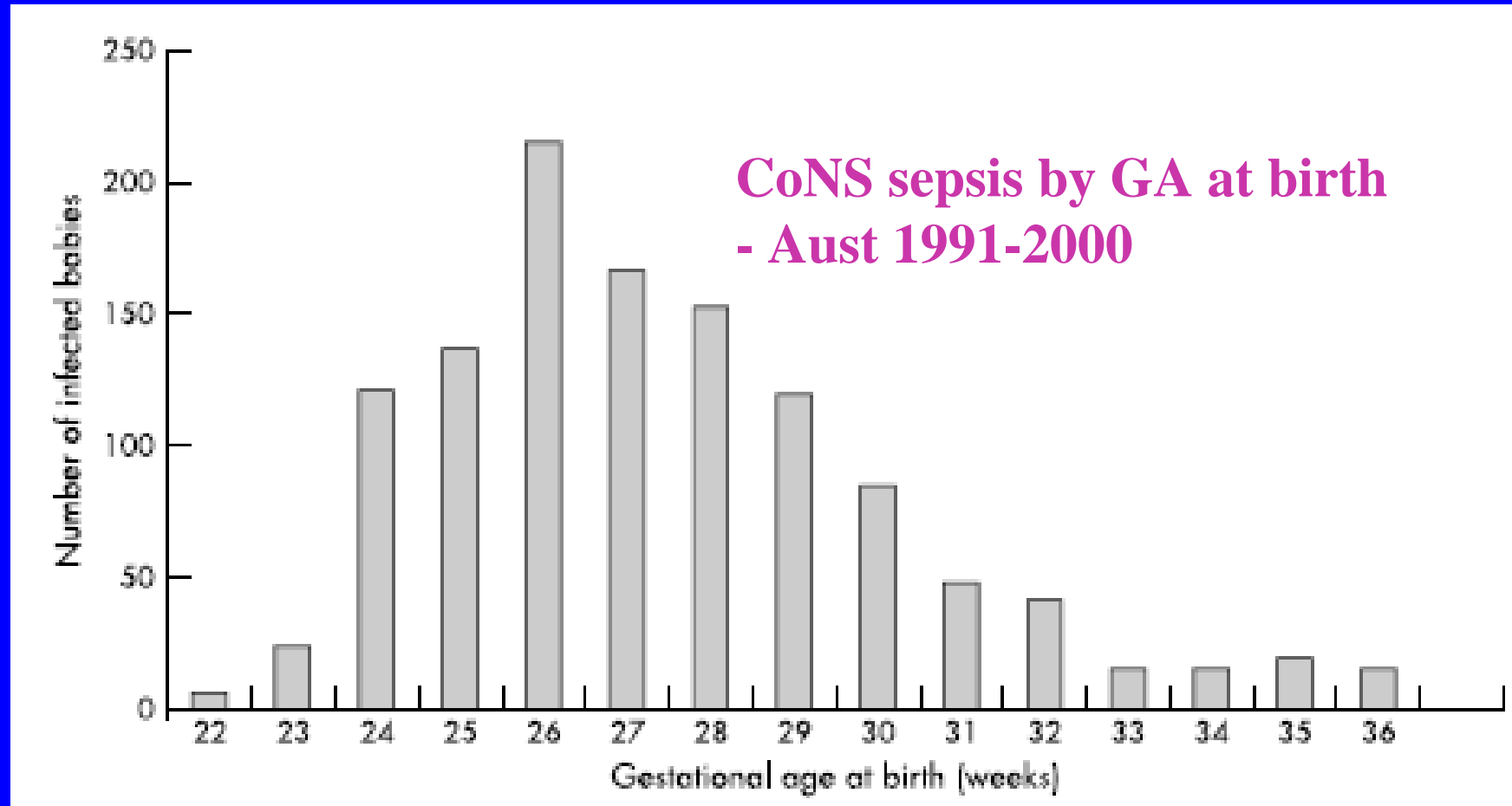
# Late onset sepsis – organisms (US experience)

**TABLE 1.** Distribution of Pathogens Associated With the First Episode of Late-onset Sepsis: NICHD Neonatal Research Network, September 1, 1998, Through August 31, 2000

Organism*	Number	%
<b>Gram-positive organisms</b>	<b>922</b>	<b>70.2</b>
<i>Staphylococcus</i> —coagulase-negative	629	47.9
<i>S aureus</i>	103	7.8
<i>Enterococcus</i> spp.	43	3.3
Group B <i>Streptococcus</i>	30	2.3
Other	117	8.9
<b>Gram-negative organisms</b>	<b>231</b>	<b>17.6</b>
<i>E coli</i>	64	4.9
<i>Klebsiella</i>	52	4.0
<i>Pseudomonas</i>	35	2.7
<i>Enterobacter</i>	33	2.5
<i>Serratia</i>	29	2.2
Other	18	1.4
<b>Fungi</b>	<b>160</b>	<b>12.2</b>
<i>C albicans</i>	76	5.8
<i>Candida parapsilosis</i>	54	4.1
Other	30	2.3
Total	1313	100

\* Patients with dual infections and patients with presumed CONS contaminants (defined in text) excluded. Using definitions in text, 276 (44%) CONS were definite infections and 353 (56%) were possible infections.

# LOS – CoNS sepsis



Arch Dis Child Fetal Neonatal Ed 2003; 88: F89-93

## Catheter related LOS – case profile

Ex-26 week prem, birthweight 820 g, now day 23;  
early problems with HMD and PDA

PCVC line in situ; nutrition 50:50 enteral: parenteral

Presents with increasing apnoea/bradycardia events,  
feed intolerance, thermal instability

CBP shows falling platelet count, and I:T ratio =  
28% with low-normal neutrophil count

Cultured and treated with antibiotics (**flucloxacillin  
and gentamicin**)

Line removed and tip cultured

Blood and line tip cultures positive for CoNS

Recovered over 2-3 days

# Catheter related LOS

Preventable with good process (requires change of culture, with focus on prevention<sup>^</sup>)

- Hand hygiene (note benefits beyond catheter related LOS)
- Skin preparation
- Insertion technique
- Hub handling (inc minimal line breaks)
- Early enteral feeding
- Minimising insertion duration
- (antibiotics / antifungals - eg candida sepsis reduced 13.2% to 3.2% in prems given prophylactic fluconazole\*)

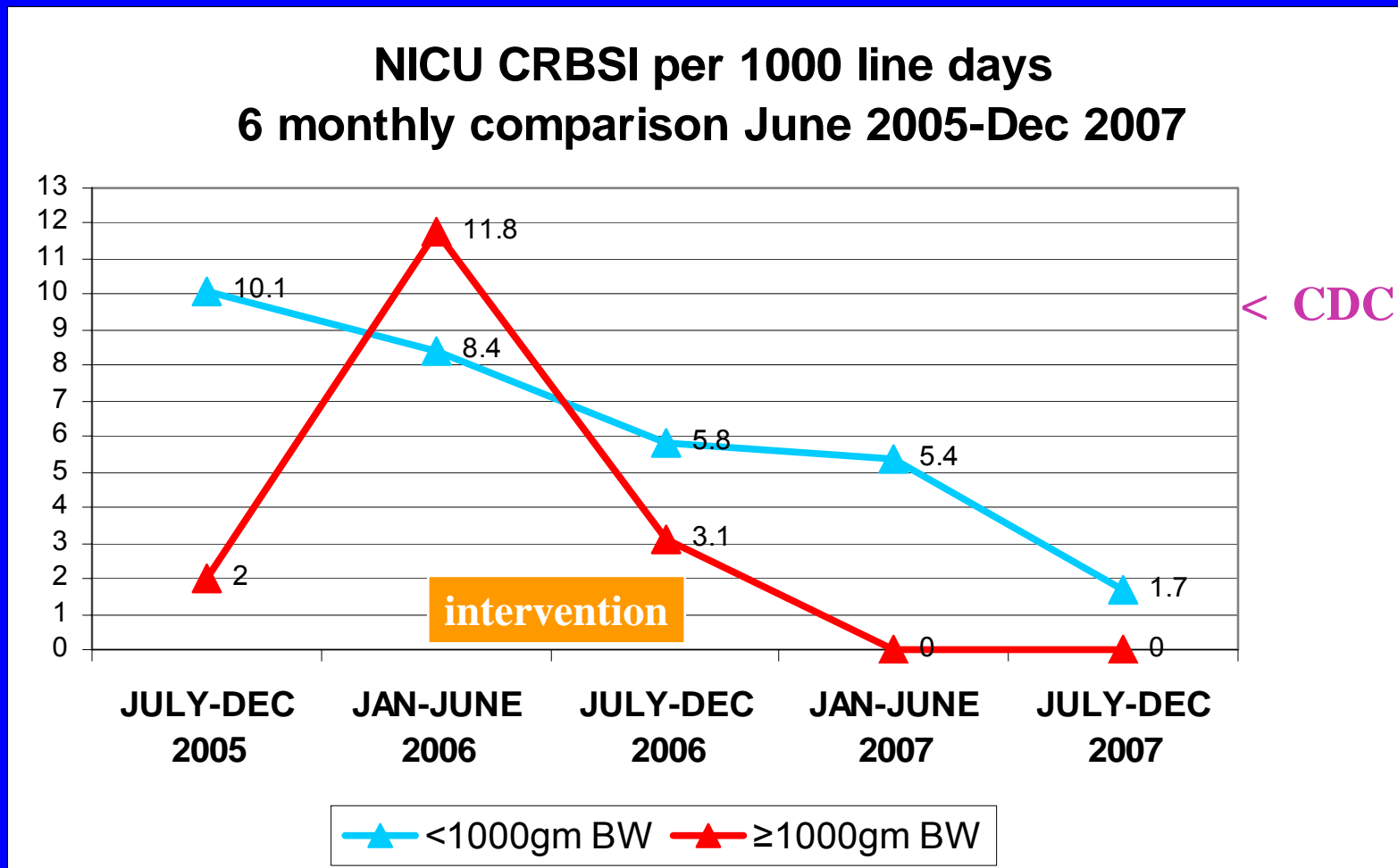
<sup>^</sup>Edwards W. Semin Neonatol 2002; 7: 325-33

\*Manzoni et al. NEJM 2007; 356: 2483-95

# LOS

## Catheter related blood stream infection (CRBSI)

### WCH Adelaide 05-07



# LOS - gram negative (bacillary) sepsis

## Aust 1992-2002

<u>Pathogen</u>	<u>no.</u>	<u>%</u>	<u>age at presentation</u> <u>(median)</u>
E coli	206	29	12
Klebsiella	160	23	16
Enterobacter	102	15	15
Ps aeruginosa	88	13	10*
Acinetobacter	59	8	8
Serratia	43	6	19
Citrobacter	21	3	12
Other	23	3	40

Rate constant over time @ 1.14 per 1000 live births

\* Mortality 52.35% for Ps aeruginosa vs 13.7% - 23.8% for others

## **LOS – nosocomial sepsis - case history**

Ex 28 week prem, now 6 weeks of age, stable in air;  
full enteral feeds

Acute onset fever, poor feeding, thermal instability and  
left neck “swelling”

CBP showed neutropenia with left shift; CRP 23,  
subsequently peaked at 130

Blood cultures positive for GBS; focal submandibular  
adenitis

Rapid resolution; CSF negative

EBM cultures positive for GBS

# **LOS – community acquired ER presentations**

Gm (-) ve organisms, GBS and S aureus

Overlap with EOS with respect to acquisition

Increased likelihood of underlying contributory factor (eg obstructive uropathy)

Typical presentation as uro- or neuro-sepsis

## **LOS – community sepsis - case history**

3 week old male infant; ex term; bwgt 3200g

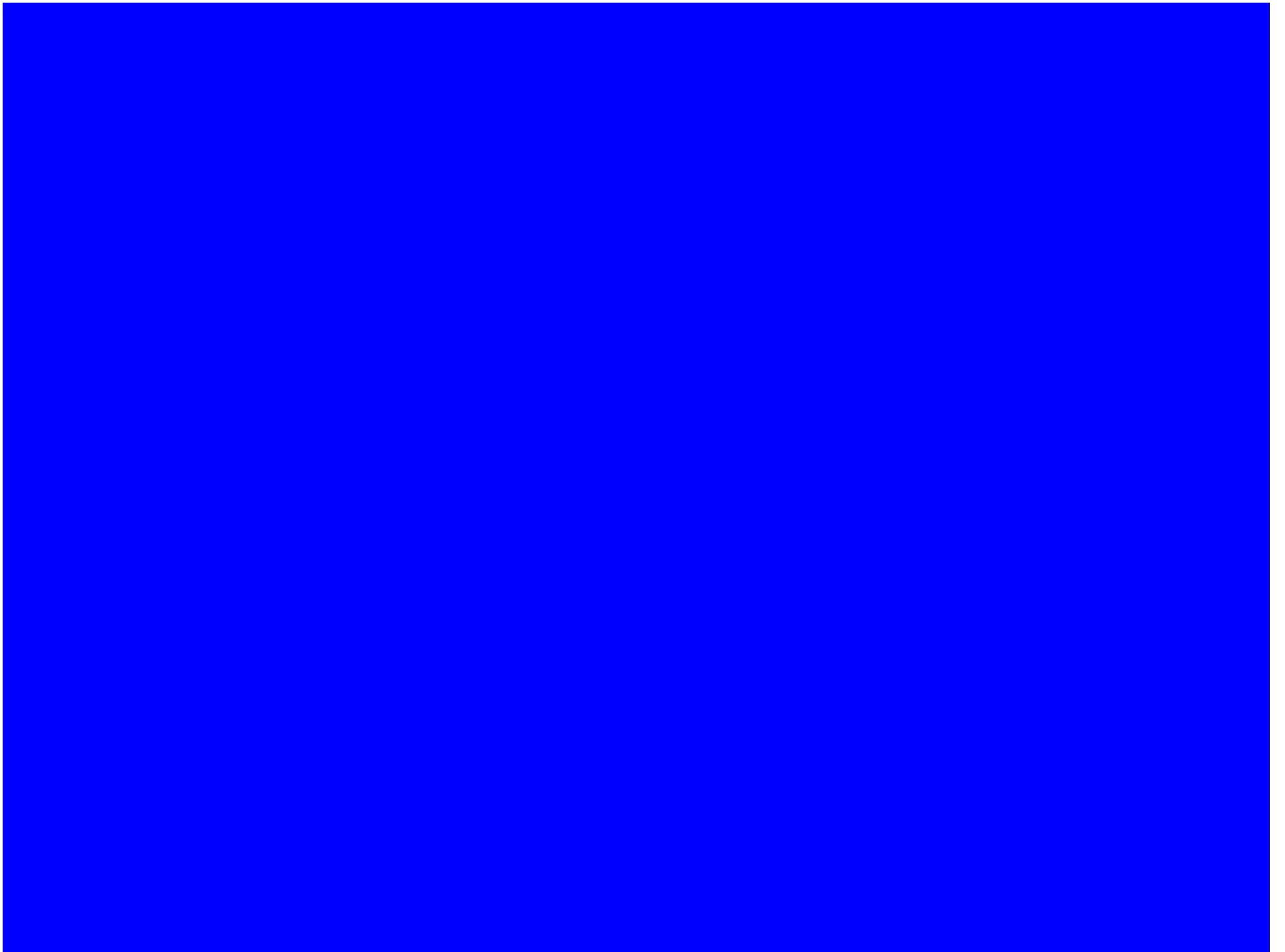
24 hour history of poor feeding, emesis and fever (39°C on admission)

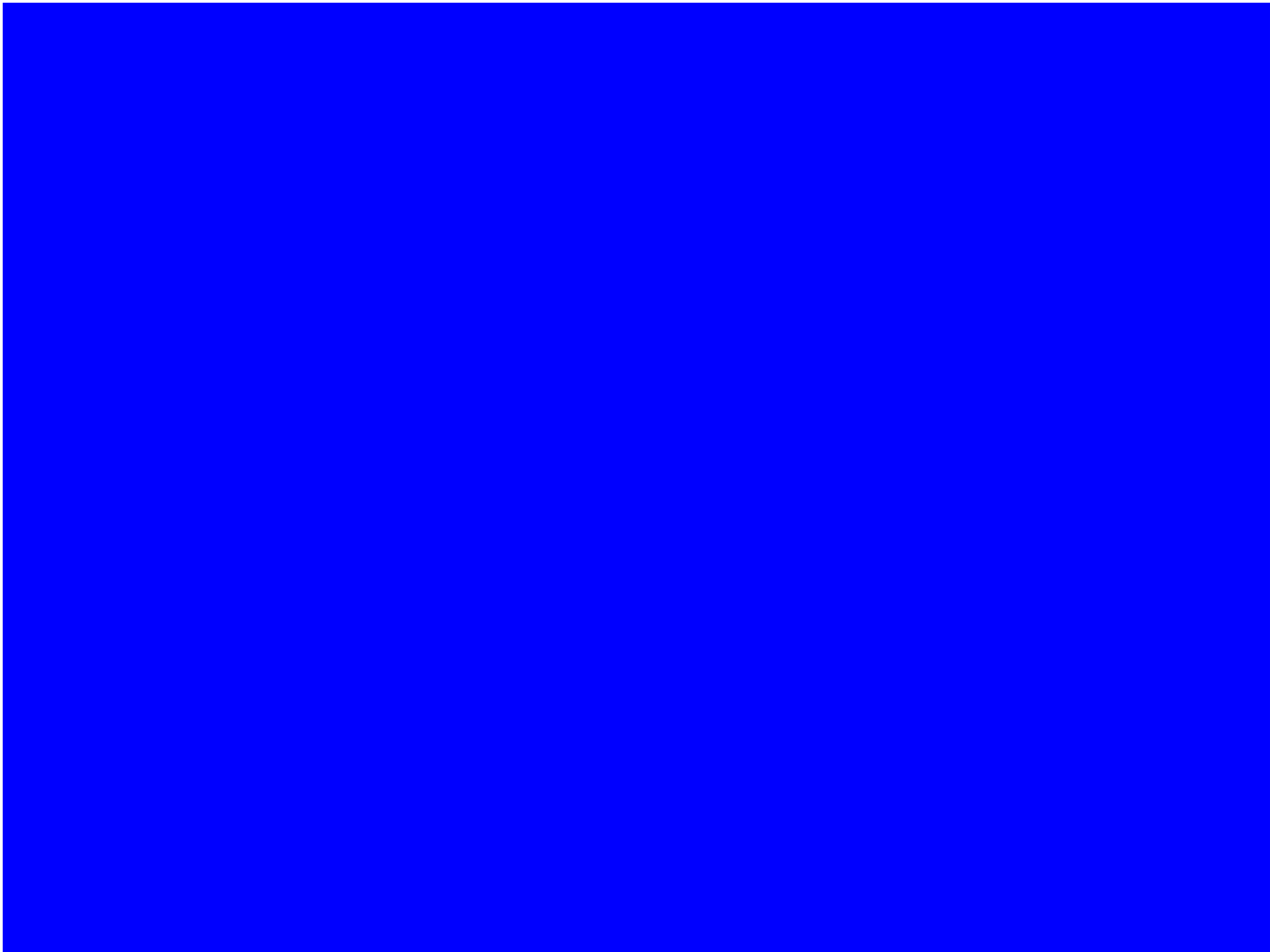
CBP showed neutrophilia, with L shift (36%)

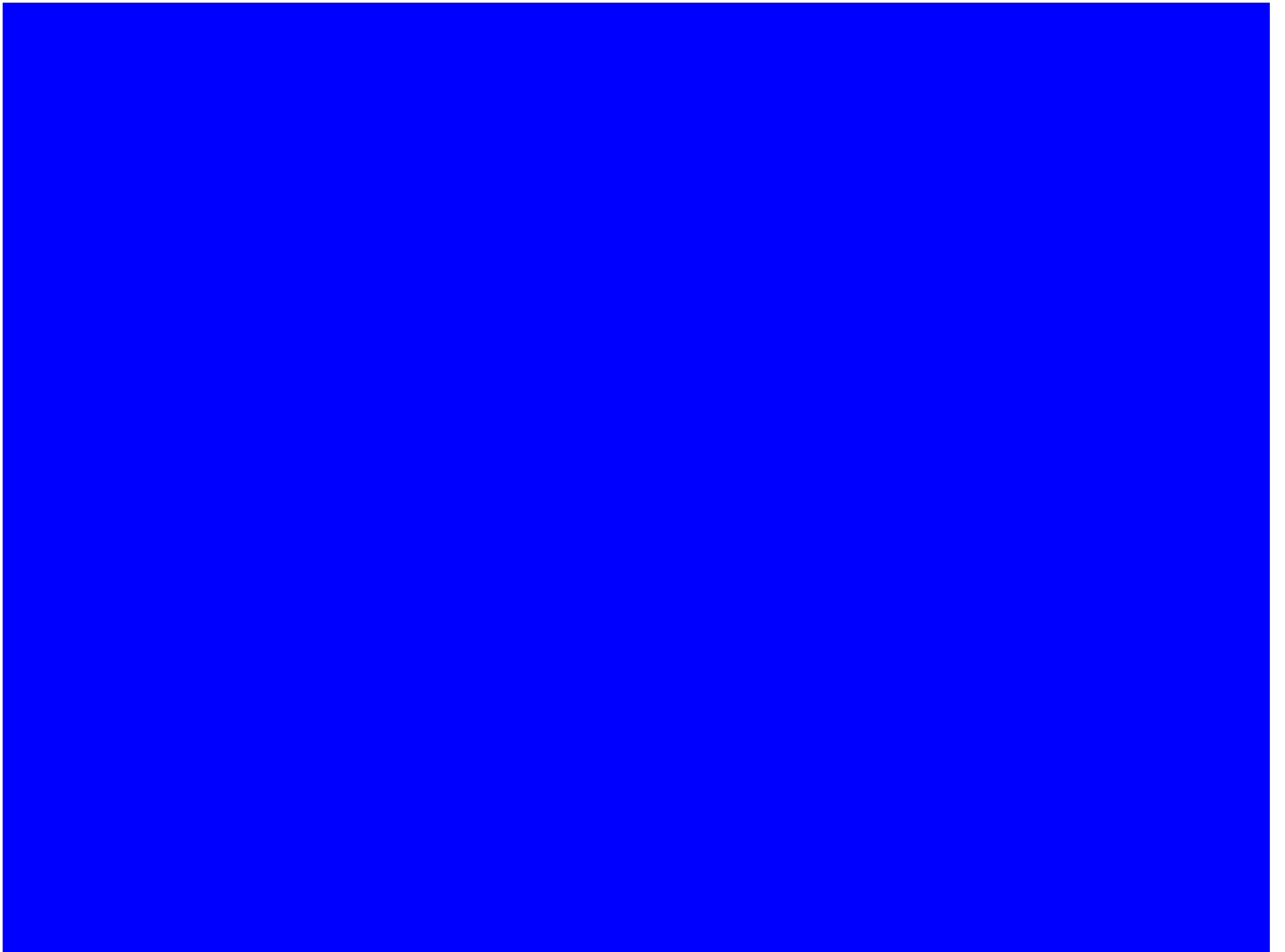
Empirical **pen and gent (? 3<sup>rd</sup> generation cephalosporin)**

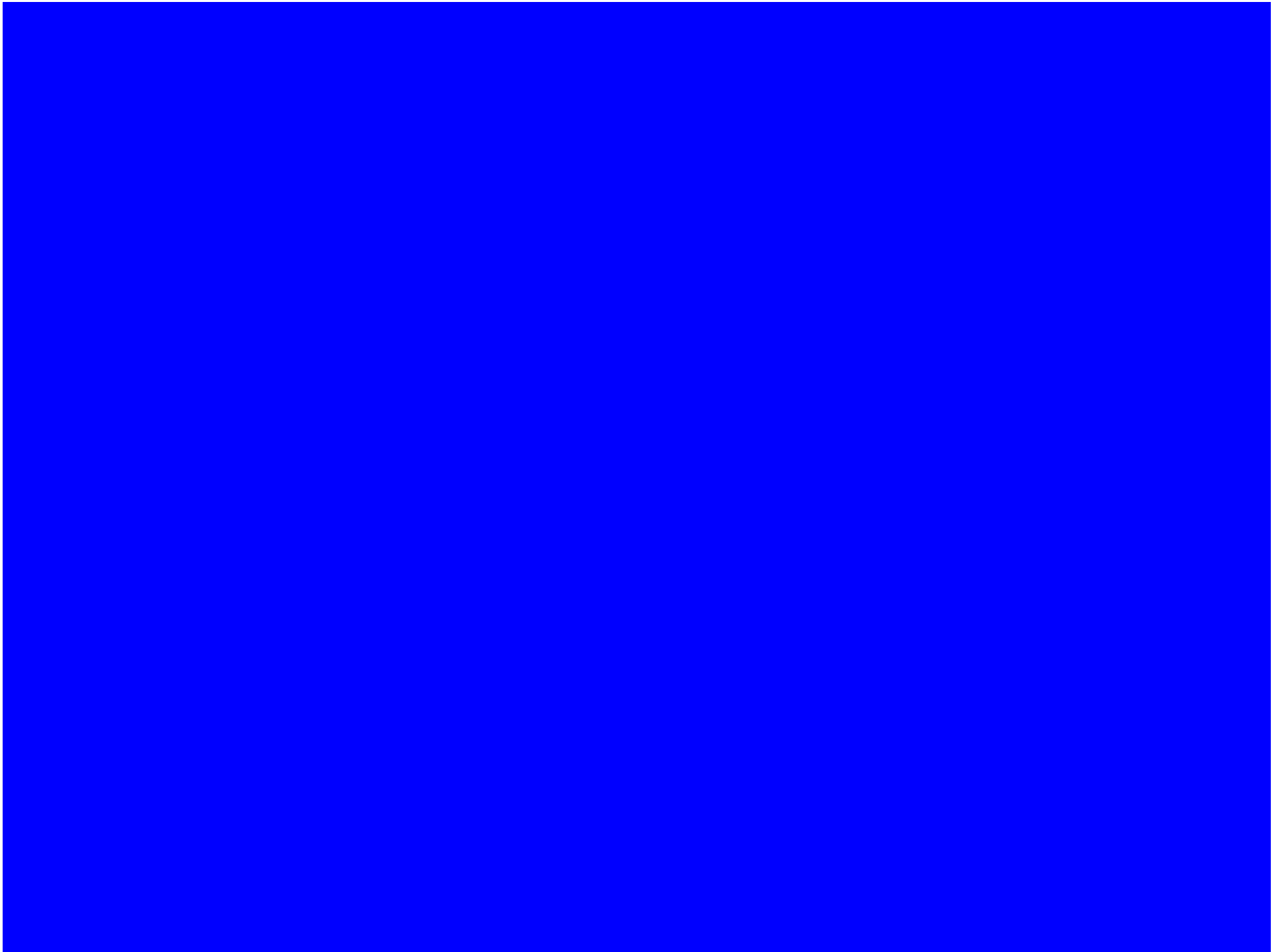
Blood and urine cultures positive for E coli

CSF negative









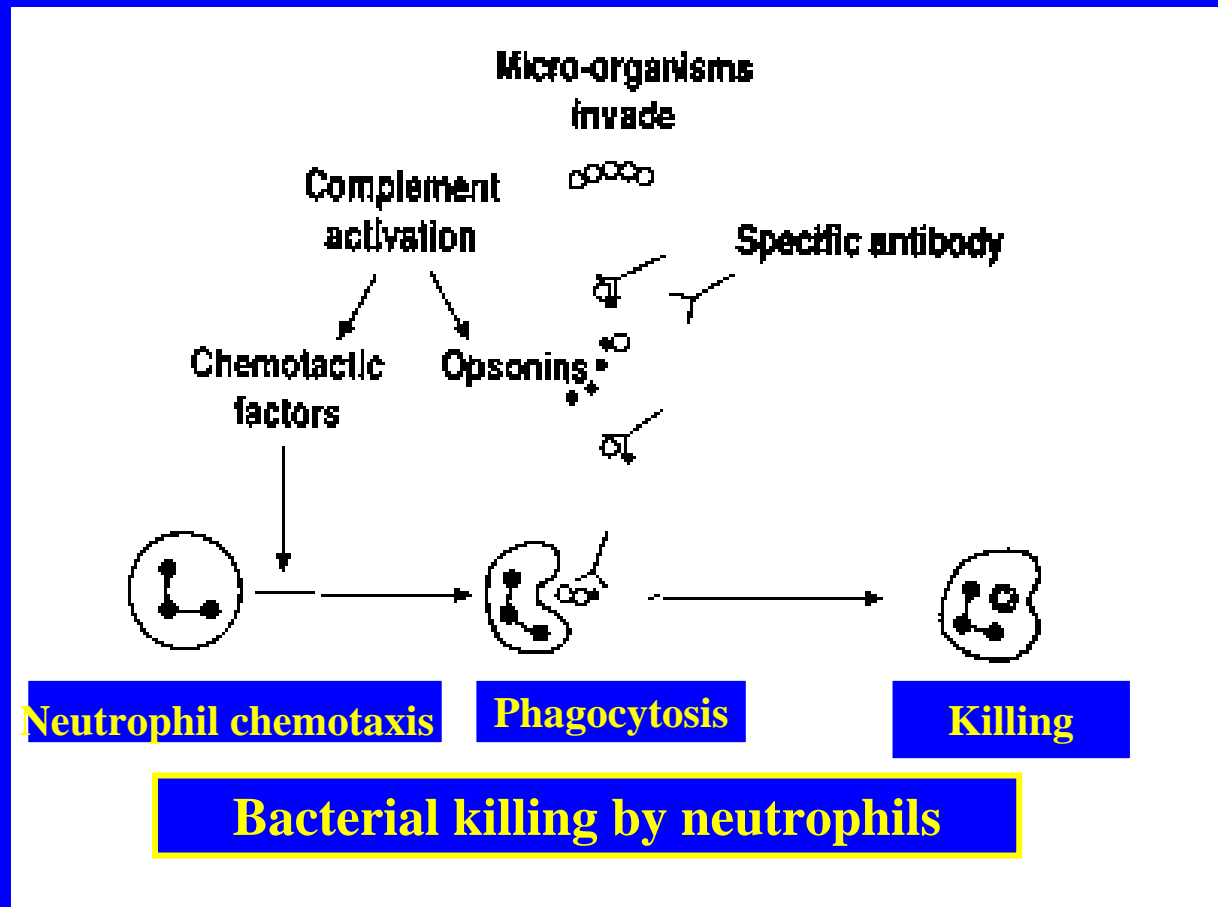
# Neonatal Early Onset Sepsis

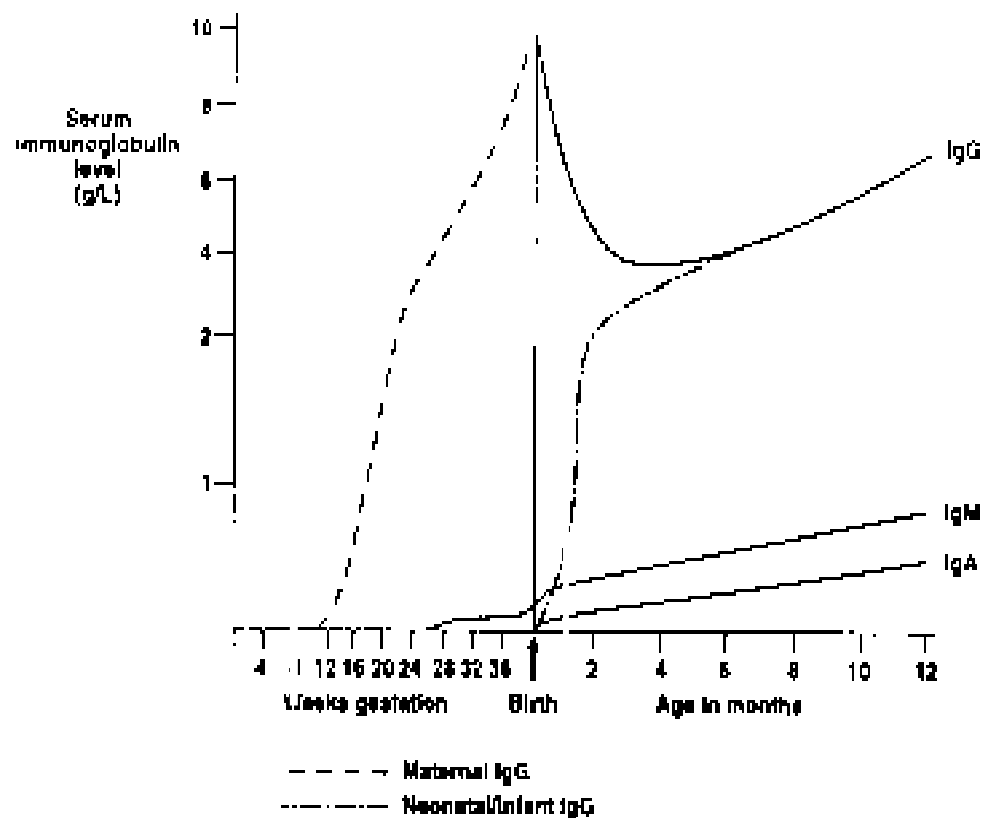
## Overview

- **Organisms**
- **Neonatal immune function**
- **Epidemiology and risk factors**
- **Prevention strategies**
- **Review of Australian trends**
- **Other issues and strategies**

## Basic steps in acute immune response to bacterial infection

- Important opsonins include secretory IgA, complement, fibronectin and type-specific IgG
- Neutrophil functions include chemotaxis, phagocytosis and intracellular killing via respiratory burst





**Changes in immunoglobulin levels over time**

- **Fetal IgG is acquired transplacentally**
- **Active and passive process**
- **Reflects maternal immune experience**
- **Neonates are poor at raising an IgM response to infections**
- **Preterm infants are deficient in IgG**

# Neonatal Early Onset Sepsis Australian Experience - ASGNI data

## GBS sepsis 1991-1997

<u>Epoch (24 mo)</u>	<u>rate / 1000 livebirths</u>	<u>(ATSIC pts)</u>
1991 - 1993	2.5	(7.4)
1993 - 1995	1.6	(3.2)
1995 - 1997	0.5	(1.3)

chi squared for trend -  $p < 0.005$

All centres used either risk factor or screening strategies

**Pediatr Infect Dis J 1999; 18: 524-8**

# Neonatal Early Onset Sepsis Australian Experience - ASGNI data

## Non GBS sepsis 1991-1997

<u>Epoch (24 mo)</u>	<u>rate / 1000 livebirths (95% CI)</u>
1991 - 1993	1.2 ( 0.8 - 1.7 )
1993 - 1995	0.8 ( 0.7 - 0.9 )
1995 - 1997	0.5 ( 0.3 - 0.7 )

chi squared for trend -  $p < 0.005$

**Pediatr Infect Dis J, 1999; 18: 524-8**

## EOS Organisms 9 Aust Perinatal Units: 1993-7

<u>Organism</u>	<u>1993-5</u>	<u>1995-7</u>
GBStrep	109	40
E Coli	24	18
H. flu	5	5
(L mono	4	3)
Other gm negs	11	3
E/coccus	2	3
Other strep	11	1
S aureus	5	1
Candida	1	0
<b>TOTAL EOS</b>	<b>179</b>	<b>77</b>
<b>TOTAL DEL</b>	<b>79,240</b>	<b>70,888</b>

**ASGNI data - Pediatr Infect Dis J, 1999; 18: 524-8**

# Neonatal Early Onset Sepsis

## Prevention Strategies - 5

### WCH Protocol - intrapartum antibiotic prophylaxis (to 2004)

- (+)ve risk factors → treat intrapartum with  
gentamicin 80 mgm  
+ ampicillin 2 gms i.v.
- screen for GBS at 35-37 wks  
if (+)ve → treat intrapartum with  
penicillin 1.2 gm i.v.  
if mother allergic to penicillin,  
consider erythromycin or lincomycin

# Neonatal Early Onset Sepsis

## South Australian Experience - WCH Data

(24 month epochs)	<u>94 - 95</u>	<u>96 - 97</u>	<u>98 - 99</u>	<u>total</u>
<u>Organism</u>				
GBS (blood cult)	6	1	2	9
GBS (antigen)	5	1	-	6
E Coli	3	4	1	8
Group A/G/F Strep	4	1	1	6
L Monocytogenes	1	-	-	1
S Pneumoniae	-	1	-	1
Enterobacter	1	-	-	1
H Influenzae	-	1	-	1
Bacteroides sp	<u>1</u>	<u>-</u>	<u>-</u>	<u>1</u>
<b>Total</b>	<b>21</b>	<b>9</b>	<b>4</b>	<b>34</b>

# Neonatal Early Onset Sepsis Australian Experience - WCH data

## Rates of EOS - WCH 1994 - 1999

	rate / 1000 livebirths ( inborn )		
(24 month epochs)	<u>94 - 95</u>	<u>96 - 97</u>	<u>98 - 99</u>
GBS (cult +ve)	0.97	0.14	0.26
GBS (antigen)	0.81	0.14	-
[All GBS	1.78	0.28	0.26]
All EOS	3.39	1.26	0.52

\*  $p < 0.05$  for all time trends

# Neonatal EOS

## SA Perinatal Protocol - 2004

- Adopts general principles of CDC 2002 guidelines
- GBS focussed - primary antibiotic “tool” is penicillin alone
- Broader spectrum antibiotics are now a clinical decision (i.e. based on culture results, or presence of clinical chorioamnionitis)

### Caveats

- Note that penicillin needs to be given as soon as possible in labour to maximise benefits of IAP
- Not necessary to give penicillin for elective LSCS in GBS (+) mother, provided membranes intact and no labour

# Neonatal Early Onset Sepsis

## Other Issues

### Balance of risks for mother and baby

e.g:- at term, with no risk factors

mother GBS (+)ve → 1-2/100 risk of neonatal sepsis

with IAP → 1/1-4000 risk of neonatal sepsis

risk of anaphylaxis - 1/10,000 - 1/100,000

