Neonatal Sepsis

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Learning Objective

1. Understand the epidemiology and etiology of neonatal sepsis
2. Understand pathophysiology of neonatal sepsis
3. Describe the clinical presentation of neonatal sepsis
4. Understand underlying risk factors
5. Discuss screening and diagnostic procedure of neonatal sepsis
6. List goals of therapy for neonatal sepsis
7. Outline the treatment strategies for neonatal sepsis

Presentation Overview

- Introduction to Neonatal Sepsis
- Probiotic Use in NICU

Definition

- Neonatal sepsis is systemic infection that occurs during early days of neonates. This infection is mainly caused by bacteria in the blood and can lead to more severe infection if left untreated.

Terminology

- Preterm infants
- Post-natal age
- Low birth weight infants
  - Very low birth weight (VLBW)
  - Extremely low birth weight (ELBW)
- Premature Rupture of Membranes (PROM)
- Chorioamnionitis

Gestational Age Vs. Conceptional (post-conceptional) Age

- **Gestational Age:** Gestational age (completed weeks): time elapsed between the first day of the last menstrual period and the day of delivery. Gestational age is calculated by adding 2 weeks to the conceptional age.
- **Post-conceptional Age:** is the time elapsed between the day of conception and the day of delivery.

Apgar Score

- **APGAR score**: **A**ppearance, **p**ulse, **g**rimace, **a**ctivity, **r**espiration
- Scores 7 and above are generally normal, 4 to 6 fairly low, and 3 and below are generally regarded as critically low.
- The resulting Apgar score ranges from zero to 10.

Early Onset Sepsis

- Early onset sepsis refers to any infection that occurs within 72 hours post birth. The pathogens causing early onset sepsis is generally acquired during the birth. Most cases, infants develop symptoms within first 6 hours after the birth.

Late Onset Sepsis

- Late onset sepsis refers to any infection that occurs after 72 hours post birth. The pathogens causing late onset sepsis is generally acquired from the postnatal environment.

Epidemiology

- 0.1-0.5 percent of live births in North America
- Preterm > Term
- In VLBW infants,
  - Early onset: 2%
  - Late onset: 20-25%
- the risk of sepsis increase with decreasing gestational age and birth weight.

Risk Factors – Early Onset

- Premature Rupture of Membranes (PROM) occurring ≥18 hours before birth
- Maternal chorioamnionitis
- Maternal colonization with GBS
- Preterm delivery
- Intrapartum maternal temperature ≥ 38^{o}C
- Five minute Apgar score ≤6
- Evidence of fetal distress

Risk Factors – Late Onset

- Prolonged use of intravascular catheters
- Preterm delivery
- Exposure to antibiotics
- Prolonged hospitalization
- IV or enteral solutions
- TPN
- Mechanical ventilation
- Arterial catheter
- Central venous line (CVL)
- Peripheral catheter

Pathogens – Early Onset

- Two of the most common pathogens that causes early onset sepsis:
  - Group B streptococcus (GBS)
  - gram-negative enteric organisms (mostly *Escherichia coli*)

Pathogens – Early Onset

- Following are list of less common but potential pathogens for early onset sepsis:
  - gram-negative bacilli (eg, *Klebsiella* sp.),
  - gram-positive bacilli (eg. *Listeria monocytogenes*),
  - enterococci (eg, *Enterococcus faecalis*),
  - group D streptococci (eg, *Streptococcus bovis*),
  - α-hemolytic streptococci and staphylococci,
  - *Streptococcus pneumoniae,*
  - *Haemophilus influenzae* type b,
  - *Neisseria meningitidis* (rare),
  - *Neisseria gonorrhoeae* (rare)

Pathophysiology – Early Onset

- Most early onset bacterial sepsis is caused during the delivery via birth canal colonized with bacteria or ascending infection through uterus.
- Hematogenous and transplacental dissemination of maternal infection can cause early onset sepsis. However this very rare.

Pathogens – Late Onset

- Common pathogens associated with late onset sepsis are:
  - coagulase negative staphylococci (CoNS)
  - other gram-positive bacteria (*Staphylococcus aureus*, Enterococcus, GBS)
  - gram-negative bacteria (*Escherichia coli*, *Klebsiella spp.*, *Pseudomonas spp.*)
  - fungi (*Candida albicans*)

Pathophysiology – Late Onset

- Initial site of late onset sepsis can be one of the followings: urinary tract, nasal sinuses, middle ear, lungs, and/or gastrointestinal tract. Once infection penetrates the bloodstream, it can disseminate to meninges, kidneys, bones, joints, peritoneum, and skin.

Clinical Presentation

- Decreased activity level
- Less vigorous sucking
- Anorexia
- Apnea
- Bradycardia
- Hyperthermia
- Hypothermia
- Seizures
- Jitteriness
- Vomiting
- Diarrhea
- Abdominal distention

Screening and Diagnosis

- Maternal GBS screening
- CBC and differential
- Lumbar puncture
- Urinalysis and culture
- Blood cultures

Prognosis

- Fatality rate is 2 to 4 times higher in LBW infants than in full-term, normal weight infants.
- Overall mortality rate of early-onset sepsis is 3 to 40%
  - Mortality from GBS infection is 2 to 10%
- late-onset sepsis is 2 to 20%
  - infections caused by gram-negative bacilli or *Candida* spp have rates of up to 32 to 36%

Goals of Therapy

- Treat suspected neonatal sepsis to prevent immediate and long term complication of the infection
- Tailor antibiotic treatments based on culture and sensitivity results to decrease unnecessary exposure to broader spectrum antibiotics.
- Use therapeutic drug Monitoring to evaluate efficacy and toxicity of antibiotic treatment

Initial Empiric Therapy

Onset of Sepsis	Suspected Microbial Agent	Antibiotics of Choice	Alternative therapy or comments
Early onset	GBS, enterococcus, listeria, gram-negative enteric bacilli (eg. E. coli)	Ampicillin + aminoglycoside	If a patient has central venous line and is clinically septic, consider the addition of vancomycin for CoNS coverage
Late onset	GBS, CoNS, listeria enterococcus, gram-negative enteric bacilli (eg. E coli)	Ampicillin + aminoglycoside	
1-3 months	Includes organisms usually seen in neonates or older children	Ampicillin + vancomycin + cefotaxime	
>3 months	S. pneumonia, N. meningitidis, S. aureus, H. influenzae	Ceftriaxone + vancomycin (only if clinically septic)	Use cefuroxime if fever without a source and not clinically septic

Ampicillin

Ampicillin (Sepsis)		
Weight	Post-natal age	Dose
<1.2kg	n/a	100 mg/kg/day IV divided q12hr
1.2-2kg	0-7 days	100 mg/kg/day IV divided q12hr
	>7 days	150 mg/kg/day IV divided q8hr
>2kg	0-7 days	150 mg/kg/day IV divided q8hr
	>7 days	200 mg/kg/day IV divided q6hr

Ampicillin (Meningitis)	
Post-natal age	Dose
≤7 days	200 mg/kg/day IV divided q8hr
>7 days	300 mg/kg/day IV divided q6hr

Cefotaxime

Cefotaxime		
Weight	Post-natal Age	Dose
<1.2kg	n/a	100 mg/kg/day IV/IM divided q12hr
1.2-2kg	0-7 days	100 mg/kg/day IV/IM divided q12hr
	>7 days	150 mg/kg/day IV/IM divided q8hr
>2kg	0-7 days	150 mg/kg/day IV/IM divided q8hr
	>7 days	200 mg/kg/day IV/IM divided q6hr

Gentamycin

Gentamycin			
Post-natal age	Weight	Gestational age	Dose
0-7 days	n/a	<34 weeks	3 mg/kg/dose IV q24hr
		≥34 weeks	3 mg/kg/dose IV q18hr
7 days	≤1kg	n/a	3.5 mg/kg/dose IV q24hr
	>1kg	<37 weeks	2.5 mg/kg/dose IV q12hr
		≥37 weeks	2.5 mg/kg/dose IV q8hr

Vancomycin

Vancomycin	
Weight	Dose
<800g	27 mg/kg/dose IV divided q36hr
800-1200g	24 mg/kg/dose IV divided q24hr
1200-2000g	18 mg/kg/dose IV divided q12hr

Targeted Therapy

- **Coagulase negative staphylococci (CoNS)**
  - Vancomycin.
- **S. aureus**
  - MSSA – any one of the susceptible antibiotics or oxacillin monotherapy.
  - MRSA – Vancomycin.
- **E coli**
  - ampicillin sensitive isolates: ampicillin monotherapy
  - resistant isolates: either aminoglycoside (gentamicin), or an extended-spectrum cephalosporin (cefotaxime)

Targeted Therapy

- **ESBL-producing organisms (Enterobacter, Citrobacter, Klebsiella and Serratia)**
  - If the organism is susceptible, an aminoglycoside (amikacin) or cefepime can be used.
  - Otherwise, meropenem.
- **Pseudomonas**
  - Combination therapy of gentamicin, and ceftazidime or piperacillin/tazobactam.

Therapeutic Drug Monitoring

Drug	Time for first TDM	Optimal sample time	Acceptable sampling time	Optimal concentration
Amikacin	3rd or 4th dose*	Trough: 0-30 min before dose Peak: 30-60 min after end of infusion	Trough: up to 60 min before dose Peak: up to 90 min after end of infusion	Trough: 2.5-10 mg/L Peak: 20-35 mg/L
Gentamycin				Trough: 0.6-2 mg/L Peak 5-10 mg/L
Tobramycin				
Vancomycin	2nd or 3rd dose**	Trough: 0-30 min before dose	Trough: up to 60 min before dose	CNS: 10-15 mg/L Other: 5-12 mg/L

Duration of Therapy

- Typical duration of antibiotic therapy:10-14 days
- Complicated sepsis with meningitis: Two to three weeks of antibiotic therapy for gram-positive meningitis, and a minimum of three weeks for gram-negative meningitis.
- The decision to continue antibiotic therapy in an infant with negative cultures is based on the clinical judgment of the attending physician.

For Pharmacists

- Initial Dose
- TDM
- Culture and Sensitivity
- Duration of Antibiotic Therapy

Probiotic Use in NICU

Severe Stage II-III NEC

PROBIOTICS VS. CONTROL (COMPARISON 1):

Severe stage II-III necrotizing enterocolitis (Outcome 1.1): Thirteen studies reported on severe stage II-III NEC (Dani 2002; Costalos 2003; Lin 2005; Lin 2008; Bin-Nun 2005; Manzoni 2006; Manzoni 2009; Kitajima 1997; Mohan 2006; Rougé 2009; Samanta 2009; Sari 2010; Stratiki 2007). The administration of prophylactic probiotics significantly reduced the incidence of severe stage II -III NEC [typical RR 0.35 (95% CI 0.24 to 0.52); typical RD -0.04 (95% CI -0.06 to -0.02), NNT 25] This effect is maintain even for subgroup of weight less than 1500 g at birth [typical RR 0.34 (95% CI 0.23 to 0.50)] and high quality studies [typical RR 0.25 (95% CI 0.13 to 0.49)]. Data pertaining to the most vulnerable infants (ELBW) could not be abstracted from the included studies. Figure 1

Severe Stage II-III NEC

	Probiotic (n/N)	No probiotic (n/N)	RR (fixed) (95% CI)	Weight (%)	RR (95% CI)
Kitajima, 1997[26]	0/45	0/46			Not estimable
Dani, 2002[20]	4/295	8/290		20·76	0·49 (0·15–1·61)
Costalos, 2003[23]	5/51	6/36		18·10	0·59 (0·19–1·78)
Bin Nun, 2005[22]	1/72	10/73		25·55	0·10 (0·01–0·77)
Lin, 2005[21]	2/180	10/187		25·23	0·21 (0·05–0·94)
Manzoni, 2006[24]	1/39	3/41		7·52	0·35 (0·04–3·23)
Mohan, 2006[25]	2/21	1/17		2·84	1·62 (0·16–16·37)
Total (95% CI)	703	690		100·00	0·36 (0·20–0·65)

Total events: 15 (probiotic), 38 (no probiotic)
Test for heterogeneity: χ^2=4·66, df=5 (p=0·46), I^2=0%
Test for overall effect: Z=3·37 (p=0·0008)

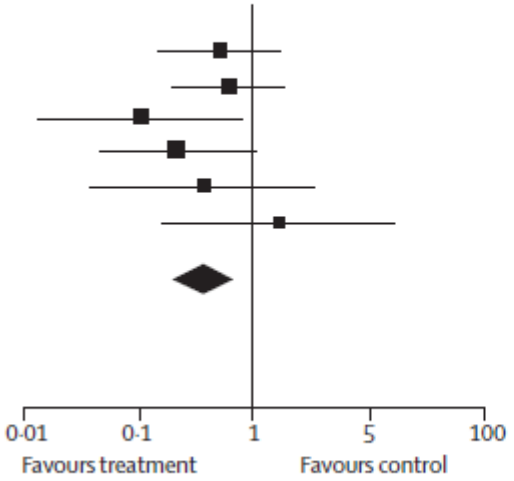

Figure 2: **Effect of probiotics on necrotising enterocolitis of stage 2 or greater**

All cause mortality

Mortality (Outcome 1.2):

Ten studies reported on mortality (Kitajima 1997; Reuman 1986; Dani 2002; Lin 2005; Lin 2008; Bin-Nun 2005; Manzoni 2006; Manzoni 2009; Rougé 2009; Samanta 2009). The number of deaths was significantly lower in the probiotics group [typical RR 0.40 (95% CI 0.27 to 0.60); typical RD -0.04 95% CI (-0.06 to -0.01), NNT 25]. Five studies (Bin-Nun 2005; Dani 2002; Kitajima 1997; Lin 2008; Sari 2010) reported NEC-related mortality. The number of NEC related deaths was also significantly lower in the probiotics group [typical RR 0.31 (95% CI 0.10 to 0.94).

All Cause Mortality

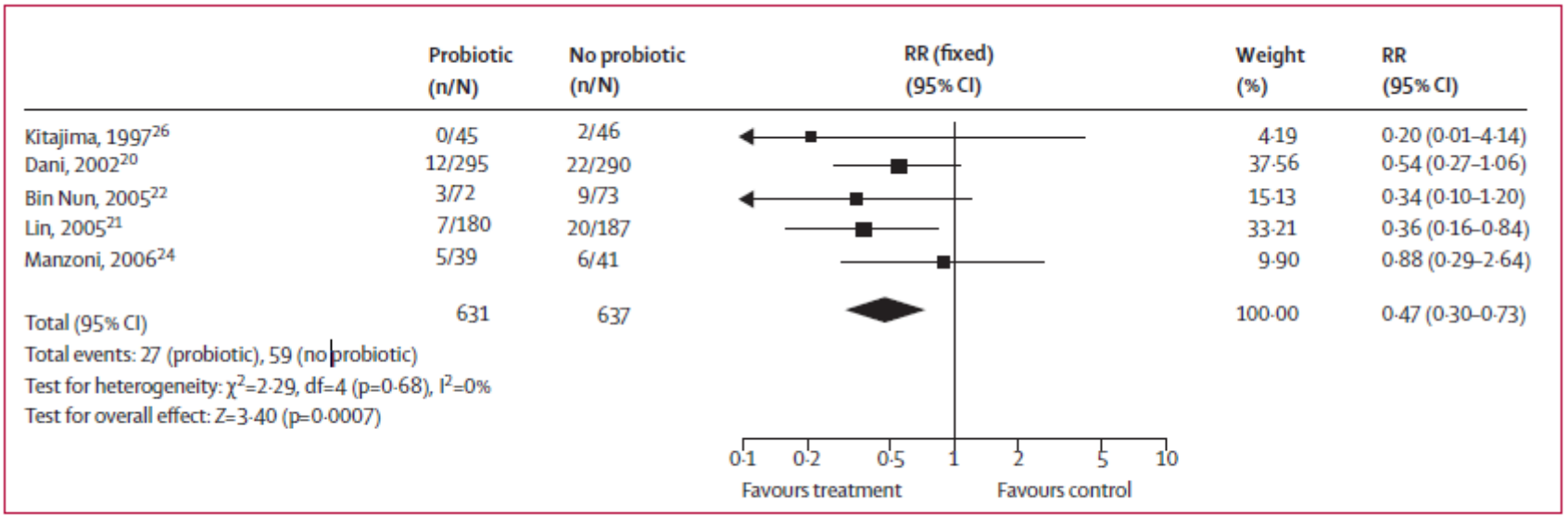

Figure 4: **Effect of probiotics on all-cause mortality**

Sepsis

Sepsis (Outcome 1.3):

Thirteen studies reported on sepsis (Millar 1993; Kitajima 1997; Costalos 2003; Dani 2002; Lin 2005; Lin 2008; Bin-Nun 2005; Manzoni 2006; Manzoni 2009; Rougé 2009; Samanta 2009; Sari 2010; Stratiki 2007). There was no significant difference among both groups in the rate of culture proven sepsis [typical RR 0.90 (95% CI 0.76, 1.07).

Sepsis

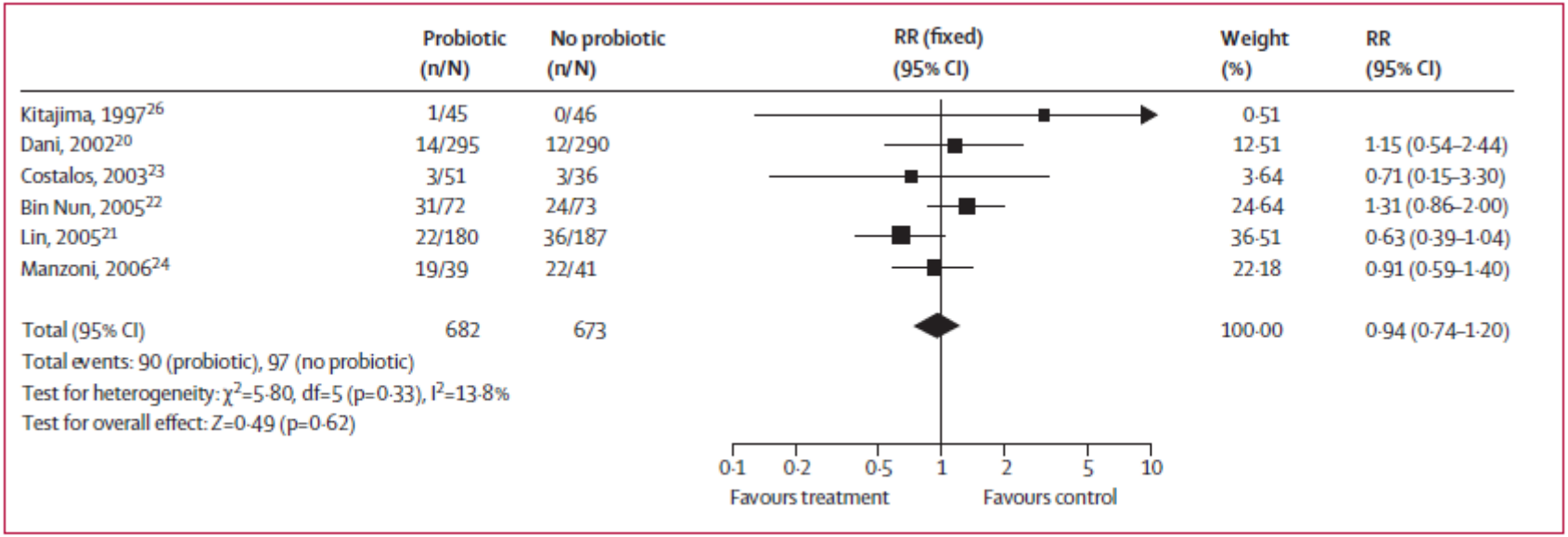

Figure 3: **Effect of probiotics on blood-culture-positive sepsis**

Clinical Bottom Line

- Probiotics do work in terms of preventing moderate to severe NEC and all cause mortality in low birth weight neonates.
- However, first line probiotic formulation, duration of therapy, cost effectiveness is still in question.
- Probiotics DOES NOT prevent neonatal sepsis.
- Safe to use if cost is not a concern.

Conversation with other children's hospitals in Canada

- Currently, Sick Kids, CHEO, Alberta Children's Hospital, and BC Children's Hosptial do not have formal protocol for probiotic use in NICU patients
- Provide probiotics as non-formulary item
- HSC does not initiate probiotics therapy for any of their NICU patients.
- Probiotics are continued if infants were already on it
- Alberta Children's Hospital is currently doing a review in regards to developing unit dose for probiotics so that it can be given to NICU patients

For Pharmacists

- Stay up to date with new clinical trials regarding first line options and treatment duration.

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