Management of Sepsis and Antibiotic Usage in the NICU

Guideline Responsibilities and Authorisation

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Target Audience	Neonatal staff
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Guideline Review History

Version	Updated by	Date Updated	Summary of Changes
3	David Bourchier	01/04/2020	Updated definitions
3.1	Jutta van den Boom	April 2022	Link to nystatin guideline
4	Miranda Bailey-Wild	Dec 2022	Document Name change to reflect and incorporate new screening and management strategies Introduction of LOS assessment guide

1 Overview

1.1 Purpose

To assist with evidence-based best practice in suspected neonatal sepsis. (use in conjunction with Early Onset Neonatal Infection Prevention (including GBS and PROM)) and Prevention of neonatal sepsis bundle.

Primary Aims include:

- To identify infection/sepsis early
- To reduce the time for commencement of antibiotics
- To reduce the use of unwarranted antibiotics

1.2 Scope

Nurses, Nurse Practitioner, Clinical Nurse Specialist, Registrar, Consultant.

1.3 Patient / client group

Neonates

1.4 Definitions

CBC	Complete blood count
CNS	Clinical Nurse Specialist
Confirmed Sepsis	A neonate with suspected sepsis where an infection agent is isolated from a normally sterile site
CVAD	Central Vascular/Venous Access Device
EOS	Early onset sepsis, ≤ 48hours after birth
GBS	Group B Streptococcus
IPC	Infection Prevention and Control
LOS	Late onset sepsis, >48 hours after birth
NNP	Neonatal Nurse Practitioner
PROM	Prolonged rupture of membranes
RMO	Registrar
SMO	Senior medical Officer
Suspected Sepsis	Clinical and/or laboratory findings raise suspicion of sepsis
WCC	White Cell count

2 Clinical Management of Early Onset Sepsis (EOS)

2.1 Risk factors

- Antenatal Risk Factors, including
  - Previous baby with GBS disease
  - GBS found in urine at any time during pregnancy
  - Incidental finding of positive GBS on vaginal swab at 35 – 37 weeks (screening not recommended)
  - Incidental finding of positive GBS on vaginal swab at any time of pregnancy (if not followed up by a negative repeat swab done specifically to detect GBS between 35-37 weeks' gestation)
- Intrapartum Risk Factors Refer to Pyrexia in Labour - Intrapartum Fever Ref 6354 / Maternity Early Warning System (MEWS) Ref 6387
  - Pre-term
  - Prolonged rupture of membranes >18 hours
  - Maternal temperature instability
  - Assessment and diagnosis of chorioamnionitis in collaboration with on call obstetric team

2.2 Clinical features concerning for EOS

- Temperature <36.5 or >37.5
- Pale, mottled appearance
- Lethargy or significant irritability
- Respiratory distress beyond 4 hours after birth
- Tachypnoea and/or apnoea
- Tachycardia, bradycardia or both (alternating tachycardia & bradycardia is a concerning sign)
- increased capillary refill time
- Hypoglycaemia or hyperglycaemia
- Increased lactate

2.3 Investigation

All babies who present with clinical features concerning for sepsis, especially in the context of the above risk factors should have the following investigations:

- FBC, CRP, blood culture, gas, consider coagulation studies
- Consider CXR if respiratory signs present
- Consider LP if concerns for meningitis

2.4 Management of EOS, (0 - ≤48h)

1. **First line Antibiotics**

- **Amoxicillin** (Amoxicillin for neonates Ref 0569) and **gentamicin** (Gentamicin for neonates Ref 2923)
  - For the initial dose: Amoxicillin is to be administered first, followed by a rapid flush, followed by gentamicin
  - Both antibiotics should be completed within 2h of suspicion of sepsis.
  - Antibiotic administration takes priority over other non-urgent medications e.g. caffeine citrate

>95% of WWH isolates were sensitive to this combination in the past 20 years

2. **Second line Antibiotics / additional considerations**

- Substitute **Cefotaxime** (Cefotaxime for neonates Ref 0601) for gentamicin if evidence of significant asphyxia, renal impairment, meningitis or planned indomethacin use.
- Consider **Aciclovir** (Aciclovir IV for neonates Ref 0550) if indicated by maternal history, concern for meningitis or suspicious skin lesions present
- Consider antifungal prophylaxis (Nystatin) as per Nystatin oral liquid for neonates Ref 6443 (infants <30/40, more than 36h antibiotic therapy)

3. **Review at 36h:**

a. Stop antibiotic therapy if blood culture negative and **no** ongoing clinical concerns

b. if blood culture positive, baby requires

- ongoing antibiotic treatment
- addition of antifungal prophylaxis (Nystatin oral liquid for neonates Ref 6443) if not already commenced
- repeat blood culture, consider LP (depending on isolated organism)
- Consider CVAD if subsequent culture negative and prolonged course prescribed

3 Clinical Management of Late Onset Sepsis (LOS)

3.1 Risk factors

- Preterm
- Prolonged ventilation
- Indwelling CVAD
- Prolonged NICU admission
- Systemic corticosteroid treatment

3.2 Assessment

Sepsis should be suspected in babies with any of the following

- Unwell appearance (could be pale or mottled)
- Quiet baby that does not respond to handling
- Reduced peripheral perfusion: increased capillary refill time, decreased peripheral temperature
- Unstable temperature
- Irritable, unsettled baby
- Tachycardia, bradycardia or both (alternating tachycardia & bradycardia is a concerning sign)
- Tachypnoea and/or apnoea
- Desaturations
- Hypoglycaemia or hyperglycaemia
- Parental or nursing concerns
- Feed intolerance

Consider Use of LOS guide (Appendix A)

3.3 Diagnosis and Management

3.3.1 Investigation

- Insert peripheral intravenous cannula and take samples for
  - Blood culture
  - CBC and check WCC, toxic ratio, platelet count (if not already done)
  - Electrolytes and CRP (if not already done)
  - Gas – check BSL and lactate (hypoglycaemia <2.6mmol/L or hyperglycaemia >8mmol/L, lactate >3)
- Consider sterile urine for culture (clean catch or catheter)
- LP if appropriate
- CXR if appropriate

3.3.2 Management

- Increase respiratory and cardiovascular support as necessary

1. **First line Antibiotics**

   - **Amikacin** (Amikacin for neonates Ref 0562) and **Flucloxacillin** (Flucloxacillin for neonates Ref 2918)
     - For the initial dose: Amikacin is to be administered first, followed by a flush, followed by Flucloxacillin
     - Both antibiotics should be completed within 2h of suspicion of sepsis.
     - Antibiotic administration takes priority over other non-urgent medications e.g. caffeine citrate
     - Every effort should be made to obtain a blood culture. However, if this was unsuccessful on 3 repeated attempts, this should not preclude the rapid initiation of antibiotic therapy.

>95% of WWH isolates were sensitive to this combination in the past 20 years

2. **Second line Antibiotics / additional considerations**

   - Consider substituting amikacin with **vancomycin** (Vancomycin IV for neonates Ref 2076) if a coagulase negative staphylococcus infection is clinically not responding adequately to amikacin.
   - Suspected Meningitis – include **cefotaxime** (Cefotaxime for neonates Ref 0601) and /or **aciclovir** (Aciclovir IV for neonates Ref 0550) in the antibiotic regimen.
   - Suspected necrotizing enterocolitis - include **amoxicillin-clavulanic acid**. (Amoxicillin - Clavulanic Acid for neonates Ref 0582)

- Suspected invasive fungal infection add **IV fluconazole** (Fluconazole for neonates Ref 2919)
- Consider antifungal prophylaxis (Nystatin oral liquid for neonates Ref 6443) as per guideline (infant <30/40, more than 36h antibiotic therapy, long term parenteral nutrition)

3. **Suggested duration of therapy**
   - See flow diagram appendix
   - Adjust antibiotics according to sensitivities of isolated organism

3.4 Potential complications

a. Extravasation at infusion site

b. Allergic reaction to antibiotics

4 Evidence base

4.1 Summary of Evidence, Review and Recommendations

The recommended antibiotics provide effective antimicrobial cover for the common neonatal pathogens in the Waikato NICU. The current prevalent early pathogens are GBS, E Coli and H. Influenza. The current late pathogens are CONS, Staph aureus and a range of gram negative bacilli.

4.2 References

- American Academy of Pediatricians (AAP) – Red Book on line (2021)
- Sivanandan Setal, Choice and Duration of Antimicrobial Therapy for Neonatal Sepsis and Meningitis. Int. J. Paediatrician (2011), Article ID 712150
- Waikato NICU Database
- Beckett S. et al. development of a Novel Assessment Tool and Code Sepsis Checklist for Neonatal Late onset sepsis. Advances in Neonatal Care 2021;22(1):6-14
- NICE guidelines for Neonatal infection (NG195) -2021. https://www.nice.org.uk/guidance/ng195/resources/neonatal-infection-antibiotics-for-prevention-and-treatment-pdf-66142083827653
- Polin, Richard A., et al. "Management of neonates with suspected or proven early-onset bacterial sepsis." Pediatrics 129.5 (2012): 1006-1015.

4.3 Associated Te Whatu Ora Waikato Documents

- Early Onset Neonatal Infection Prevention (including GBS and PROM) (Ref. 4381)
- NICU Drug Guidelines:
  - Aciclovir IV for neonates (Ref. 0550)
  - Amikacin for neonates (Ref. 0562)
  - Amoxicillin for neonates (Ref. 0569)
  - Amoxicillin - Clavulanic Acid for neonates (Ref. 0582)
  - Cefotaxime for neonates (Ref. 0601)
  - Flucloxacillin for neonates (Ref. 2918)
  - Gentamicin for neonates (Ref. 2923)
  - Nystatin Oral Liquid for neonates (Ref. 6443)
  - Vancomycin IV for neonates (Ref. 2976)

Appendix A – LOS assessment guide

	Of concern	Monitor	Normal	Monitor	Of concern
VITAL SIGNS					
Temperature ©	<36.0 Or change in incubator support	36.0 - 36.4 Or change in incubator support	36.5 – 37.5	37.6 – 37.9 Or change in incubator support	≥38.0 Or change in incubator support
Heart rate (bpm)	<100 Or ↓from baseline, ↑Bradys	100 – 120 Or ↓from baseline	120 – 160 Or prior baseline	160 – 180 Or ↑ from baseline	>180 Or ↑ from baseline
Blood Pressure (mmHg)	Mean<GA Or below baseline	↓from baseline	Mean ≥ GA or prior baseline	↑ from baseline	>95th %ile
Capillary refill (seconds)	>4, skin cool, pale or mottled, ↓pulses	3 – 4	<3		Warm extremities, bounding pulses
Respiratory Rate (bpm)	<20 or ↓from baseline, ↑apnoea events, ↑Resp support	20 – 30 or ↓from baseline	30 – 60 Or prior baseline	60 – 80 Or ↑ from baseline	>80 Or ↑ from baseline
Oxygen Saturation (%)	<85 or or ↓from baseline, ↑FiO_2	85 – 90 or ↓from baseline	>90 or prior baseline		
CLINICAL					
Neurological	Change in behaviour (lethargy, ↓tone, ↓responsiveness, seizures)	↓activity	Normal activity	restless	Change in behaviour (periods without sleep, irritability, inconsolable, seizures)
Urine Output (ml/kg/h)	<1 or below baseline	1 – 2 or ↓from baseline	>2 Or prior baseline		>6
Feeding tolerance	Vomits, Bile staining	Small – mod spills Or ↑ from baseline	Tolerating feeds, no distension	Mild abdominal distension	Marked abdominal distension, visible loops, shiny, veiny
LAB VALUES					
WBC (x10^3/mm^3)	<5		<1wk: 5-34 1-4wk: 5-19.5 >4wk: 5-17.5		<1wk: >34 1-4wk: >19.5 >4w: >17.5
Neutrophil	<1	<2	Range as per lab	As lab	
Toxic ratio			< 0.2	0.2 – 0.3	>0.3
Platelets (x10^3/mm^3)	<50 or ↓from baseline	<100 or ↓from baseline	150 – 450 or prior baseline		
CRP (mg/dL)			<1	1-10	>10
Gas pH	<7.20	7.20 – 7.3	7.3 – 7.45	7.45 – 7.5	>7.5
pCO_2 (kPa)	↓ from baseline	↓from baseline	4.5 – 6.0 or prior baseline	↑ from baseline	↑ from baseline
BE (mmol/L)	<-10	-10 to -4 or ↓from baseline	-4 to +4 or prior baseline		
Glucose (mmol/L)	<2.6		2.6 – 8.0 or prior baseline	8.0 – 10 Or ↑ from baseline	>10
Lactate			<2	2-4	>4

Appendix B – Flowchart for assessment and management of LOS