LOCAL OPERATING PROCEDURE

NEONATAL SERVICES DIVISION

Approved by Quality & Patient Safety Committee
May 2019

ANTIMICROBIAL GUIDELINES – NEWBORN CARE CENTRE

This Local Operating Procedure is developed to guide safe clinical practice in Newborn Care Centre (NCC) at The Royal Hospital for Women. Individual patient circumstances may mean that practice diverges from this Local Operating Procedure.
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1. AIM

- To rationalise antimicrobial use aiming to maximise efficacy while minimising adverse effects, including antimicrobial resistance.

2. PATIENT

- Newborns

3. STAFF

- Medical, nursing and pharmacy staff

4. EQUIPMENT

- Not applicable

5. CLINICAL PRACTICE

- Any infant with a suspected infection or at high risk of infection should be promptly assessed by the clinical team.
- The following table provides the preferred empirical antimicrobial agent based on the clinical indication.
- "Early-onset" sepsis is defined as sepsis occurring within the first 72 hours of life. "Late-onset" sepsis is defined as sepsis occurring after the first 72 hours of life.

Indication	Antimicrobial Treatment	Comments
Early-onset sepsis	Benzylpenicillin PLUS Gentamicin[1,2] STOP ANTIBIOTICS AFTER 24 HOURS IF BLOOD CULTURES ARE NEGATIVE and sepsis is not clinically suspected.[3]	In the setting of true bacteraemia, blood cultures will mostly become positive within 36 hours of collection. As the antibiotic is still maintaining good plasma concentrations for another 12 hours after 24 hour administration, antibiotics can be recommenced without any gap if the blood culture becomes positive.
Late-onset sepsis	Flucloxacillin or Vancomycin PLUS Gentamicin[3-7] STOP ANTIBIOTICS AFTER 24 HOURS IF BLOOD CULTURES ARE NEGATIVE and sepsis is not clinically suspected (infant is well ± CRP is low < 10). In case of positive blood culture, all efforts should be made to remove the existing central line as soon as possible.	RHW NCC Antibiogram data 2016 showed Vancomycin sensitivity to CoNS & Staph aureus is 100%. Flucloxacillin sensitivity to CoNS is 26%.[3] If there is suspicion or confirmation of multi-resistant organism, discuss with Neonatologist and ID team on Meropenem or alternative agent. Piperacillin/Tazobactam (Tazocin) can be used as monotherapy provided no CoNS is present in blood cultures. RHW NCC data suggests resistance of CoNS to Tazocin.

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Indication	Antimicrobial Treatment	Comments
Necrotising Enterocolitis	Vancomycin PLUS Tazocin OR Vancomycin PLUS Gentamicin PLUS Metronidazole DISCONTINUE VANCOMYCIN ONCE CULTURES NEGATIVE FOR CONS	Tazocin can be used as monotherapy once blood cultures return negative for CoNS.
Meningitis	Benzylpenicillin/Ampicillin PLUS Cefotaxime	If Herpes Simplex encephalitis is suspected add Aciclovir.
Urinary Tract Infection / Pyelonephritis	Ampicillin PLUS Gentamicin	If there is suspicion or confirmation of multi-resistant organisms discuss with neonatologist on duty, the ID team and consider Meropenem or alternative agent.
Skin and soft tissue infections	Flucloxacillin	If MRSA is suspected, ADD Vancomycin while awaiting culture results. If infection is severe consider adding Gentamicin.
Omphalitis	Flucloxacillin +/- Gentamicin	If MRSA is suspected ADD Vancomycin while awaiting culture results. If infection is severe consider adding Gentamicin.
Balanitis	Mupirocin 2% ointment or cream topically	
Cytomegalovirus	Ganciclovir[8]	Commence treatment only after discussion with Neonatologist on duty and SCH Infectious Disease team. Inform Pharmacy ASAP.
Candidiasis (systemic)	Fluconazole	If previous known Candida infection or patient has received Fluconazole previously, discuss with SCH Infectious Diseases.
Pertussis (prophylaxis or treatment)	Azithromycin	Ensure contact tracing occurs and alert Infection Control and Public Health.

6. DOCUMENTATION

- eMR
- Medication chart

7. EDUCATIONAL NOTES

- The early and appropriate initiation of antimicrobial agents in high-risk neonates before the result of blood culture susceptibility is defined as "empirical antibiotic therapy.[6] The ratio of non-infected to blood-culture-positive neonates treated with antibiotics can be between 15:1 and 28:1.[9] However, initial clinical manifestations of sepsis can be non-specific and a delay in in the initiation of treatment can increase morbidity and mortality.

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- Early-onset sepsis: Prospective randomised controlled trials (RCTs) on the appropriate choice of antimicrobial therapy in the neonate with suspected sepsis are limited. Cochrane meta-analysis failed to show one regime was superior to other.[10]
- Late-onset sepsis: In the developed countries, where CoNS is the predominant nosocomial pathogen and where resistance of these isolates to penicillin, semisynthetic penicillin, and gentamicin are common, experts recommend the use of vancomycin as empirical therapy.[11] However, to reduce the growing emergence of resistant strains due to injudicious use of vancomycin, Karlowicz et al. studied the impact of changing empiric antibiotic therapy for LOS from vancomycin and cefotaxime to oxacillin and gentamicin. There was no impact on the frequency of fulminant sepsis due to CoNS even though 85% of CoNS isolates were resistant to either oxacillin or gentamicin. Most cases of fulminant LOS were caused by Gram-negative organisms rather than CoNS.[12] Similarly, Lawrence et al compared the duration of CoNS sepsis and mortality before and after implementation of a policy of selective vancomycin use. Late-onset sepsis was treated empirically with vancomycin and gentamicin during period 1, and cloxacillin and gentamicin during period 2. Duration of sepsis was similar between periods. In their retrospective study, restricting vancomycin for confirmed cases of CoNS sepsis resistant to oxacillin appeared to be effective and safe, and significantly reduced vancomycin use in the NICU.[13]
- C-reactive protein (CRP): CRP is an excellent marker for established neonatal bacterial infections. However, it is not useful for early diagnosis because levels are elevated only in 35% to 65% of neonates at the onset of illness.[14] Serial CRP measurements can be used as a guide to the duration of antibiotic therapy. Two consecutive CRP levels <10 mg/L 24 hours apart, 8–48 hours after presentation, have a negative predictive value for sepsis of 99%.[15] CRP levels of <10 mg/L determined 24 hours after beginning antibiotic treatment correctly identified 120 of 121 infants as not needing further antibiotics.[16]
- Necrotising enterocolitis: Cochrane meta-analysis found insufficient evidence to recommend a particular antibiotic regimen for the treatment of NEC.[17] Piperacillin-tazobactam has been found to be safe and well tolerated as mono-therapy in nosocomial infections in preterm infants, particularly NEC in a non-comparative study.[18]
- Any neonate suspected of sepsis requires urgent empiric antimicrobial therapy. Premature infants are more vulnerable to sepsis. All infants with suspected sepsis require discussion with fellow/neonatologist on duty.
- Obtain blood cultures (and other clinical specimens e.g. urine, CSF as appropriate). Do not delay antibiotic administration if unable to obtain specimens promptly.
- Infants with bacteraemia or complex infections may also be discussed with SCH infectious diseases team. Choice of antimicrobial therapy depends on maternal factors, age at onset of infection, prematurity, focus of infection, any surgery undertaken and the presence or recent usage of central venous lines.
- For drug dosing refer to Australasian neonatal medicines formulary (ANMF) on RHW website.
- All neonates receiving antibiotics should be placed on oral nystatin 50,000 units PO every 6 hours as prophylaxis against systemic candidiasis.
- Antibiotic recommendations in this guideline is the consensus opinion derived from the meeting held on 28th November 2018 attended by Neonatologists, Paediatric Infectious Diseases consultants and SEALS Microbiology consultant. The aim of the meeting was to prescribe antibiotics safely and wisely as part of antimicrobial stewardship program.[19-21]
    - RHW NCC antibiogram data for 2016 was presented in the meeting: Flucloxacillin sensitivity to CONS was 26% and vancomycin sensitivity to CoNS was 100%.
    - It was decided that antibiotics can be ceased at 24 hours in suspected EOS & LOS where the blood culture is negative (ie: a culture negative sepsis screen) providing the infant is well (and the CRP is low <10 in LOS).

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- The reason for 24 hours cessation is the short time to positivity of blood cultures providing a good volume of blood is taken (1ml) and the antibiotic is still maintaining good plasma concentrations for another 12 hours[20]. If 36 hour culture returns positive, antibiotic can be recommenced without any gap.
- By new cessation guidelines of antibiotics at 24 hours, it is estimated that vancomycin usage will be reduced by 50%. Current NICUS QI data shows RHW has high usage of vancomycin among the NSW and ACT NICUs. By stopping vancomycin at 24 hours, usage of vancomycin will come down by 50%.
- Empiric antibiotics for LOS – either flucloxacillin & gentamicin or vancomycin & gentamicin can be used depending on whether the infant is considered high or low risk (gestation/severity of symptoms/signs).
- Once a blood culture is positive for CoNS in the context of definite/probable clinical sepsis, every effort should be made to remove the central line as soon as possible, and consideration given for stopping flucloxacillin and starting vancomycin while waiting for sensitivity report.

8. RISK RATING

- Low

9. NATIONAL STANDARD

- Clinical Governance
- Preventing and Controlling Healthcare Associated Infections
- Medication Safety
- Comprehensive Care
- Recognising and responding to acute deterioration

10. ABBREVIATIONS AND DEFINITIONS OF TERMS

NCC	Newborn Care Centre	LOS	Late-Onset Sepsis
RHW	Royal Hospital for Women	NICU	Neonatal Intensive Care Unit
CoNS	Coagulase Negative Staphylococcus	NEC	Necrotising Enterocolitis
CRP	C-Reactive Protein	CSF	Cerebrospinal Fluid
MRSA	Methicillin-Resistant Staphylococcus Aureus	EOS	Early-Onset Sepsis
SCH	Sydney Children's Hospital	QI	Quality Improvement
RCT	Randomised Controlled Trial		

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12. AUTHORS

Primary	2010	S Bolisetty (lead clinician)
Major Revision	April 2019	J Smyth (neonatologist), S Bolisetty (lead clinician), B McMullan (paediatric infectious diseases specialist), M Lahra (SEALS microbiologist)

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