Local Guideline and Procedure

John Hunter Children's Hospital
CHILDREN, YOUNG PEOPLE AND FAMILIES

NSW GOVERNMENT Health
Hunter New England Local Health District

Late Onset Sepsis in the Neonate

Sites where Local Guideline and Procedure applies	Neonatal Intensive Care Unit and Special Care Unit JHCH
This Local Guideline and Procedure applies to:	
1. Neonates – less than 29 days	Yes
Target audience	Clinicians caring for infants in NICU and SCN
Description	Information and pathway for investigations and management of late onset sepsis in the neonate

Hyperlink to Procedure

Keywords	Antibiotics, blood stream infection, infection, JHCH, late onset sepsis (LOS), meningitis, neonatal, NICU
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Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- NSW Health Policy Directive 2014_036 Clinical Procedure Safety http://www0.health.nsw.gov.au/policies/pd/2014/pdf/PD2014_036.pdf

Prerequisites (if required)	N/A
Local Guideline and Procedure note	This document reflects what is currently regarded as safe and appropriate practice. The guideline section does not replace the need for the application of clinical judgment in respect to each individual patient but the procedure/s **require mandatory compliance**. If staff believe that the procedure/s should not apply in a particular clinical situation they must seek advice from their unit manager/delegate and document the variance in the patients' health record.
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RISK STATEMENT

This local guideline has been developed to provide guidance to clinical staff in NICU to assist in assessment and management of neonates with suspected late onset sepsis (LOS). It ensures that the risks of harm to the infant whilst being assessed and managed for LOS are identified and managed.

Any unplanned event resulting in, or with the potential for injury, damage or other loss to infants/staff/family as a result of this management must be reported through the Incident Information management System and managed in accordance with the Ministry of Health Policy Directive: Incident management PD2007_061.

This would include unintended injury that results in disability, death or prolonged hospital stay.
Risk Category: *Clinical Care & Patient Safety*

GLOSSARY

Acronym or Term	Definition
CONS	Coagulase negative Staphylococci
CRP	C-Reactive Protein-inflammatory marker
CSF	Cerebrospinal fluid
EUC	Electrolytes/Urea & Creatinine
FBC	Full blood count
GBS	Group B Streptococcus (Streptococcus agalactiae)
IV/CVL	Intravenous/central venous line
LOS	Late onset sepsis
PCR	Polymerase chain reaction
TPN	Total parenteral nutrition

GUIDELINE

This Guideline does not replace the need for the application of clinical judgment in respect to each individual patient.

Late Onset Sepsis in the Neonate

- One Page Summary and Checklist(Ctrl+Click on **Coloured** words to jump to that section)

Background

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Sepsis is the leading cause of morbidity and mortality in the newborn period. Sepsis is defined as a syndrome characterised by systemic inflammatory response (SIRS) to an infection, immune dysregulation, micro-circulatory derangement and end organ dysfunction. An episode of sepsis that develops after 72 hours of age is usually called Late

Onset Sepsis (LOS).[1] However, it is possible that the organisms vertically transmitted from mother to baby can produce infection after 3 days of birth. The source of infection in LOS is either nosocomial (hospital-acquired) or community-acquired due to the horizontal transmission of pathogens from the environment or the hands of the caregiver.

The risk of LOS is inversely associated with the gestational age and birth weight of infants. Apart from prematurity, other well- recognised risk factors for LOS include use of invasive interventions such as mechanical ventilation, intravascular catheterisation, longer use of parenteral nutrition (PN), prolonged hospitalisation and surgical interventions and inappropriate use of broad spectrum antibiotics in nurseries. [1, 2]

Sepsis can originate from any organ, but often the primary site of infection is not known.

The medical literature quotes LOS rate varying from 0.6% to 27% depending upon the gestational age of the included infants. [1, 2, 3, 4] The Incidence of LOS in JHCH (John Hunter Children's Hospital) neonatal unit is about 3% of all admissions and 22% in extremely preterm neonates (GA < 28 weeks at birth). In this nursery approximately 60% of episodes of LOS are caused by coagulase negative staphylococci (CONS), 5% by *Staphylococcus aureus*, 7% by *Streptococcus agalactiae* (GBS) and 15-17% by other bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Enterobacter cloacae*. Rarely, *Candida* species and viruses such as *Herpes* and *Enteroviruses* may also cause late onset infections in neonates.[4] Approximately 96% of the CONS isolated in JHCH nursery between 2012-2015 were resistant to B-lactam antibiotics.[4]

Pathophysiology

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Sepsis exists on a continuum of severity ranging from infection and bacteremia to sepsis and septic shock, which can lead to multiple organ dysfunction syndrome (MODS) and death.

An inflammatory stimulus (eg, a bacterial toxin) triggers production of pro-inflammatory mediators such as, tumour necrosis factor (TNF), interleukins (IL-1, 2), leukotrienes, lipoxygenase, histamine, bradykinin and serotonin. These cytokines cause neutrophil–endothelial cell adhesion, activate the clotting mechanism, and generate micro thrombi.

Initially, arteries and arterioles dilate, peripheral arterial resistance falls and cardiac output typically increases. This stage has been referred to as warm shock. Later, cardiac output may decrease, blood pressure falls (with or without an increase in peripheral resistance), and typical features of shock appear. Even in the stage of increased cardiac output, vasoactive mediators cause blood flow to bypass capillary exchange vessels (a distributive defect). Poor capillary flow from this shunting along with capillary obstruction by micro thrombi decreases delivery of O2 and impairs removal of CO2 and waste products.

Decreased perfusion secondary to cardio-vascular impairment causes dysfunction and sometimes failure of one or more organs, including the kidneys, lungs, liver, brain, and heart. Coagulopathy may develop because of intravascular coagulation with consumption of major clotting factors and excessive fibrinolysis.

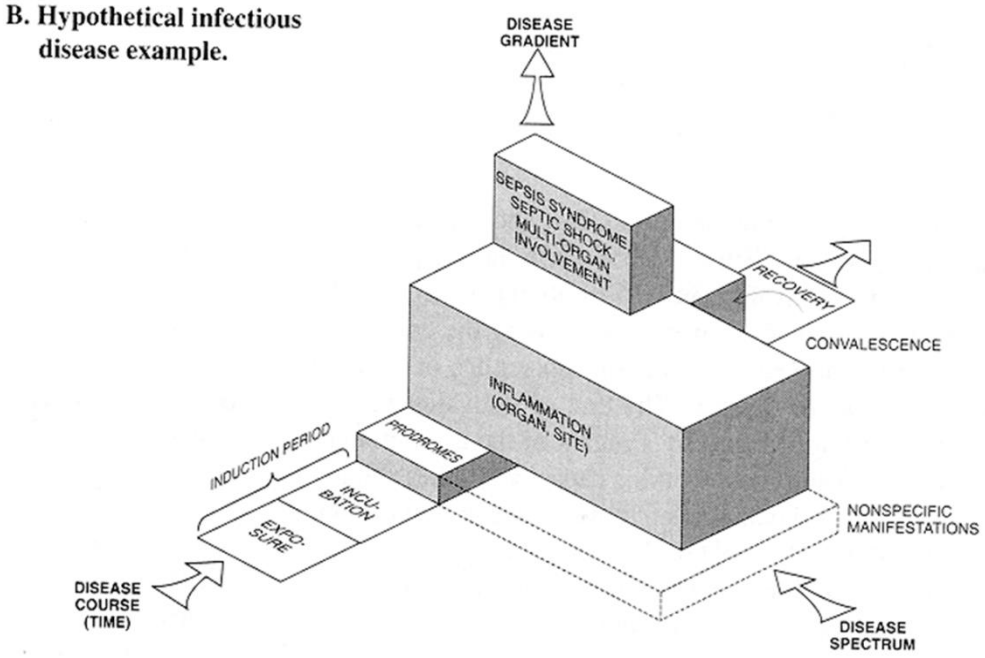

Fig 1 Pathway of sepsis

Clinical presentation

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The clinical presentation of infection in the newborn is often non-specific and the neonate may experience an acute deterioration**.**

SIRS	Tachypnoea, Tachycardia Temperature abnormality Leucocytosis, Leukopenia Increased Immature/ Total neutrophils ratio
Sepsis	SIRS + proven or suspected infection
Severe Sepsis	Lethargy, reduced activity ,hypotonia Irritability, bulging fontanelle Apneoa, seizures Poor feeding, vomiting, feeding intolerance Pale, off coloured, mottled skin Prolonged capillary refill time Reduced urine output Elevated lactate levels (>2meq/L) Respiratory distress, need for respiratory support Thrombocytopenia
Septic Shock	Systemic hypotension Metabolic acidosis (Base excess >5meq/L) Blood lactate levels >4meq/L Hypotension resistant to fluid boluses Need for ionotropic support
Multi-organ dysfunction	Disseminated intravascular coagulation Renal/ hepatic/neurological impairment Hypoxia, hypercarbia, need for mechanical ventilation Cardiac dysfunction

Table 2 Clinical features along the sepsis pathway

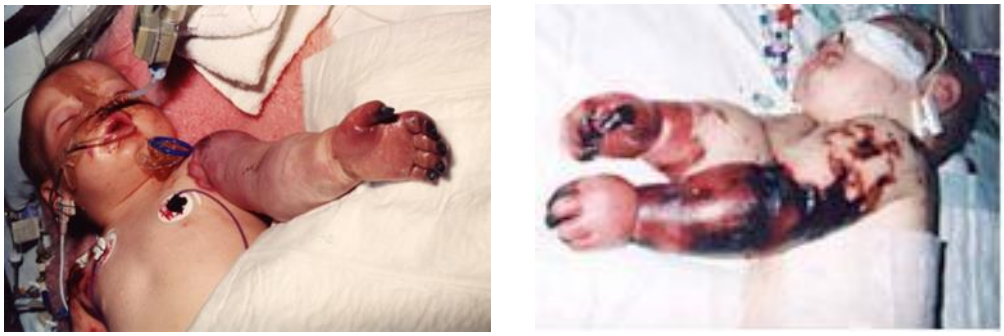

Fig 2: Infant with sepsis and DIC

Investigations

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Investigations should be guided by infant's clinical condition, likely diagnosis and causative organism.

Diagnosis of sepsis

Full blood count (FBC)
Total and differential white cell count
C- reactive protein (CRP)
Blood culture
Chest/ abdominal X-ray (if indicated)
Sterile specimen of urine for microscopy and culture
Culture of specific sites as indicated, e.g. trachea, skin, umbilicus and stool etc.
Swabs for viral infections e.g. lesions, rash, throat, rectum etc.
CSF microscopy and culture and PCR for viruses
Review of maternal vaginal swab and placental histopathology results

Additional Investigation

Blood gas
Electrolytes, urea and creatinine (EUC)
Liver function tests
Coagulation profile
Radionuclide bones scan for possible osteomyelitis
MRI brain to rule out complications of meningitis

FBC and CRP are most commonly used markers to screen for neonatal sepsis. However, the studies evaluating their usefulness in LOS yield variable results. [6, 7, 8, 9]
As shown in the table below, the specificity (probability to correctly exclude negative cases) and negative predictive value of these markers are reasonable (likelihood of test negative subjects not having an infection) but individually or in combination, their sensitivity (probability to correctly pick up positive cases) and positive predictive value (likelihood of test positive subjects of having an infection) at the time of clinical suspicion of

sepsis are low to moderate. Serial values of inflammatory markers taken 24– 48 h after the onset of symptoms have an improved sensitivity and specificity.8 Two consecutive CRP levels <10 mg/L 24 hours apart, have a negative predictive value for sepsis of 99%.

Parameter	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
WBC > 20,000	20-40%	80-90%	15-50%	80-90%
WBC<5000	30-40%	80-90%	30-60%	80-90%
IT ratio >0.2	60-70%	80-90%	40-60%	80-90%
CRP >10mg/L	60-80%	90-100%	65-100%	75-90%
IT ratio + CRP	22-60%	75-98%	55-75%	65-95%
CRP + WBC	25-75%	50-90%	10-50%	75-95%
WBC + IT ratio	60-65%	75-85%	30-40%	90-95%

Table 2 Utility of full blood count and CRP in late onset neonatal sepsis

NSW health's **Sepsis Kills** program recommends consideration of Herpes infection in infants who are very sick, have vesicular rash, hepatosplenomegaly, interstitial pneumonitis and exposure to maternal genital herpetic lesions.[10] An index of suspicion should also be maintained for possible fungal infection in sick infants, who have received broad spectrum antibiotics, TPN and have had indwelling tubes and catheters.[18]

Management

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Sepsis can rapidly kill neonates. Quick, stepwise execution of therapeutic interventions aimed to restore normal physiology and timely commencement of antimicrobial therapy can be lifesaving.

Supportive care

Temperature, cardio-respiratory status, clinical course, neurology, and blood sugar levels , acid-base status, renal function, liver function and coagulation profile should be closely monitored in all infants with sepsis. To manage shock and organ dysfunction, fluid resuscitation should be initiated promptly and guided by the clinical picture. Infants should be closely monitored and regularly re-assessed for improvement during and after commencement of an intervention. Inotropes should be used in accordance with the hypotension guideline to quickly restore systemic arterial blood pressure, cardiac performance and perfusion. Inotropes should be used in accordance with the NICU hypotension guideline 'Hypotension and poor circulation in neonates' JHCH_NICU_13.04 to quickly restore systemic mean arterial pressure, cardiac performance and perfusion. Non-invasive or invasive ventilation may be required to optimize blood gas physiology. Blood and blood products should be used as per unit's guideline to manage haematological issues such as anaemia, thrombocytopenia and deranged coagulation profile in very sick infants

Commencement of Antimicrobial Therapy

Antibiotics should be considered in any baby with signs of sepsis, particularly in the presence of risk factors. However, most newborn babies who are given antibiotics for LOS do not have any infection (suspected sepsis). Risk factors for infection may be an indication for investigation but are not in themselves an indication for starting antibiotics especially if the baby is clinically well.
If there are any doubts about commencement of antibiotics, a more senior member of staff should be consulted. Sepsis kills program recommends administration of antibiotics **within one hour** of recognition of suspected sepsis.[10] However, sometimes this can be challenging as the early clinical features in neonates can be subtle and non-specific.

Choice of antimicrobial therapy

The microbiological colonisation and sensitivity pattern (epidemiology) of the nursery should be known, and previous colonisation of the infant should be taken into account. Empiric antibiotic therapy must be targeted to the sensitivities of the likely causative organism.
Subsequently, the antimicrobial therapy should be modified as per the culture results. In situations where risk of toxicity is considered higher, Gentamicin can be replaced by Timentin.

Infant's GA < 29 weeks at birth	Vancomycin + Gentamicin
Infant's GA >29 weeks at birth	Flucloxacillin + Gentamicin
Sepsis of suspected gastrointestinal origin	Ampicillin + Gentamicin + Metronidazole
Suspected Meningitis	Add Cefotaxime
Suspected Herpes/ Varicella infection	Acyclovir
Suspected fungal sepsis	Fluconazole

Table 3. A guide to empiric antimicrobial therapy

Source control
If intravenous catheter is likely to be the source of infection, consideration should be given to removal of the catheter and the catheter tip should be sent for culture. Surgical drainage and debridement may be required for skin and deep infections

Duration of Antimicrobial Therapy [1, 10, 11, 12, 13, 14, 15,16,17,18]

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Definite sepsis
The typical course of antibiotics for a definite episode of sepsis would be directed by the severity, site of infection and causative organism. The following table provides a guide to the duration of antimicrobials for confirmed infection. The antimicrobial course could be modified in consultation with a neonatologist/microbiologist in atypical situations.

Infection Type	Duration of Therapy
Culture positive blood stream infection without meningitis/ deep seated infections	CoNS: 5-7 days Staphylococcus aureus :14 days (consider possibility of bone and joint infections) Other gram positive organisms: 7-10 days Gram negative coliforms: 7-10 days

	Pseudomonas aeruginosa :14 days
Pneumonia	7 days [Some complications (abscess, empyema) and organisms may need longer course. D/W neonatologist/microbiologist]
Uncomplicated Meningitis	Gram Positive organism = 14 days Gram Negative organism = 3-4 weeks (course duration for complications such as intracranial collections and ventriculitis should be discussed with a microbiologist)
Urinary tract infections	IV until clinical improvement Complete total 14 days with oral if feasible
Skin and mucous membrane infections	7-10 days
Bone and Joint infections	4-6 weeks total IV/CVL until clinical response, then oral if feasible
Herpes sepsis	Skin and Mucus membranes = 14 days Systemic infection = 21 days
Fungal sepsis	3 weeks after microbiologic clearance

Table 4. A guide to duration of antimicrobials in various situations.

Suspected sepsis

The recommendations for treatment of infants with suspected sepsis but who have negative cultures are not based on strong evidence. The standard practice is to discontinue antibiotics as soon as blood cultures are confirmed negative (48–72 hours) and there are no clinical or hematologic signs of infection.

Presumed sepsis

If sepsis is strongly suspected clinically but the cultures are negative; antimicrobials may be continued for 5-7 days.

Vascular Access for administration of antibiotics

Central venous access should be considered for infants who need antimicrobials for longer duration (>5-7 days).

Repeat lumbar puncture (LP)

Repeat lumbar puncture to document CSF sterilization and improvement of CSF parameters is not indicated routinely.1 However; it should be done in all patients who have not responded clinically after 48 hours of appropriate antimicrobial therapy. A consideration should be given to repeat LP in neonates with meningitis due to Gram-negative bacilli.1

Long term follow up

Infants with meningitis/encephalitis should receive long term neurodevelopmental follow up.

Prevention of LOS

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Meticulous hand hygiene and other standard infection control precautions are the most important methods of preventing the spread of nosocomial infections.[19]
These precautions include bare below elbow clothing standard, maintaining asepsis during all invasive procedures and intravenous medication preparation, environmental cleaning and disinfection and disinfection of all clinical equipment and infant beds.
Establishing early enteral feedings, promoting use of breast milk, immune supportive oral care (ISOC) see CPG 'Immune Supportive Oral Care (ISOC) for Neonates in NICU/SCN' JHCH_NICU_03.08, minimising invasive procedures may also be protective against infection.[19] Administration of topical Nystatin for infants < 1kg, infants receiving PN, and antibiotics may reduce the risk of fungal infections.[19]

Appendix: Pathway for suspected LOS

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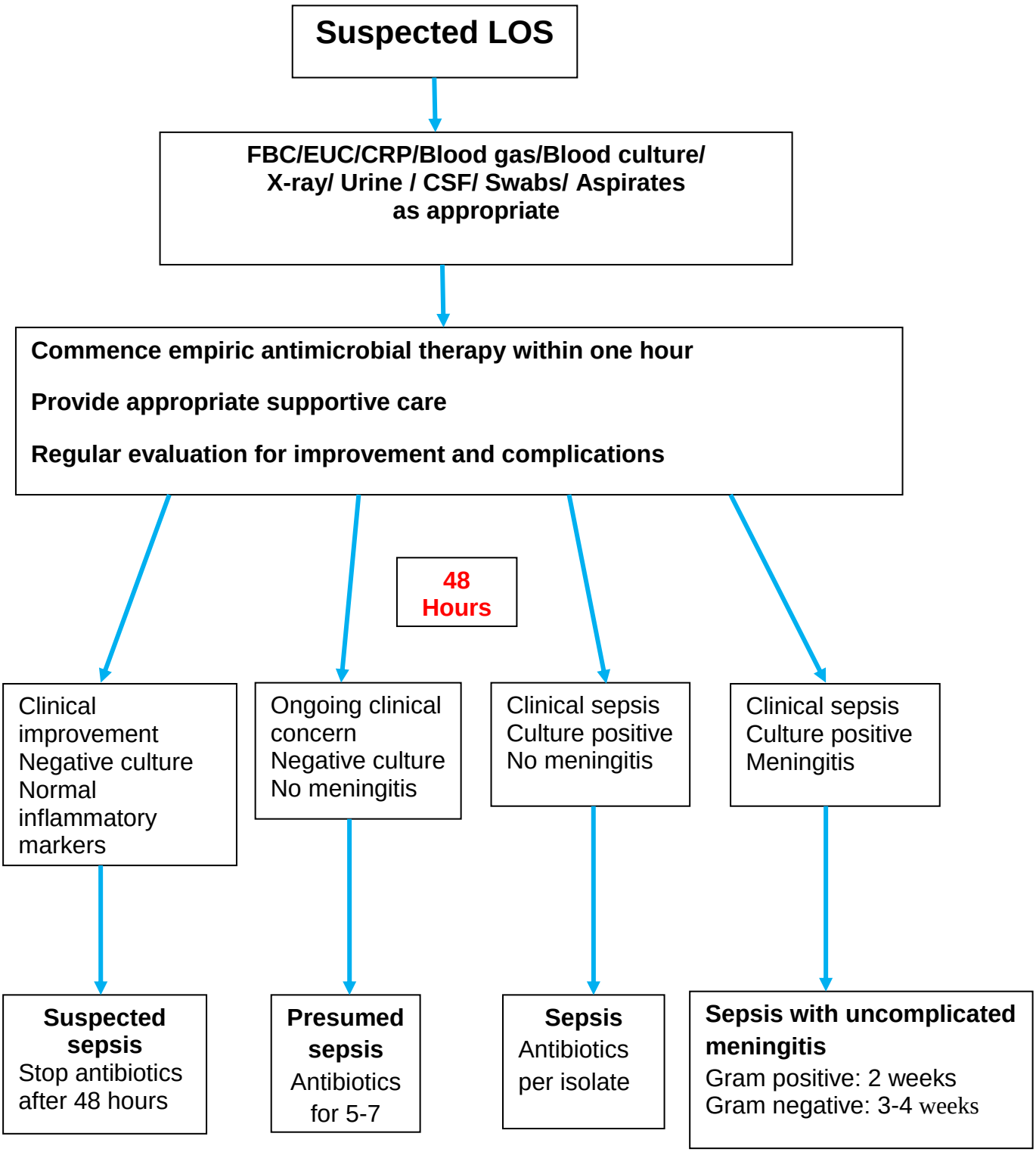

References

1. Sivanandan S, Soraisham A, Swarnam K. Choice and duration of antimicrobial therapy for neonatal sepsis and meningitis Int J Pediatr. 2011; 2011:712150.

2. Chiu C, Michelow I, Cronin J, et al. Effectiveness of a Guideline to Reduce Vancomycin Use in the Neonatal Intensive Care Unit. Pediatr Infect Dis J 2011; 30: 273–278.

3. Dong Y, Speer C. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed 2015; 100:257–263.

4. Infection prevention service HNELHD. Healthcare-associated infection indicator report late onset neonatal intensive care bloodstream infections to end of 2014.

5. Aggarwal R, Sarkar N, Deorari A, Paul V. AIIMS protocols in Neonatology 2014. http://www.newbornwhocc.org/clinical_proto.html

6. Hornik C, Benjamin D, Becker K, et al. Use of the Complete Blood Cell Count in Late-Onset Neonatal Sepsis. Pediatr Infect Dis J. 2012 Aug; 31(8): 803–807.

7. Delanghe J, Speeckaert M. Translational research and biomarkers in neonatal sepsis. Clin Chim Acta. 2015;451(Pt A):46-64

8. W. E. Benitz, M. Y. Han, A. Madan, and P. Ramachandra, “Serial serum C-reactive protein levels in the diagnosis of neonatal infection,” Pediatrics, vol. 102, no. 4, p. E41, 1998

9. Fowlie P, Schmidt B. Diagnostic tests for bacterial infection from birth to 90 days—a systematic review. Arch Dis Child Fetal Neonatal Ed 1998;78:F92–F98

10. http://www.cec.health.nsw.gov.au/__data/assets/pdf_file/0009/292194/sepsis-newborn-infant-pathway-nov2015.PDF

11.http://www.adhb.govt.nz/newborn/Guidelines/Infection/AntibioticsForNeonatalSepsis.htm

12. A.R.Tunkel, B. J. Hartman, S. L. Kaplan et al., “Practice guidelines for the Management of bacterial meningitis,” Clinical Infectious Diseases, vol. 39, no. 9, pp. 1267–1284, 2004

13. Neonatology Clinical Guidelines, King Edward Memorial Hospital, Perth, Australia: Infection, septic screening and management 2010.

14. Herpes simplex virus meningitis and encephalitis in neonates. Herpes. 2004; 11 (S2):65-76.

15. Palasanthiran P, Starr M, Jones C, Giles M. Management of perinatal infections. Australasian Society for Infectious Diseases 2014.

16. S. S. Saini, S. Dutta, P. Ray, and A. Narang, “Short course versus 7-day course of intravenous antibiotics for probable neonatal septicemia: a pilot, open-label, randomized controlled trial,” Indian Pediatrics, vol. 48, no. 1, pp. 19–24, 2011

17. Williams G, Hodson E, Isaacs D, Craig J. Diagnosis and management of urinary tract infection in children. Journal of Paediatrics and Child Health 48 (2012) 296–301

18. Hsieh E, Smith PB, Benjamin Jr D. Neonatal fungal infections: when to treat? Early Hum Dev. 2012; 88(2): S6–S10

19. Risk Factors and Prevention of Late Onset Sepsis in Premature Infants.

Early Hum Dev. 2010; 86(S1): 7–12.

20. http://www.merckmanuals.com/professional/critical-care-medicine/sepsis-and-septic-shock/sepsis-and-septic-shock

Feedback

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