INFECTION – LATE ONSET
Supporting Information

This guideline has been prepared with reference to the following:

NICE. Neonatal infection (early onset): antibiotics for prevention and treatment. 2012. London. NICE

http://www.nice.org.uk/guidance/CG149

Muller-Pebody B, Johnson AP, Heath PT et al. Empirical treatment of neonatal sepsis: are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed 2011 96: F4-F8

http://fn.bmj.com/content/96/1/F4.long

Royal College of Obstetricians and Gynaecologists. Malaria in Pregnancy, Diagnosis and Treatment (Green-top Guideline No. 54B). 2010. London. RCOG

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg54b/

Neonatal infection can be predicted by surface swabs

A study of 24,584 surface cultures obtained from 3,371 infants over a 3 year period (Evans, 1988) found the optimum sensitivity, specificity and positive predictive value in predicting sepsis was 56%, 82% and 7.5% respectively. The authors concluded that surface swabs were of limited value in this context.

A later, similar study in 35 premature infants (Puri, 1995) found results of 60%, 27% and 60%, respectively and came to a similar conclusion.

Another study (Jolley, 1993) commented that antimicrobial treatment was rarely altered as a result of pathogens isolated from surface swabs and as such the practice was inefficient and not cost-effective.

A study in 221 preterm infants (Berger, 2004) concluded that “Surface swabs add no additional information and hence should not be performed routinely.”

In a systematic review of 14 studies on the use of laboratory tests to identify serious infections in febrile children (Van den Bruel, 2011), the prevalence of serious infections ranged from 4.5% to 29.3%. Tests were carried out for C reactive protein (five studies), procalcitonin (three), erythrocyte sedimentation rate (one), interleukins (two), white blood cell count (seven), absolute neutrophil count (two), band count (three), and left shift (one). The tests providing most diagnostic value were C reactive protein and procalcitonin. Bivariate random effects meta-analysis (five studies, 1379 children) for C reactive protein yielded a pooled positive likelihood ratio of 3.15 (95% CI 2.67 to 3.71) and a pooled negative likelihood ratio of 0.33 (0.22 to 0.49). To rule in serious infection, cut-off levels of 2 ng/mL for procalcitonin (two studies, positive likelihood ratio 13.7, 7.4 to 25.3 and 3.6, 1.4 to 8.9) and 80 mg/L for C reactive protein (one study, positive likelihood ratio 8.4, 5.1 to 14.1) were recommended; lower cut-off values of 0.5 ng/mL for procalcitonin or 20 mg/L for C reactive protein were necessary to rule out serious infection. White blood cell indicators were less valuable than inflammatory markers for ruling in serious infection (positive likelihood ratio 0.87-2.43), and had no value for ruling out serious infection (negative likelihood ratio 0.61-1.14). The best performing clinical decision rule (recently validated in an independent dataset) combined testing for C reactive protein, procalcitonin, and urinalysis and had a positive likelihood ratio of 4.92 (3.26 to 7.43) and a negative likelihood ratio of 0.07 (0.02 to 0.27).

Berger A, Witt A, Haiden N, et al. Amniotic cavity cultures, blood cultures, and surface swabs in preterm infants: useful tools for the management of early-onset sepsis? J Perinat Med 2004;32:44-52

Evans ME, Schaffner W, Federspiel CF, et al. Sensitivity, specificity, and predictive value of body surface cultures in a neonatal intensive care unit. JAMA 1988;259:248-53

Jolley AE. The value of surveillance cultures on neonatal intensive care units. J Hosp Infect 1993;25:153-9

Puri J, Revathi G, Faridi MM, et al. Role of body surface cultures in prediction of sepsis in a neonatal intensive care unit. Ann Trop Paediatr 1995;15:307-11

Van den Bruel A, Thompson MJ, Haj-Hassan T, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. BMJ 2011; 342:d3082
http://www.bmj.com/content/342/bmj.d3082.long

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Evidence Level: I

Neonatal infection can be predicted by White cell count

A study in 6,207 infants (Bonsu, 2003) found that no threshold of the total peripheral white blood cell (WBC) count had both good sensitivity and specificity. At a count cutoff of 5,000 cells/mm^3, sensitivity and specificity were 79% and 5%; at a cutoff of 15,000 cells/mm^3, 45% and 78%. The authors concluded that the test was relatively inaccurate and that decisions to obtain blood cultures should not rely on it alone. A practice guideline (Baraff, 1993) had previously suggested that a WBC count threshold of 15,000/mm^3, having a negative predictive value of 97.6%, but a positive predictive value of only 13%, could be used to avoid unnecessary requests for blood cultures.

Another study, comparing WBC with absolute neutrophil count (ANC) in 170 infants (Gombos, 1998), concluded that both tests were "fair indicators for occult bacteremia". WBC had a sensitivity of 61% and a sensitivity of 59%, with 61% and 68% for ANC.

A prospective study of 1920 patients (Purcell, 2007) found that "The probability of an abnormal WBC count <5000 and 15,000-30,000 being associated with a concurrent serious bacterial infection was very low and no different from that of a normal WBC count in febrile patients admitted with respiratory syncytial virus lower respiratory tract infection."

Baraff LJ, Bass JW, Fleischer GR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Pediatrics 1993;92:1-12

Bonsu BK, Harper MB. Identifying febrile young infants with bacteremia: is the peripheral white blood cell count an accurate screen? Ann Emerg Med 2003;42:216-25

Gombos MM, Bienkowski RS, Gochman RF, et al. The absolute neutrophil count: is it the best indicator for occult bacteremia in infants? Am J Clin Pathol 1998;109:221-5

Purcell K, Fergie J. Lack of usefulness of an abnormal white blood cell count for predicting a concurrent serious bacterial infection in infants and young children hospitalized with respiratory syncytial virus lower respiratory tract infection. Pediatr Infect Dis J 2007;26:311-5

Evidence Level: III

Neonatal infection can be predicted by C-reactive protein

A 2020 systematic review of cohort and cross sectional studies concluded that determination of serum CRP level at initial evaluation of an infant with suspected late-onset infection is unlikely to aid early diagnosis or to select infants to undergo further investigation or treatment with antimicrobial therapy or other interventions (Brown, 2020).

A 2019 systematic review of RCTs concluded that the serum CRP level at initial evaluation of an infant with suspected late-onset infection is unlikely to be considered sufficiently accurate to aid early diagnosis or select infants to undergo further investigation or treatment with antimicrobial therapy or other interventions (Brown, 2019). Most studies included in the review used a prespecified serum CRP threshold level as the definition of a 'positive' index test (typical cut-off level between 5 mg/L and 10 mg/L) and the culture of a pathogenic micro-organism from blood as the reference standard. At median specificity (0.74), sensitivity was 0.62 (95% CI 0.50 to 0.73).

Brown JVE, Meader N, Cleminson J et al. C-reactive protein for diagnosing late-onset infection in newborn infants. Cochrane Database Syst Rev. 2019 Jan 14;1:CD012126
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012126.pub2/full

Brown JVE, Meader N, Wright K et al. Assessment of C-Reactive Protein Diagnostic Test Accuracy for Late-Onset Infection in Newborn Infants: A Systematic Review and Meta-analysis. JAMA Pediatr. 2020;174:260-68
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7042944/

Evidence Level: I

Neonatal infection can be predicted by respiratory distress

A study in 3,339 neonates (Galanakis, 2002) found that respiratory distress syndrome was the main risk factor for late-onset sepsis (RR 5.70).

A prospective study in 145 infants referred because of respiratory distress (Dorond, 1979) found a 4.8% incidence of bacteremia, with confirmed septicaemia in 3.5%. The authors concluded that

antibiotics should not be given routinely in such cases, in view of the low incidence of confirmed septicaemia.
In a prospective study of 116 infants with respiratory distress (Boyle, 1978), 9 (8%) were septic. WBC count would have provided early identification of 8 of these, as well as false positive results for 14% (15/105) of the remainder, which, in the authors estimation, would have justified antibiotic treatment for those with a cutoff of <10,000/mm^3.

Boyle RJ, Chandler BD, Stonestreet BS, et al. Early identification of sepsis in infants with respiratory distress. Pediatrics 1978;62:744-50

Dorond RD, Cook LN, Andrews BF. Incidence of sepsis in neonates with clinical respiratory distress. South Med J 1979;72:1262-4

Galanakis E, Krallis N, Levidiotou S, et al. Neonatal bacteraemia: a population-based study. Scand J Infect Dis 2002;34:598-601

Evidence Level: III

Neonatal infection can be predicted by prolonged rupture of membranes
A retrospective study of 117 women with PROM (Chua, 1995) found that prolongation of PROM to delivery interval for >48 hours increased the incidence of infection in their infants (33% vs 8.8% and 8.9% for intervals of <12 hours and 12-24 hours respectively.
In a secondary analysis of data from 5,041 women in the International Multicenter Term PROM Study (Seaward, 1998), the following were identified as independent predictors of neonatal infection:

- Clinical chorioamnionitis (OR 5.89, P<.0001)
- Positive maternal group B streptococcal status (vs negative or unknown, OR 3.08, P<.0001)
- 7-8 vaginal digital examinations (vs 0-2, OR 2.37, P=.04)
- 24-<48 hours from membrane rupture to active labour (vs <12 hours, OR 1.97, P=.02)
- >/= 48 hours from membrane rupture to active labour (vs <12 hours, OR 2.25, P=.02)
- Maternal antibiotics before delivery (OR 1.63, P=.05)

Chua S, Arulkumaran S, Sailesh KS, et al. Prelabour rupture of membranes to delivery interval related to the incidence of maternal and neonatal infection. J Obstet Gynaecol 1995;21:367-72

Seaward PG, Hannah ME, Myhr TL, et al. International Multicenter Term PROM Study: evaluation of predictors of neonatal infection in infants born to patients with premature rupture of membranes at term. Am J Obstet Gynecol 1998;179:635-9

Evidence Level: III

Neonatal infection can be predicted by discharging eyes
Discharging eyes in neonates are commonly due to vertical transmission of a sexually transmitted disease (chlamydia or gonorrhoea) from the mother (Winceslaus, 1987). Group B streptococcus may, however, also be a causative organism (Poschl, 2002).

Poschl JM, Hellstern G, Ruef P, et al. Ophthalmia neonatorum caused by group B streptococcus. Scand J Infect Dis 2002;34:921-2

Winceslaus J, Goh BT, Dunlop EM, et al. Diagnosis of ophthalmia neonatorum. BMJ 1987;295:1377-9
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1248537/pdf/bmjcred00048-0017.pdf

Evidence Level: V

Neonatal infection can be predicted by inflammation of umbilical cord
Acute inflammation of the umbilical cord (funisitis) was associated with a significantly higher rate of congenital sepsis in a study of 315 consecutive singleton preterm births (Yoon, 2000): 12% (8/66) vs 1% (3/216).

Yoon BH, Romero R, Park JS, et al. The relationship among inflammatory lesions of the umbilical cord (funisitis), umbilical cord plasma interleukin 6 concentration, amniotic fluid infection, and neonatal sepsis. Am J Obstet Gynecol 2000;183:1124-9

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Evidence Level: IV

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