INFECTION
Supporting Information

This guideline and supporting information has been prepared with reference to the following:

NB – Forthcoming NICE guideline: “Antibiotics for neonatal infection” (Publication date TBC)

Neonatal infection can be predicted by:
- Surface swabs
- White cell count
- C-reactive protein
- Respiratory distress
- Prolonged rupture of membranes
- Discharging eyes
- Inflammation of umbilical cord

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).


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Evidence Level: I

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/mm³, sensitivity and specificity were 79% and 5%; at a cutoff of 15,000 cells/mm³, 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/mm³, 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 1,186 infants (Benitz, 1998) concurred with this view, but concluded that two CRP measurements <1 mg/dl obtained 24 hours apart, 8-48 hours after presentation, indicate that bacterial infection is unlikely and thus that antibiotics are not needed.

Alternatively, many studies have observed that CRP in combination with other tests (such as WBC count) results in improved sensitivity (Arnon, 2004; Hengst, 2003; Laborada, 2003; Manucha, 2002). A prospective study off 711 patients with pneumonia (Clark, 2007) found that C-reactive protein was not associated with the degree of severity of the illness. A systematic review (Sanders, 2008) concluded that poor sensitivity associated with CRP meant that it should not be used as a single test for excluding bacterial infection.

Evidence Level: III

A prospective study of 301 screening episodes for neonatal sepsis (Garland, 2003) found that no single test alone was sufficiently reliable to accurately predict early onset sepsis. C-reactive protein (CRP) had a sensitivity of 67% and a negative predictive value of 86%. This compared to 63% and 80% for full blood examination and 57% and 83% for gastric aspirate. Another prospective study in 1,186 infants (Benitz, 1998) concurred with this view, but concluded that two CRP measurements <1 mg/dl obtained 24 hours apart, 8-48 hours after presentation, indicate that bacterial infection is unlikely and thus that antibiotics are not needed.

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Garland SM, Bowman ED. Reappraisal of C-reactive protein as a screening tool for neonatal sepsis. Pathology 003;35:240-3

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Hengst JM. The role of C-reactive protein in the evaluation and management of infants with suspected sepsis. Adv Neonatal Care 2003;3:3-13


**Evidence Level: III**

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/mm³.


**Evidence Level: III**

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)


**Evidence Level: III**

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).

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Evidence Level: V

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).


Evidence Level: IV

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