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Neonatal bacteraemia: diagnosis and management

Their incomplete muster of immune-inflammatory responses makes newborn infants more susceptible to bacterial invasion of the blood stream than older children and adults, and the risks are even higher in those born prematurely. Infection may be acquired early (intrapartum) from the mother or later as contact with the environment widens; the timing determines to some extent the bacteria responsible, the presentation of the illness, and the helpfulness or otherwise of quick diagnostic tests. In later bacteraemia distinction has to be made, too, between infections accompanying major illness or congenital anomaly[1] and those in which there is no preceding illness or obvious portal of entry.

Retrospective studies of neonatal infection mostly show that the infants were at risk from factors such as maternal infection, prolonged rupture of membranes, abnormal delivery, and birth asphyxia.[2 3] Infants of low birth weight are known to be particularly susceptible, and the lower the birth weight the greater the susceptibility.[4] Nevertheless, diagnosis may be difficult: the early signs of bacteraemia can be subtle, may be different at different gestational ages, and are unfortunately common to various illnesses. Intrapartum infection most often presents signs of respiratory distress,[5 6] and masquerades convincingly as hyaline membrane disease. Either early or later infections of the blood stream may cause features as diverse as lethargy, jaundice, poor feeding (if the infant is mature enough to suck), abdominal distension, hepatomegaly, enlarged kidneys, vomiting, diarrhoea or delay in stool passage, and recurrent apnoea (particularly in the most immature).[1 2] Variation in temperature is another sign, but one that can be masked in the hours after birth if loss of heat has been allowed to occur at delivery, or later if servo-mechanisms are in use for environmental temperature control. Late signs of bacteraemia may include convulsions, sclerema, shock, and a bleeding diathesis. Pustular skin lesions have become much less common since the decline of coagulase-positive staphylococcal infections; but ill-defined rashes, a spreading cellulitis, or necrotic lesions may be seen late in some opportunist infections with Gram-negative bacteria.[2]

When an infant has suspicious clinical features and a suggestive maternal history there should be no delay in drawing blood for culture. Blood should be taken from a peripheral vein whenever possible, though preliminary findings suggest that a sample from the umbilical artery catheter will not give false-positive results in the first hours of life.[7] Small samples of carefully collected capillary blood have been successfully used for culture[8] but will not detect bacteraemia when the density of organisms is below 50 colony-forming counts/ml.[9] When samples of cerebrospinal fluid and urine and any necessary swabs have also been collected for microscopy and culture, the doctor has to decide whether to start antimicrobial treatment. While, unfortunately, a bacteraemic infant may die many hours before the results of culture are available, most infants presenting with the same signs are probably not seriously infected, and no doubt many are treated unnecessarily.

Clearly we need an infallible test or combination of tests for bacteraemias that is easily performed, with results available within a short time. Among those evaluated[10–21] have been total neutrophil and immature neutrophil or "band" counts; smears of the buffy coat; smears of pharyngeal or gastric aspirates, of ear swabs at birth, and of the cut surface of the umbilical cord; and also erythrocyte sedimentation rate (ESR), haptoglobin, C-reactive protein, and counterimmunoelectrophoresis. None of those capable of being done within one hour in a ward side room—neutrophil counts, buffy coat smears, other stained smears, and ESR—is totally reliable: for example, Faden[14] found that seven of 10 infants with clinical bacteraemia confirmed by culture had positive buffy coat smears. Other stained smears when positive suggest that the infant may have come from an infected environment and some may indicate a likely pathogen.

Neutrophil counts are least helpful during the first 48 hours of life. Total neutrophils first rise and then fall towards normal during this period. Many bacteraemic infants stand out from normal babies by having strikingly low counts, but their neutropenia is already a late sign of poor prognosis.[12 23] Such low counts occur, too, in infants dying of necrotising enterocolitis,[24] whether or not blood cultures are positive. Infants who have strikingly high counts during this period have often been born after a long delay since rupture of the membranes; the fact that they are able to summon this early response seems a good prognostic sign, and they rarely become ill.[23] After 48 hours, however, a finding of total neutrophil and band counts deviating from normal standards,[25–27] with an abnormal ratio of total immature to mature neutrophils,[12 13] seems to be the most rapidly completed (though still not infallible) test available. The search for the perfect quick diagnostic combination should go on—especially on behalf of the hard-pressed house officer responsible for a neonatal intensive care unit in the small hours. At present, and justifiably in the circumstances, after blood for culture has been withdrawn antimicrobial drugs are prescribed in a very high proportion of cases. Unfortunately the subtle changes in bacterial flora

that such widespread use of antimicrobial treatment induces among the vulnerable inhabitants of neonatal units (whether treated or not) may contribute to their problems.

Meanwhile, Pichichero and Todd[29] have shown that 96% of carefully assessed bacteraemic cultures are positive after 48 hours of incubation and 98% after 72 hours. When the culture remains negative after two to three days the risk of stopping antimicrobial treatment is therefore slight; prompt abandonment of unnecessary treatment could perhaps lessen alteration of host flora and the emergence of resistant organisms. No arbitrary rule can be laid down for length of treatment when cultures are positive: both gestational age and the presence or absence of meningitis have to be taken into account.

The combination of penicillin and an aminoglycoside such as gentamicin should meet most bacterial eventualities; higher penicillin blood concentrations are, however, needed to deter group B beta-haemolytic streptococci (at present the most common cause of early bacteraemia) than other susceptible organisms.[30] The importance of anaerobic sepsis has been underestimated in the past, but as yet there are few reports of the use of metronidazole in the newborn. Though there is no proof of its efficacy by controlled trials, exchange transfusion with fresh blood may boost the infant's immune defences.[31–33] Ventilatory support may be needed for some severely ill infants. Other complications that should be borne in mind are both hypoglycaemia and hyponatraemia. Finally, previously unsuspected underlying diseases[34] must be considered if the infant does not improve when infection is controlled.

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Epidemiology of multiple sclerosis

Although both environmental and genetic factors probably contribute to multiple sclerosis, environmental causes are thought to be the more important. Epidemiologists studying multiple sclerosis are sometimes said to be working "with their hands tied behind their backs" because there is no diagnostic laboratory test for the disease,[1] but in fact epidemiological research has provided most of the information on environmental factors. Much of this research has been essentially descriptive, concentrating on analysis of the prevalence, geographical distribution, and varying incidence of the disease among different populations.

Multiple sclerosis is most frequent in Western Europe, southern Canada, the northern United States, southern Australia, and New Zealand; and in these so-called high-frequency areas its prevalence runs as high as 30-80 cases per 100 000 population. In low-frequency areas such as Asia, Central America, and most of Africa the rates are fewer than five per 100 000.[2] Broadly speaking, the disease is prevalent in areas with temperate climates and less common in largely tropical or subtropical and often developing countries with a lower level of hygiene and health services. In the high-frequency areas the disease seems to occur in clusters or foci; and in Scandinavia, for example, there may be a single focus extending across all three countries.[3]

One of the most fruitful subjects of research has been the changes in prevalence in migrants, major differences being found among people of the same genetic stock living in different environments. Such studies have been reported from South Africa,[4] Israel,[5] Hawaii,[6] and America,[7] and the findings are remarkably similar: the migrant tends to carry with him most but not all of the risk of his native land. The age of migration seems to be important. For example, someone who moves from a high- to a low-risk zone after the age of 15 has a much higher risk of later developing multiple sclerosis than someone moving before the age of 15. This clearly implies an important environmental factor in the pathogenesis of multiple sclerosis operating in the first 15 years of life.

What this factor might be has been much debated. The possibility examined in most detail has been infection. Studies of specific immunoglobulins have shown that titres of antibodies to certain childhood infections, notably measles,[8] are increased in patients with multiple sclerosis; and at least one study has shown association of the disease with childhood infectious illnesses.[9] Further support for an infectious cause for multiple sclerosis has come from a recent epidemiological study in the Faroe islands.[10] From 1920 to 1977 a total of 25 cases of multiple sclerosis occurred among native-born resident Faroese and in 24 of these the onset of disease was between 1943 to 1960. These 24 cases are said to meet all the criteria for a point-source epidemic, and—at least in the Faroes—multiple sclerosis may prove to be a transmissible disease.

Unfortunately, one of the problems of epidemiological studies in multiple sclerosis is that the picture has become even more confused as more information has become available. For example, in 1971 an association was suggested between the disease and dental caries, possibly with dental trauma and its accompanying local anaesthesia as a precipitating factor.[11] A recent study[12] has explored this association further and shown that death rates due to multiple sclerosis in Australia and American do show a positive correlation with dental caries.