LEADING ARTICLE

SEPSIS IN YOUNG INFANTS - RATIONAL APPROACH TO EARLY DIAGNOSIS AND TREATMENT

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Newborn infants are uniquely susceptible to overwhelming bacterial infection. The incidence of such infections ranges from 1 to 10 per 1,000 live births[1], with the preterm infants having significantly higher rates than term newborns. The mortality rate from early-onset bacterial infection in the neonate currently ranges between 15% and 30% and morbidity in survivors is high. Approximately one-third of septic newborn infants develop meningitis. When meningitis occurs, serious sequelae occur in 30% to 50% of survivors[2]. Thus, despite the advancements in life support technology and the development of potent new antimicrobial agents, we continue to lose far too many neonates to bacterial infection.

The early and efficient diagnosis of neonatal bacterial sepsis is one of the most difficult problems in clinical medicine. Babies who develop sepsis often deteriorate rapidly. Failure or delay in treatment is likely to result in significant mortality and morbidity. Antibiotics are therefore given 'routinely' or at the slightest suspicion to infants 'not behaving normally'. It is estimated that between 11 and 23 non-infected newborns are treated in intensive care nurseries for every one with proven infection[3]. This approach of overtreatment has to be balanced against the risks of blunderbuss antibiotic therapy such as the alteration in normal flora and emergence of resistant organisms, side effects of the medications, and excess financial and emotional cost to the parents. It is therefore necessary to develop a rational approach to the diagnosis of neonatal sepsis based on the relative importance of symptoms and known risk factors. Whilst accepting some overtreatment in the high-risk group, the duration of therapy should be minimized once they have been proven uninfected. The low-risk group should continue to be observed by a safe protocol.

CAUSATIVE ORGANISMS

Knowledge of the most commonly isolated bacteria in a nursery, coupled with the antimicrobial susceptibility of these organisms, is invaluable in treating infants with suspected sepsis. The principal pathogens responsible for neonatal sepsis have tended to change with time. Primary sepsis must be contrasted with nosocomial sepsis. The agents associated with primary sepsis are usually vaginal flora. Most centres report group B beta-hemolytic streptococci as the most common, followed by gram-negative enteric organisms, especially *Escherichia* coli (capsular group K1). Other pathogens include *Staphylococcus, Listeria monocytogenes,* other streptococci (including the enterococci), anaerobes, and nontypeable *Haemophilus influenzae.* In addition, many unusual organisms are documented in primary neonatal sepsis, especially in premature infants. The flora causing nosocomial sepsis varies in each nursery and may change rather abruptly in any one unit. The predominant organisms are the coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), *Staphylococcus aureus* (including methicillin-resistant strains), and gram-negative rods (including *Pseudomonas, Klebsiella, Proteus,* and *Serratia*).

NON-SPECIFICITY OF CLINICAL MANIFESTATIONS

The newborn infant responds to many varieties of noxious stimuli (infectious, metabolic, respiratory, traumatic) with a limited repertoire of stereotyped reactions. As a result, many of the manifestations of sepsis have their counterparts in hypoglycaemia, hypocalcaemia, hypoxaemia, and haematologic disorders. Most infants with infections cannot be differentiated from other neonatal disorders on the basis of the presenting signs and symptoms.

Temperature instabilities are observed frequently as initial complaints. Thermoregulatory disturbances commonly become obvious when the nurse reports the need to make frequent changes in the Isolette's thermostat to accommodate the infant's loss of regulatory control. About 10% of newborn infants with fever had positive cultures for bacterial infections[4]. In contrast, hypothermia is more non-specific as many neonates have some problems in temperature control in the transition to postnatal life.

Respiratory distress occurs in up to 90% of infants with sepsis. The clinical presentation may vary from apnoea, cyanotic episodes, tachypnoea, or a slight increase in oxygen requirement to severe distress requiring mechanical ventilation.

Approximately a third of infants will have gastrointestinal findings, including poor feeding, regurgitation, vomiting, a weak suck, abdominal distension, and diarrhoea. While in most cases, conditions other than sepsis explain these findings, bacterial disease always must be considered. Unexplained jaundice at any age in the neonatal period can be due to sepsis. Although the increased bilirubin in sepsis is usually in the unconjugated fraction, it is not uncommon to see some elevation of the conjugated fraction, especially in association with urinary tract infection due to coliform organisms[5].

Sepsis may also present with such subtle findings as diminished activity or lethargy, irritability , glucose intolerance or instability, hepatosplenomegaly, petechiae and purpura, seizures, poor perfusion or shock, or just 'not doing well'.

The decision to treat an infant for possible sepsis based on symptoms is a matter of clinical judgement and cannot be dictated by any protocol. The physician must be guided by a complete perinatal history eliciting those factors which place the infant at high risk, by a thorough physical examination attentive to signs suggestive of infection, and by clinical experience. When infection is likely, a laboratory workup is indicated. When infection is unlikely and not substantiated by history, physical examination, and clinical judgement, investigation for an infectious process is usually unnecessary. If doubt exists, it is good practice to proceed with a workup.

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CLINICAL ANTECEDENTS AND RISK FACTORS

A number of clinical situations place infants at particular risks. In some cases these situations are related to prenatal events and in others to postnatal events.

1. Prematurity is the single most significant factor correlated with sepsis. The risk increases in proportion to the decrease in birth weight. The attack rate for sepsis was 26 times greater in infants weighing less than 1000 g compared with those weighing more than 2500 g[6]. The rate of sepsis was 8 times greater in infants weighing 1000 to 1500 g compared with those weighing 2000 to 2500 g. The increased susceptibility is related to the inherent deficiencies in the immune system, including immunoglobulin production, complement, opsonic functions, and phagocytic capability.
2. Prolonged rupture of membranes (>24 hr) and chorioamnionitis : The incidence of documented sepsis in neonates born to mothers with rupture of membranes greater than 24 hours is approximately 1%[7]. When signs and symptoms of chorioamnionitis are present, the risk of sepsis increases to 3 to 5%.
3. Premature rupture of membranes and preterm labour without adequate explanations such as multiple pregnancy, abruptio placentae, and so on.
4. Maternal fever or other evidence of maternal infection. Maternal urinary tract infection is associated with an increased risk of infection in the neonate, presumably by increasing the risk of preterm birth and by increasing the rate of chorioamnionitis[8]. Maternal colonization with group B streptococcus (GBS) without other clinical complications carries a neonatal sepsis risk of about 1 to 2%[9].
5. Sophisticated equipment for respiratory and nutritional support combined with invasive techniques provides life support to the ill infant. Arterial and venous umbilical catheters, central venous catheters, peripheral arterial and venous cannulas, urinary indwelling catheters, and tracheal intubation give enormous opportunity for pathogens of relatively low-grade virulence to establish infection and to invade the host.
6. Other contributory risk factors include : male gender[7], perinatal asphyxia[7], multiple gestation, and amniotic fluid problems (eg meconium-stained amniotic fluid prior to 36 weeks' gestation is unusual and has been associated with *Listeria* infection).

When a single risk factor is present, investigation of the infant for sepsis may be relatively unrewarding. The yield is considerably improved when more than one risk factor is present. The observed risks are additive. Thus, although the attack rate for perinatally acquired sepsis in newborn infants born to GBS-colonized women is 1 to 2%, the rate increases to 15% with preterm onset of labour, 10% for chorioamnionitis or prolonged rupture of membranes (>24 hr), and 9% for maternal postpartum bacteraemia[6]. Attempts have been made to develop a screening score to identify high-risk infants for early treatment. While the use of such a scoring system decreased the frequency of inappropriate use of antibiotics, it did not result in a decreased total use of antibiotics in these infants[7].

DIAGNOSTIC LABORATORY TESTS

At the present time, there is no single test that can be relied on to provide a rapid and accurate diagnosis of neonatal infection. For neonatal infection, a test or combination of tests with a high sensitivity (how frequently the test is positive if infection is present) is desirable because it is a serious but treatable condition whose treatment should not be missed or delayed. A high negative predictive value (NPV) (how frequently infection is absent when the test is negative) is also desirable so that neonatal infection can be confidently excluded with negative test results. On the other hand, it is also desirable to have a test with as high a specificity (how frequently the test is negative if infection is absent) and a positive predictive value (PPV) (how frequently infection is present when the test is positive) as possible. The highest efficiency (how frequently the test predicts correctly - excluding false positives and false negatives) is desired when the disease is serious but treatable and false positives and false negatives are equally serious and damaging.

1. ***Cultures :*** The "traditional sepsis workup" consists of cultures of blood, cerebrospinal fluid (CSF), urine, and chest x-ray. Positive bacterial cultures will confirm the diagnosis of sepsis. 96% of blood cultures are positive within 48 hours and 98% positive within 72 hours[10]. However, a number of factors may result in negative cultures in the presence of sepsis. These include antepartum maternal antibiotic therapy, organisms that are difficult to grow and isolate (ie, anaerobes), and sampling errors with small sample volumes, wrong methods and inappropriate sites. Negative blood cultures were found in up to 50% of neonates with congenital bacterial pneumonia and a positive tracheal aspirate culture[11], and up to 15% of newborns with positive CSF cultures[12]. Both CSF and urine cultures have a low yield during the first 72 hours of life[13]. In infant on ventilator, tracheal aspirate cultures may be useful in the presence of pneumonia and a negative blood culture.
   Isolation of an organism from mucocutaneous sites, such as skin, ear canal, nasopharynx, gastric aspirate, or rectum, usually does not reflect the cultural status of blood, CSF, or other body tissues. The colonization-to-disease ratio for the major pathogens of the neonate is approximately 100 to 200:1.
2. ***Antigen Detection Tests :*** The presence of bacterial antigens in blood, CSF, or urine confirms the diagnosis of systemic bacterial disease. Latex particle agglutination (LPA) tests are available for GBS, *E coli (K1), N meningitidis, H influenzae,* and *Streptococcal pneumoniae.* Similarly, endotoxin elaborated from gram-negative bacteria can be detected by Limulus lysate assay on blood and urine. These methods may complement other laboratory tests, particularly in the setting of antenatal maternal treatment with antibiotics or parenchymal lung disease with negative blood cultures. There are, however, problems of false-positive reactions and may be the results of cross-reaction with other bacterial species and skin or urine contamination[14]. Further experience with LPA test for GBS sepsis showed that the sensitivity may be as low as 67% to 90% and a PPV of only 56%[15].
3. ***Gram stains of various Fluids :*** Gram staining is especially helpful for study of CSF. Gram staining of the buffy coat has been helpful in several series of proven sepsis in infants. Gastric aspirate Gram stain has low PPV. Generally, if there are more than 5 neutrophils per high-power field or a large number of bacteria, the test is positive. However, a positive aspirate reflects an infected intrauterine environment, not a foetal inflammatory response.
4. ***Adjunctive, Non-specific Diagnostic Tests :*** Many adjunctive tests have been evaluated to provide a rapid and useful means to indicate the presence of infection, but they do not identify the causative organisms.

a. *White cell count and differential:* These values alone are very non-specific. Manroe et al has established the normal reference ranges for total neutrophil counts and indices of immature neutrophils as a function of postnatal age[16], thus refining the leucocyte count into a more sensitive test for diagnosing sepsis. A total WBC<5000 mm^3, a total neutrophil count <1000/μ1, or an immature (band) to total neutrophil ratio > 0.2 (I/T ratio) have all been

correlated with an increased risk of bacterial infection[16,17]. To further improve the diagnostic accuracy, Rodwell et al developed a seven-point haematologic scoring system based on the white cell count, total and immature neutrophil counts and ratios, degenerative changes in neutrophils, and thrombocytopaenia[18]. This approach had a 96% sensitivity and 99% NPV.

Many factors may affect the WBC and differential counts. Maternal hypertension, perinatal asphyxia, and intraventricular haemorrhage may cause neutropaenia. Antenatal steroids may cause leukocytosis. Maternal fever and non-specific stresses in labour can elevate the I/T ratio. The WBC counts can be higher in capillary than in arterial or venous samples, and the test is highly operator dependent. Thrombocytopaenia may be important in supporting the diagnosis of sepsis, but it appears to be a late finding and is very nonspecific.

b. *Acute Phase Reactants :* There is increasing amount of information about the value of acute phase reactants in diagnosing and in following the course of neonatal sepsis. The ability to perform rapid quantitative C-reactive protein (CRP) measurements has been made possible with the advent of rubidometric or nephelometric techniques. The micro-ESR is an inexpensive, easy bedside screening test, but seems to be less sensitive than CRP. False-positive reactions can occur in disseminated intravascular coagulation due to consumption of fibrinogen which decreases rouleaux formation. Haptoglobin and orosomucoid are other acute phase reactants under investigation, but their use is limited by their slower response to infection than is found for CRP.

c. Miscellaneous tests: Nitroblue Tetrazolium test (NBT), Immunoglobulin M levels, umbilical cord histology, fibrinogen levels... have been used. They are usually not done as a routine in most labaoratories and are also of doubtful values.

COMBINATION OF TESTS : THE SEPTIC SCREENS

It is obvious from the preceding discussion that the sensitivity and specificity of each of the tests do not justify their individual use in the newbom infant. However, when tests are used in various combinations, the diagnostic capability can be significantly improved and the septic screens are cost-effective in decreasing antibiotic usage. Philip et al[17] combined the results of five tests into a septic screen (WBC < 5000/mm^3, I/T > 0.2, positive CRP, elevated haptoglobin, and mESR > 15 mm/hr). If each of five separate tests were negative, the probability was 99% that infection was not present. When two or more of five tests were positive, both sensitivity and PPV were greatest. Of these tests, the I/T ratio was the most useful, with a NPV comparable with the full battery of five tests. However, not all septic patients were identified, and the screen was not quite as sensitive in detecting late-onset infection[19].

The importance of serial measurement of the septic screens was demonstrated by Gerdes et al[20] who performed two separate screens (WBC, I/T, CRP, mESR) 12 to 24 hours apart. Infants who had normal initial screens were positive on repeat testing. The method identified all septic patients and had a 100% NPV.

APPROACH TO ANTIBIOTIC TREATMENT

Although elaborate flow diagrams for decision-making can be designed, it may be simpler to think of factors that either favour or oppose the use of antibiotics. Clinical judgement and skill in evaluating the individual infant undoubtedly are important part of thoughtful antibiotic administration because, unfortunately, it is too easy to treat everybody for the least indication. The burden of proof is on the clinician to prove there is no infection, not on the infant to prove that he or she is sick.

The following factors favour the use of antibiotics : preterm infant, multiple risk factors suggesting exposure to infection, clinical signs suggesting infection, and positive septic screening tests (eg WBC, I/T, CRP, mESR, and their various combinations). The following factors oppose but do not negate the use of antibiotics : term infant, single risk factor, absence of clinical signs (ie 'asymptomatic'), and negative screening tests. The absence of risk factors should not dissuade one from treating a symptomatic infant. On the other hand, the decision to treat an at-risk infant for possible sepsis should be based on the level of risk the clinician is willing to accept, not on what seems more worrisome to the clinician.

In those infants for whom a decision not to use antibiotics has been made, careful obsrevation may be all that is required. Alternatively, a septic workup could be done and culture results should be available for review within 48 to 72 hours. It is also appropriate to do septic screens, serially if necessary, to assist in decision-making. If GBS infection is prevalent or strongly suspected, a GBS LPA test on urine may be helpful, especially if intrapartum antibiotics have been given.

When the decision is to use antibiotics, a septic workup should be done before antibiotics are initiated. Re-evaluation at 48 to 72 hours is required to decide whether or not antibiotics can be stopped at that time. Sequential septic screening tests can also provide reliable means of deciding when to stop treatment.

Presumptive antibiotic therapy is directed toward the treatment of the most common pathogens for a given clinical setting. In the first month of life, the pathogens of greatest concern are GBS, *E coli,* and *Listeria.* Ampicillin and an aminoglycoside, usually gentamicin, are effective against these bacteria. This combination also provides broad coverage for many other gram-positive and gram-negative bacteria less commonly isolated from the septic infant. Both in vivo and in vitro synergy have been demonstrated for penicillins and amnioglycosides, especially against GBS and *Listeria.* Third-generation cephalosporins are also effective against gram-negative infections, but they have limited activity against *Listeria.* Nevertheless, with gram-negative meningitis, third-generation cephalosporins are recommended on the theoretical basis of greater killing power in CSF.

The ampicillin-gentamicin combination may not be preferred for nosocomial infections. 'Water bugs' such as Pseudomonas aeruginosa, Klebsiella species, may predominate. Considering the predominance of MRSA and coagulase-negative staphylococci as the principal cause of nosocomial sepsis, vancomycin has become the antibiotic for presumptive gram-positive bacterial coverage. Presumptive gram-negative coverage is provided with a third-generation cephalosporins or an amnioglycoside. Organisms resistant to gentamicin may be prevalent. A good alternative is amikacin as resistance to this antibiotics has been low.

Because the duration of antibiotics currently is rather empirical, it is usually advised that in cases of sepsis, antibiotics should be given for 7 to 10 days and in cases of meningitis for 14 to 21 days, depending on the organism. Objective data on which to base such decisions are still lacking.

CONCLUSION : IMMUNOTHERAPIES IN THE 1990s - PROMISE OR FANTASY?

Before the era of sulphonamides and penicillin, almost all infants with bacterial sepsis died. The mortality rate for sepsis began its decline in the 1950s as a result of technological advances in life support and the availability of more effective antimicrobial agents. Mortality rate reached a plateau in the early 1970s, and since that time, there have been no significant reductions. Although it is likely that pharmaceutical compa-

nies will continue to produce increasingly effective antibiotics, it is doubtful that antimicrobials alone will bring about the next significant reduction in neonatal mortality. The probability is that any further improvements in mortality will result from either increasingly accurate and sensitive methods to detect infants with possible sepsis or from immunotherapies.

The objective of adjuvant immunologic therapy is the administration of blood and tissue factors to enhance the neonatal host defence. Investigations and clinical trials are currently being conducted on the use of granulocyte transfusions, prophylactic or therapeutic uses of intravenous gammaglobulin (IVIG), the administration of specific monoclonal antibacterial antibodies, and most recently the prophylactic and therapeutic administration of fibronectin and haematopoietic colony-stimulating factors like cytokines. It is highly likely that some of these immunotherapies will eventually prove useful for preventing infection or treating infants with life-threatening sepsis. However, early diagnosis of sepsis is still crucial in the consideration of these modalities of treatment.

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