NEWER CONCEPTS AND MANAGEMENT OF NEONATAL SEPSIS

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ABSTRACT

Despite extensive research into its patho-physiology, investigations and treatment, sepsis remains an important cause of neonatal morbidity and mortality. The incidence in developing countries is 10 times that in the developed world. A large number of pro- and anti-inflammatory cytokines (interleukins, eicosanoids, tumour necrosis factor-alpha, nitric oxide) have been identified, the inter-play of which leads to the Systemic Inflammatory Response Syndrome (SIRS) which can have devastating consequences on all systems of the body. In India the common organisms include *Staphylococcus*, *E coli*, *Klebsiella* and *Candida*. A number of maternal and neonatal risk factors have been identified. The initial signs and symptoms are subtle and can easily be missed. Early investigations and screening tests are important and a promising number of new tests are being studied. The gold standard for diagnosis is a positive culture from a body fluid or local source in the presence of SIRS. The threshold for starting antibiotics should be low in high-risk neonates and broad spectrum antibiotics covering the likely organisms should be given intravenously in all suspected cases in a hospital setting. This should be continued for at least 24-48 hours (till negative reports are available) in suspected cases and for 2-3 weeks in proven cases. Prophylaxis is aimed at preventing nosocomial and cross infections. Strict hand-washing, meticulous asepsis protocols, identification of high risk groups and prompt and better screening tests are essential in controlling this problem.

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KEY WORDS : Neonate; Sepsis; Systemic inflammatory response syndrome

Introduction

Sepsis is one of the commonest conditions responsible for morbidity and mortality in the neonate. The incidence of both suspected and proven sepsis in India is around 8-10% but less than 1% in developed countries. However, when only culture positive cases are considered the incidence varies from 9-34/1000 live births in our country as compared to 1-12/1000 live births in the developed countries [1]. Unpublished data from large service hospitals has shown the incidence of culture-proven sepsis to be 4-8/1000 live births. Though it has been the focus of intensive research for many years, the mortality continues to be high (approximately 25%). The accepted definition is that sepsis is a Systemic Inflammatory Response Syndrome (SIRS) to a documented infection which may be local or systemic. Blood cultures do not need to be positive for a diagnosis [2].

Etiology

The fetus develops in a sterile environment but in certain situations may get exposed to infectious agents before birth. However, during and after birth, the newborn becomes colonized by bacteria acquired from the birth canal and external environment. Hospitalized neonates tend to get colonized with multi-drug resistant *Staphylococcus*, *Klebsiella* and *Pseudomonas*. In certain situations this may become overwhelming leading to systemic infection. Infection occurs due to

an inter-play of host, organism and environmental factors. Low birth weight, prematurity, breaks in the skin and mucous membrane barriers and introduction of IV lines, tubes and catheters are contributing host factors. Whereas the term neonate has an immune system that is appropriate for his or her needs, the preterm baby is immune deficient. Besides a low level of maternally acquired immunoglobulin, preterms also have low complement levels and a lesser ability to generate cytokines by B and T lymphocytes [3]. In India the most common organisms causing neonatal sepsis are *Klebsiella pneumonia*, *Staphylococcus aureus* and *E coli* [4]. *Group B Streptococcus* (GBS) has been surprisingly infrequently reported in our country though it remains the most common cause of early onset sepsis in the developed countries. Other organisms include *S epidermidis* (coagulase negative *S aureus*), *Proteus*, *Pseudomonas*, *Candida*, *S viridans*, *Acinetobacter* and *Enterobacter*. Ascent of vaginal organisms into the uterine cavity prior to rupture of membranes is rare but once the membranes rupture the risk progressively increases with time. Vaginal flora varies considerably from woman to woman and many cases of early onset sepsis result from vaginal carriage of opportunistic pathogens. Maternal and fetal major risk factors for early onset sepsis [5,15] include pyrexia >38°C, preterm premature rupture of membranes (PPROM) or prolonged rupture of membranes (PROM) >24 hours and features of chorioamnionitis.

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Sustained tachycardia in the fetus is also considered a major risk factor. Genitourinary colonization with GBS, rupture of membranes of >12 hours, maternal fever >37.5°C, maternal WBC count >15000 cu mm, low Apgar scores, birth weight <1500gm, prematurity, male sex and twins are considered minor risk factors. It is recommended that even asymptomatic infants with one major or two minor risk factors should have a blood count and blood culture done [5].

Pathogenesis

The pathogenesis of sepsis involves a complex interplay of various bacterial products and cytokines. SIRS, related to sepsis, results from tissue damage following the host's response to bacterial products such as endotoxin from gram-negative bacteria and the lipoteichoic acid-peptidoglycan complex from gram-positive bacteria. When bacterial cell wall components are released into the blood-stream, cytokines are activated and these in turn can lead to physiologic derangements. Endogenous mediators of sepsis continue to be identified and currently include TNF-alpha, interleukins (IL-1, 2, 4, 6 and 8), platelet-activating factor (PAF), interferon-gamma, eicosanoids (leukotrienes B₄, C₄, D₄, E₄; thromboxane A₂; prostaglandins E₂, I₂) and granulocyte-macrophage colony-stimulating factor. These mediators ultimately result in altered micro-perfusion and damage to capillary endothelium. Nitric oxide (NO) has been detected and used as a prognosis marker in case of sepsis as higher levels are associated with a poorer outcome. Detailed analysis of pathogenic mediators are opening newer vistas for therapeutic interventions [6].

Definitions [7] : Early onset sepsis (EOS): definitions range from 24 hours to seven days but here the term means infection presenting within 48 hours of life. It is commonly caused by organisms acquired from the mother before or during birth. The course is usually fulminating and the mortality rate is high.

Late onset sepsis : this is infection presenting after 48 hours of age and is generally caused by organisms acquired from the environment. The terms used for this pattern of infection are nosocomial (hospital acquired) and horizontally transmitted.

Clinical features [5,7] : A high degree of clinical suspicion for the early recognition, diagnosis and treatment of serious infection in the neonate is essential. However, a balance between over diagnosis and missed diagnosis is essential. In the early stages the signs are subtle and often noted by nurses or the mother. These include lethargy and poor suck. Occasionally, irritability and moaning may be seen. Tem-

perature instability is common, with preterms manifesting with hypothermia and term babies with fever. In the latter it is important to exclude overheating. An extended posture, an increased core (rectal) temperature (which is sustained for more than one hour) and a core-periphery temperature difference of >2-3° C are suggestive of pyrexia. Jaundice, with a significant direct component, is suggestive of infection although both direct and indirect components may be raised. Respiratory signs include either apnoea or tachypnoea. Poor cutaneous refill is a subtle sign of cardiovascular instability. A Capillary Refill Time (CRT) of >3 seconds measured over a central area (forehead or sternum) is significant. Abdominal distension, feed intolerance and increased pre-feed residues should also be taken seriously. The more obvious signs only appear with advanced infection. Cyanosis, grunting and retractions are the classical signs of neonatal lung disease. Signs of intestinal obstruction may be due to generalized sepsis as well as necrotising enterocolitis (NEC). A high-pitched cry, neck retraction, bulging fontanelle and convulsions are late features of neonatal meningitis. DIC may present with petechiae and bleeding from puncture sites and is a late sign of sepsis. Thrombocytopenia without DIC may also be seen, especially in fungal infections. Sclerema, or thickening of the subcutaneous tissue, is a non-specific feature of any serious neonatal illness and is usually associated with a poor prognosis.

Decreased movements of one limb or crying when moved may suggest septic arthritis or osteomyelitis. A thorough examination is essential. Examine the baby completely naked in a thermo-neutral environment and look for : (a) signs of respiratory distress or cardiovascular instability (b) signs of dehydration due to fluid loss, vomiting, diarrhoea or pyrexia (c) lesions of the skin or subcutaneous tissues (d) discharging umbilicus or periumbilical erythema. (e) Examine the chest for tracheal shift, decreased air entry or adventitious sounds. (f) Check for heart rate, pulse, murmurs or triple rhythm. (g) Look for hepatosplenomegaly. (h) Carefully palpate kidneys for tenderness. (j) Check for tender or distended abdomen and visible peristalsis. Are bowel sounds present? (k) Check fontanelle for tension and measure head circumference. Check spinal column and skull for pits or other skin defects. Is the baby obtunded or in coma? How is the response to painful stimuli? [1]. Check limb movements for exclusion of septic arthritis or osteomyelitis (m) Do not forget otitis media.

Investigations : A clinical suspicion of sepsis warrants early investigation and timely treatment. How-

ever, according to conservative estimates, between 10-30 non-infected neonates are treated in neonatal intensive care units for every one with a documented, culture-proven infection [1]. This is inevitable considering the rapid progress and implications of delayed treatment and the limitations of screening tests. However, the clinician should aim at developing a systematic diagnostic approach based on the relative importance of known risk factors and clinical features. The aims are to miss no cases in identified high-risk groups, minimize the duration of treatment for those neonates who later turn out to be non-infected and provide a safe observation protocol for low risk neonates. If the history and examination suggest infection, investigation followed immediately by treatment is indicated. The gold standard for the diagnosis of sepsis is a combination of features of a systemic inflammatory response with positive cultures from a local or systemic source (blood, CSF, urine or other body fluids).

Screening tests show the inflammatory response in the blood. Evidence of infection in local sites, amniotic fluid or maternal genital tract also increases the level of suspicion. Given the limited predictive value of existing screening tests, decision of antibiotic prescribing for unwell babies continues to be made on clinical grounds. However, positive screening test is sufficient reason to begin therapy even when level of clinical suspicion is not high in a high-risk case.

Specific Tests

1. Blood culture : This is gold standard test as the vast majority of neonatal infections are associated with bacteraemia. Radiometric methods usually allow a positive blood culture to be reported within 12-24 hours and virtually all cultures have grown by 48 hours. Mixed organisms or growth that does not appear within 72 hours should raise a suspicion of contamination [8]. However, it must be remembered that certain organisms like *H influenzae*, *L monocytogenes* and yeasts take longer to grow.

2. Urine culture : There are two practical ways to obtain urine from babies for purpose of diagnosing infection. One is to use urine collection bag and the other is to perform supra pubic aspiration. The former is notoriously unreliable due to contamination. Though the latter is preferred, it has a low yield in the first 72 hours of life [15].

3. Lumbar puncture : Lumbar puncture is more likely to produce a positive result in late onset sepsis than in early onset sepsis. It should be performed with strict sterile precautions. There is controversy regard-

ing whether babies with suspected sepsis should undergo lumbar puncture. Exceptions can be made for babies with respiratory distress and term, asymptomatic neonates with only risk factors for sepsis as in the former it may lead to destabilization and in the latter the yield is very low [9]. In all other cases a CSF study is a must to document meningeal involvement which in turn will decide the duration of antibiotic therapy. A new development in the diagnosis of meningitis in neonates and infants is the measurement of cytokines such as IL-6 and TNF alpha in the CSF [7].

4. Genetic techniques : It is now possible to amplify highly conserved DNA sequences from a variety of organisms using PCR. This method has potential of rapid diagnosis of bacteraemia.

5. Antigen detection tests : Counter immuno-electrophoresis has been used to detect the presence of bacterial antigens in blood, urine and CSF but is little used in neonatal practice.

6. Antibody detection tests : These are of more value in viral infections when four fold or greater rise in antibody titre in samples drawn 2 weeks apart is diagnostic.

7. Acridine Orange test : This involves direct staining of the organisms with acridine orange within the white cells in the buffy coat layer. It has a high degree of sensitivity and specificity [7].

Non-specific tests :

1. Surface swabs : Swabbing sites of inflammation is important but routine swabbing of sites such as umbilicus, groin, ears, nose, throat, pharynx and rectum is much less so. Surface swabs are informative about colonization. Routine surface culture may have some value when taken from ear or throat swab in suspected early neonatal sepsis, within 6 hours of birth.

2. Gastric aspirate : This can be viewed as sample of amniotic fluid and swallowed secretions from the birth canal. Polymorphs of more than 5 per high power field immediately after birth are considered to be significant [5].

3. Maternal High Vaginal Swab (HVS) : When babies present with signs of infection within first 24-48 hours of birth the source is likely to be the maternal vagina and HVS may grow the responsible organism.

4. Tracheal secretions : Endotracheal tube secretions and micro-organisms recovered from the upper airway may be those causing colonization. It has been suggested that using bronchial brush technique may give better results.

5. Catheter tip cultures : The tips of umbilical cannulae, central lines and thoraco-centesis tubes should

be sent for culture when removed. "Macki roll" technique can help distinguish genuine line infection from skin contamination during removal of the line.

6. *Radiology* : All babies suspected of sepsis should have a chest X-ray. Abdominal X-ray and ultrasound are indicated if there are abdominal signs or suspicion of urinary tract infection.

Screening Tests

(a) *White blood cell count* : Total white cell count is the least useful index because the normal range is so wide. Many non-infective catastrophies like periventricular haemorrhage, convulsions and asphyxia can raise the total WBC count. The absolute neutrophil count is of more value. There are well-documented normal ranges in term and preterm infants at various postnatal ages [10]. Within first 48 hours of life a count $< 2.25 \times 10^9/l$ suggests bacterial infection. Thereafter, both neutropenia and neutrophilia have useful predictive value. A more useful indicator of infection is the ratio of immature to mature neutrophils (IT ratio). The maximum normal value is < 0.20 during the first month. IT ratio > 0.2 is a useful marker of infection [5].

(b) *C-reactive protein (CRP)*: This acute phase reactant is produced by the liver during any generalized inflammatory process, probably as a result of stimulation of IL-1 and IL-6. Systemic bacterial and fungal infections produce a sharp rise in CRP but there is a delay of 10-12 hours between the onset of infection and CRP increase. Viral infections often do not cause a rise in the CRP. Quantitative assessment is more useful as is serial estimations. A negative CRP and a negative blood culture together suggest that presumptive antibiotic treatment can be stopped [11].

(c) *IL-6 and TNF alpha* : Because IL-6 plays a critical role in inducing CRP synthesis it should provide an earlier indication of infection than CRP. The combination of interleukin-6, an early marker of infection, with CRP a later sepsis marker, may allow the clinician to monitor the evolution of neonatal infection and detect more accurately infected neonates. Studies that have measured IL-6 and CRP together show that the combination is more sensitive than either marker alone, with little change in the specificity, and hence fewer false positive results [12].

(d) *Other acute phase reactants* : Micro-ESR of greater than 15 mm in the first hour at any time in the newborn period is suggestive of infection. Orosomucoid (alpha-1 acid glycoprotein), haptoglobin, alpha-1 antitrypsin and alpha-1 chymotrypsin have all been used in assessing neonatal infection. Serum granulo-

cyte colony stimulating factor has been shown to have a 40% positive predictive value and 99% negative predictive value in the diagnosis of culture proven neonatal sepsis [13].

(e) *Platelet count* : This may be low due to consumptive coagulopathy and low counts without this complication should suggest fungal infection.

A number of studies have attempted to combine screening and non-specific tests and formulate a scoring system to increase the probability of detecting true positive cases. A commonly used screen is a combination of five tests (white blood cell count, I/T ratio, CRP, haptoglobin and micro-ESR). The screen is considered positive if 2 or more tests are positive [14]. Gerdes and Polin have excluded haptoglobin and micro-ESR from the above screening tests and given points for different values of the tests. If repeated after 12-24 hours any patient having at least 2 points is considered infected. They have found this to have a 100% negative predictive value [15].

Treatment

The most important consideration is prompt and effective treatment. Supportive treatment involves maintaining oxygenation, correction of shock and maintaining temperature and acid base homeostasis. Babies can be critically ill and require intensive care management. There should be a low threshold for starting antibiotic treatment pending test results. In EOS, intravenous antibiotics on the higher end of recommended dose range must be started immediately, once the diagnosis is suspected. A combination of ampicillin (100mg/Kg/day) and gentamycin (5mg/Kg/day) is a good choice for blind treatment of EOS because of synergism between these antibiotics. In areas where resistance to these antibiotics is common, a third generation cephalosporin (100mg/Kg/day) and a lesser used of aminoglycoside (amikacin 15 mg/Kg/day) or netilmicin (5mg/Kg/day) may be more appropriate. A cephalosporin alone is unsatisfactory in the initial therapy of EOS as it will not cover *L monocytogenes* or *Enterococci*. In late onset sepsis the initial choice of antibiotics would depend on the knowledge of the unit bacterial flora, their resistance pattern and the history of the antibiotics previously received by the patient. Treatment should be aimed at CONS and gram-negative bacteria. In our country a combination of a third generation cephalosporin, cloxacillin (100mg/Kg/day) and an aminoglycoside should be effective. In many places newer antibiotics like vancomycin (30mg/Kg/day) is the current drug of choice in CONS due to the resistance pattern. Antibiotics may need to be changed

later depending on culture and sensitivity patterns. Several newer antibiotics are finding a role in difficult cases. Among the newer antibiotics aztreonam and imipenem are invaluable in the treatment of resistant gram-negative sepsis. The duration of antibiotic treatment varies with the situation. In suspected cases if the clinical signs are absent and the screening tests and blood culture are negative, antibiotics may be stopped after 24-48 hours. However, if clinical suspicion persists despite negative tests it is recommended to continue for at least 5 days. In culture proven cases or those with a persistently strongly positive screening test a full course of 10-14 days should be given. In *S aureus* systemic infections, meningitis and pyelonephritis, the treatment is prolonged for at least 3 weeks. In deep seated infections like osteomyelitis and ventriculitis, treatment is recommended for 6 weeks.

Adjunctive Treatment

Immunoglobulins have been tried in a large number of studies with conflicting results. However, the general consensus is that there is insufficient evidence to support their routine use in suspected or proven sepsis [17]. G-CSF and GM-CSF may be useful in neutropenic newborns. Fresh frozen plasma, exchange transfusion and granulocyte transfusions have also been tried. SIRS modulators like TNF antagonists and IL-1 receptor antagonists are the newer drugs which are still investigational [6].

Prevention

The simple principles of prevention of cross infection in the unit should be strictly adhered to. Unit design, cleaning of equipment and meticulous hand washing have been proven to decrease the incidence of nosocomial infections. Over-crowding and over-worked staff have been shown to be the causes of outbreaks of infections in units [7]. Screening all members of the health team who come into contact with the neonate and his environment for colonization with pathogenic organisms is essential. Though prophylactic antibiotics by and large have no role in the prevention of sepsis, a recent review of studies using low-dose vancomycin as a continuous infusion in ELBW neonates on hyperalimentation has shown that it reduces the incidence of both total neonatal nosocomial sepsis and coagulase negative staphylococcal sepsis. However, there is insufficient evidence to ascertain the risks of development of vancomycin resistant organisms in the nurseries involved in these trials [18]. Prophylactic IVIG has been shown to result in a 3-4% reduction in the incidence of sepsis but the cost factor is a major deterrent to its routine use [19].

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