Review

NEONATAL SEPSIS

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ABSTRACT

Neonatal sepsis continues to be a major cause of morbidity and mortality in India. To aid the diagnosis several direct and indirect methods are available. Sepsis screen has resulted in decrease in indiscriminate use of antibiotics. C-reactive protein can be easily estimated and is a useful indicator for favourable outcome or complication. The bacterial flora causing sepsis has changed over the years. Antimicrobial chemotherapy should be based on the prevalent organisms in the neonatal ICU. Outcome can be improved by judicious use of newer antibiotics and exchange transfusion when indicated.

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KEYWORDS : Antibiotics; Meningitis; Neonatal sepsis.

Introduction

Neonatal sepsis is one of the major factors contributing to the high perinatal and neonatal mortality and morbidity. Early clinical symptomatology of neonatal sepsis is mimicked by several other disorders affecting the newborn. Delay in starting antimicrobial therapy is fraught with dangers of several complications and increased mortality. Isolation of infecting organism from blood provides the definitive diagnosis. However, the culture procedure requires 48-72 hrs and yields a positive result in 30-70 per cent of cases [1]. Therapy cannot wait this long in a critically sick neonate. To rationalise therapy in neonatal sepsis certain perinatal risk factors have been identified [2] and several indirect early markers have been identified. Use of these indicators in addition to the clinical judgement has made the approach to the management of neonatal sepsis more logical.

DIAGNOSIS

Direct Method

1. Culture and gram's stain :

Blood culture is the 'gold standard' for diagnosis of neonatal sepsis. Cultures of blood, cerebrospinal fluid (CSF) and urine should be taken before initiating antibiotic therapy. It is recommended that inoculated blood sample should be 5-10 per cent of the total amount of liquid broth medium in the culture bottle [3]. Urine sample is taken by suprapubic puncture which is both feasible and safe. Catheterization should be avoided. Superficial cultures such as throat, umbili-

cus, skin etc. are usually not helpful. Gram's stain of CSF and pus may be rewarding and should always be done.

Buffy-coat examination :

To detect bacteria, buffy coat examination has been found useful in the rapid diagnosis of neonatal septicaemia [4]. Acridine orange staining is reported to be more sensitive than gram's stain in the identification of bacteria in the buffy coat [5].

Counter Immuno-electrophoresis (CIE) :

CIE is a method of identifying bacterial antigens and has been used to detect a number of pathogenic bacteria by use of specific antisera within 2 hours in blood, CSF and urine. There are very few false positives but true false negatives are common [6].

Agglutination Tests

Latex agglutination of antibody-coated latex particles by bacterial antigens, has been effective in early detection of bacterial antigens in the CSF of patients with meningitis.

Monoclonal Antibody Technique

Offers high sensitivity and specificity, unlimited supply of antibody and may be less expensive than existing commercial antisera/antibodies.

Enzyme radioisotope assay (ERA)

A number of micro organisms produce beta-lactamase which can be detected by using enzyme radioisotope assay [7].

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Radiometric detection

Radiometric detection of bacteria by measurement of ^{14}C labelled carbon dioxide produced by the metabolism of ^{14}C labelled substrate in the culture medium have been used to provide more rapid and accurate method of identifying bacteria and holds promise [8].

Advantage of direct methods is that they also identify the etiological agent causing sepsis, a draw back with indirect methods.

Indirect methods

A number of indirect markers have been used for early detection of sepsis. TLC, absolute neutrophil count and morphology, band/neutrophil ratio, platelet count, c-reactive protein (CRP), Fibrinogen, haptoglobin, orosomucoid, micro-ESR etc. Individually most have poor sensitivity and specificity. When used as a 'sepsis screen', positive predictive value approaches 89 per cent, while negative predictive value approaches 99 per cent [9]. By virtue of its high negative predictive accuracy, sepsis screen has resulted in significant decrease in use of antibiotics. C-reactive protein (CRP) can be estimated by a single radial immuno-diffusion technique or by more rapid semi quantitative latex agglutination technique and is useful in areas lacking adequate microbial laboratory facilities. Some workers have reported high sensitivity (83%) and specificity (92%) with CRP determination in blood and CSF [10]. Moreover CRP has a short half life of only 4 to 6 hours and its fall indicate a favourable outcome and hence provides an index for determining the effectiveness of antibiotics and occurrence of relapse or complications [11].

Changing pattern of bacterial flora causing neonatal sepsis

Bacteria causing neonatal sepsis has varied considerably from time to time the world over. Changing

pattern is evident from the data from various medical institutions in our country (Table). Over the last 10-15 years the incidence of Klebsiella infections is increasing [12-14]. Staphylococcus aureus still plays an important role as causative organism for neonatal sepsis. Coagulase negative staphylococcal sepsis, listeria and candida are being increasingly reported [14].

Antimicrobial chemotherapy

The initial choice of antimicrobial agents for treatment of suspected sepsis is based on knowledge of the prevalent organisms responsible for neonatal sepsis and their sensitivity pattern.

Newer penicillins

Ticarcillin is a semi-synthetic penicillin with properties identical to carbenicillin, with exception that it is more active against *P aeruginosa* [15]. Acylampicillins (meslocillin, azlocillin and piperacillin) have limited role in management of neonatal sepsis.

Cephalosporins

First generation cephalosporin which include cefazolin, cephalixin and cephalothin have good activity against gram positive organism but limited activity against gram negative organisms.

Second generation cephalosporins which includes Cefuroxime, readily diffuse into the CSF and is useful in treating meningitis.

Third generation cephalosporins which include cefotaxime, ceftazidime and Ceftriaxone, have excellent activity against gram negative bacteria.

Aminoglycosides

This group includes gentamicin, amikacin and sisomicin. They are active against gram-negative organisms such as *E coli*, *Klebsiella*, *Acinetobacter*, *citrobacter*, *Proteus*, *H influenzae*.

TABLE
Blood culture isolate (percentage) from cases of neonatal sepsis

Organism (%)	Bhakoo Chandigarh (12)			Singh Delhi (13)			Chaturvedi Wardha (14)		
	1971-74 n=132	1974-76 n=113	1977-79 n=113	1975 n=100	1980 n=124	1984 n=92	1983 n=177	1985 n=315	1987 n=193
Klebsiella	8.3	8.0	18.6	14.0	76.1	58.6	23.7	21.0	24.3
E. coli	17.4	22.1	12.4	13.0	7.2	9.8	16.4	19.5	10.9
Pseudomonas	12.8	9.7	3.5	24.0	7.2	7.6	9.6	14.0	16.6
Streptococcus fecalis	5.33	8.8	12.4	—	—	—	—	—	—
Staphylococcus aureus	12.0	35.4	30.0	21.0	4.8	1.1	11.3	11.8	19.2
Staphylococcus albus	—	—	—	19.0	4.8	11.9	22.0	24.5	19.2
Others	43.4	16.0	23.1	6.0	—	10.0	23.0	10.2	9.8

Ciprofloxacin

Is one of the newer synthetic quinolones. Most gram negative bacteria are highly susceptible in vitro and many gram-positive bacteria are susceptible [16].

The choice of antibiotic depends on the type of bacterial isolates from a given nursery and their sensitivity pattern, which should be regularly reviewed. Since in our country the major organisms causing neonatal sepsis are *Klebsiella*, *E. coli*, *S. aureus*, the initial choice may be a combination of aminoglycoside (amikacin/gentamicin) along with a penicillin or cephalosporin. When *Pseudomonas* is suspected carbencillin or ceftazidime should be used. The therapy may be modified in light of the culture reports and clinical response. Antimicrobial therapy should be given for 14 days for proven sepsis without complications and for atleast 21 days for meningitis.

Newer treatment modalities

Exchange Transfusions

Several studies have shown significant improvement in neonatal survival with the use of exchange transfusion as an adjunct to antimicrobial therapy [19]. Available evidence suggests that exchange transfusion holds promise for treatment of neutropenic septicemic, infants with disseminated intravascular coagulation and with sclerema.

Granulocyte Transfusions

Several studies have shown improved survival with granulocyte transfusion in neonates with septicaemia with neutropenia and neutrophil storage pool depletion [18] (immature to total neutrophil ratio greater than 0.8). However, Stork et al [19] in a prospective randomised study failed to show any benefit of granulocyte transfusion amongst neutropenic, septicemic neonates. However, granulocyte transfusions can currently be recommended only in severely neutropenic neonates unresponsive to conventional therapy and in institutions with facilities for leucopheresis.

Intravenous Immunoglobulin (IVIG)

The availability of IVIG has prompted its use in prophylaxis and treatment of neonatal sepsis, especially in the severely immunodeficient very low birth weight neonates. IVIG in doses ranging from 120-150 mg/kg has shown significant reduction in mortality.

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