*Personal Practice*

# Neonatal Sepsis

**N.B. Mathur**

## Definitions and Current Concepts of Terminology

Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia in the first month of life(l). Once bacteria gain access to the bloodstream, mechanisms are activated by the host for their elimination. Usually the bacteria are efficiently cleared by the monocyte-macrophage system after opsonization by antibody and complement. Sometimes, however, a systemic inflammatory response syndrome is established and can progress independently of the original infection (2). In many patients with sepsis, it is difficult to document a bacterial cause. The term systemic inflammatory response syndrome includes several stages of infection from sepsis, sepsis syndrome and early septic shock to refractory septic shock, which can eventuate in multiple organ dysfunction and death (3). *Fig. 1* depicts the clinical criteria for the diagnosis of these conditions (4).

Sepsis is considered when there is a systemic response to possible infection. Evidence of bacteremia or an infectious focus is not required. When a pathogen is recovered from blood cultures or identified by other means, sepsis caused by that organism is the preferred term. It is felt that the term septicemia should be abandoned to avoid confusion. Septic shock ensues when systolic blood pressure drops below the 5th percentile or peripheral hypoperfusion (poor capillary refill) is present. If shock responds promptly to parenteral fluid administration and pharmacologic treatment, it is defined as early septic shock (hyperdynamic or warm phase of septic shock). Refractory septic shock is hypodynamic or cold phase of septic shock, which persists beyond 1 hour inspite of adequate treatment.

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## Current Concepts in Pathophysiology

The systemic inflammatory response depends on the host's ability to recognize foreign substances. Although this response facilitates microbial clearance, the host must pay the price of some tissue damage to achieve this goal. *Fig. 2* depicts a schematic outline of the putative pathophysiologic events in the septic process (4).

Earlier it was believed that the bacteria or their cell wall components (endotoxins of Gram-negative organisms and lipoteichoic acid-peptidoglycan complex of Gram-positive bacteria) were largely responsible for the direct toxic effects on tissues. Recent research indicates that the physiologic effects generated by bacterial infections are largely mediated by interaction of pro-inflammatory cytokines activated in response to the presence of microbial components within the vascular compartment(5-ll). The prominent among these cytokines are tumor necrosis factor (TNF)

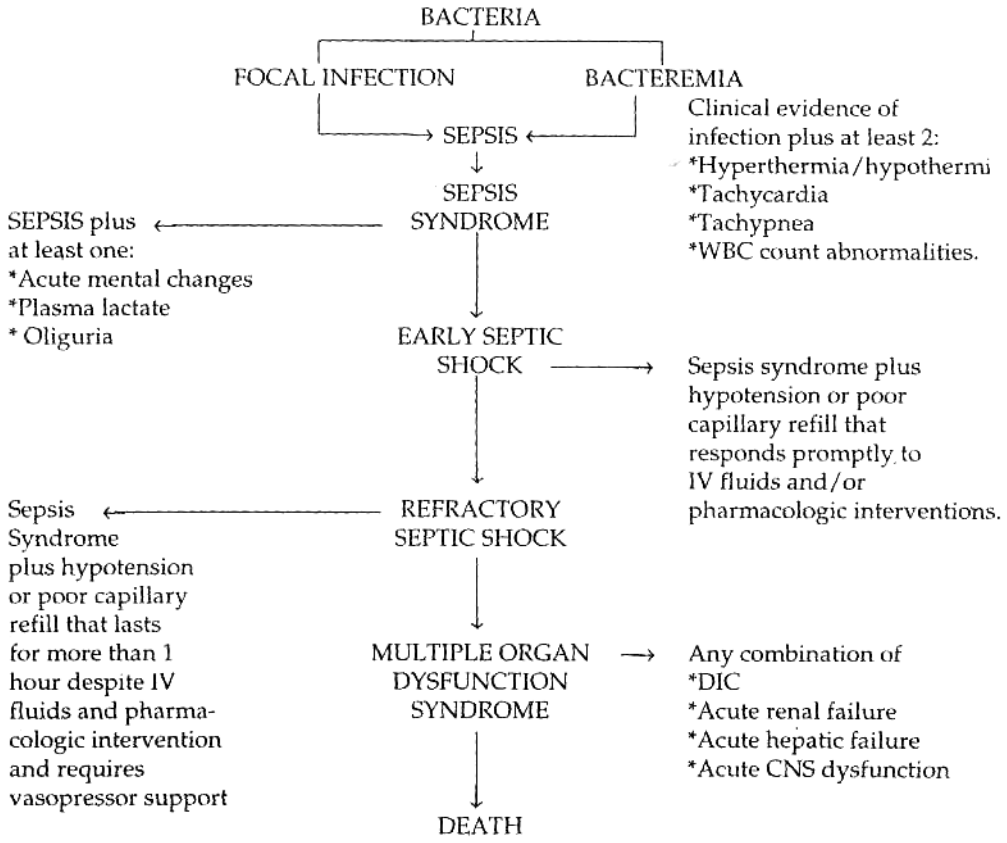


*Fig. 1. Proposed terminology of the septic process (systemic inflammatory response syndrome). The risk of dying increases as one moves down the algorithm. Adapted from Saez-Llorens and McCracken GH(4)*

and interleukin (IL)-l, which are rapidly produced by macrophages, endothelial cells and many other cellular elements on exposure to bacterial products. Administration of these cytokines has induced fever, acute phase changes, hypotension and endothelial injury, alterations similar to those observed after endotoxin or bacterial inoculation(12-16). Several studies have demonstrated elevated TNF level in adults with bacterial sepsis which correlated with mortality rates(17,18). Data regarding plasma cytokines in children with sepsis is scanty. However, higher levels of IL-1, IL-6 and TNF have also been observed in children(14-20) and neonates(21-23) with sepsis and found to correlate with fatality. A number of other mediators like IL-8, platelet activating factor, interferon gamma, macrophage derived proteins, arachidonic acid metabolites and some still unidentified substances also amplify the systemic inflammatory response. Two components of complement C3a and C5a are cationic peptides with anaphylatoxin activities capable of provoking release of histamine from mast cells and basophils, contraction of smooth muscle and increased capillary permeability, which can aggravate hypotension in sepsis(24).

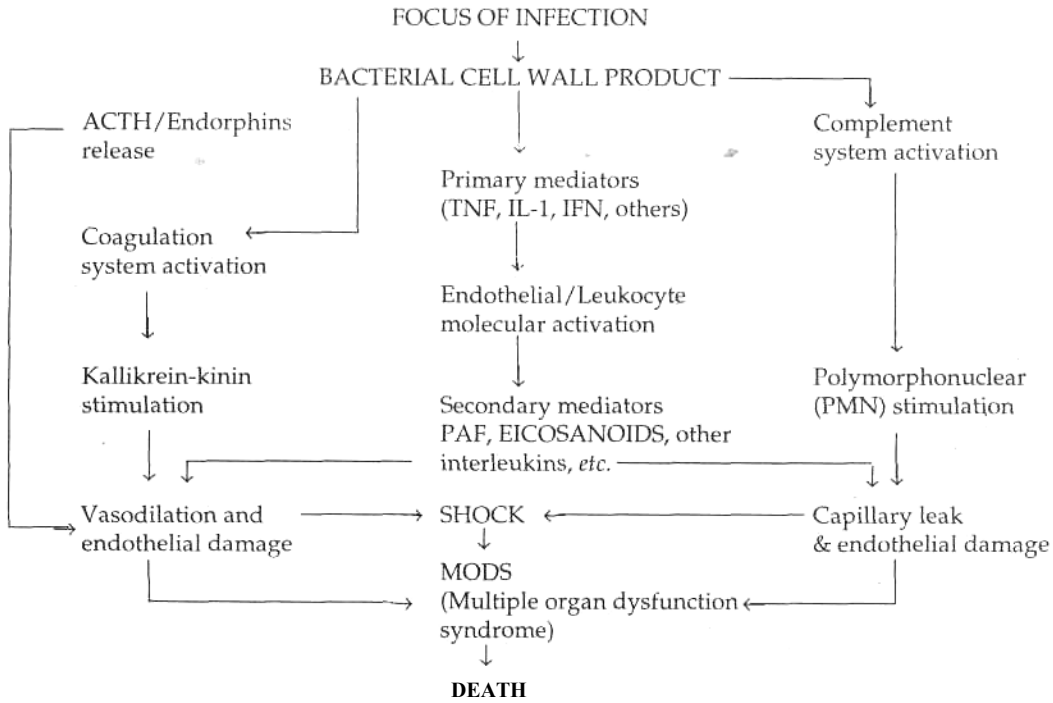


*Fig. 2. Hypothetical pathophysiology of the septic process. Adapted from Saez-Llorens and McCracken GH(4).*

The intrinsic coagulation pathway may be activated by a direct interaction between endotoxin and coagulation factor XII. Endotoxins can induce the release of the tissue factor by monocytes and endothelial cells directly or through cytokines. Thus factor VII and the extrinsic coagulation pathway is also activated, leading to the development of disseminated intravascular coagulation. Factor XII also stimulates the conversion of prekalikrein to kallikrein and the subsequent conversion of kininogen to bradykinin which is a potent vasodilator(25).

Polymorphonuclear leukocytosis is frequently seen with sepsis. The release of neutrophils from marrow reserves is induced by endotoxin, cytokines, complement or granulocyte-colony stimulating factors (26,27). Neutropenia may occur due to inadequate marrow function, increased destruction or consumption of circulating neutrophils or margination and attachment of neutrophils to endothelial cells. Bone marrow granulocyte reserve pool is small in neonates and neutropenia is associated with a high fatality.

Neutrophils initiate phagocytosis and microbial killing by degranulation and release of several proteolytic enzymes and toxic oxygen radicals, a process that can also cause damage to nearby tissues. Additionally, neutrophil induced digestion of surrounding tissue contributes to separation of tight endothelial cell junctions and development of capillary leak syndrome and septic shock.

## Bacteriology

The microbial etiology of neonatal sepsis is variable and often changes temporally. Group B streptococcus is a common cause of neonatal sepsis in the West but infrequent in India and other tropical countries. In Indian studies, Gram negative organisms have been more frequently responsible for sepsis (65-85%) as compared to Gram positive organisms. Commonly found organisms are *Klebsiella, E. coli, Pseudomonas, Staph. aureus* and coagulase negative *Staphylococcus. Enterobacter, Citrobacter, Proteus mirabilis* and *Serratia,* are also seen. Group B streptococcus is an infrequent cause.

## Extent of Problem

Neonatal sepsis continues to be a major cause of neonatal mortality in India accounting for one-fourth to nearly half of neonatal deaths (28-30). Fatality due to sepsis ranges between 40 and 65% (31-34). Preterm and small for gestational age infants are more prone to develop sepsis than term and appropriate for gestational age infants.

In the United States, sepsis (positive blood or cerebrospinal fluid culture) accounts for 30% of the neonatal deaths(35) and the incidence of neonatal sepsis among all live births ranges from 2-8 per 1000(35,36). The overall fatality in neonatal sepsis in the USA remains at 25%. In addition, nearly 50% of infants die when there is a fulminant onset of sepsis within the first day of life and 80-90% of neutropenic infants may die of sepsis when there is depletion of the bone marrow neutrophil storage pool(35). The mortality rate is close to 100% in infants with early onset Group B streptococcal sepsis weighing less than 1500 g at birth compared to a rate of 20% in infants weighing more than 2500 g at birth(37).

The risk of fatality is expected to increase with progressive stages of systemic inflammatory response syndrome and the fatality in septic shock in adult patients is 80%. Correlation of fatality with the stage of the systemic inflammatory response syndrome has not been studied in neonates. In a recent study(38), designed to evaluate risk factors at admission in fatal sepsis in neonates brought to a referral neonatal unit, we observed that the independent factors significantly associated with death were neutropenia, metabolic acidosis, increased prothrombin time and refractory septic shock (Odd's ratio 0.9, 1.14, 1.04 and 11.82, respectively). Recognition of these factors at admission of septic neonates to referral units are important for targeting them for intensive care and immunotherapy.

### *Investigatory Approach*

It is important to note that infants with bacterial sepsis may have negative blood cultures. The investigatory approach is summarized in *Table I.*

## Management

The important aspects of management include: *(i)* Administration of parenteral fluids, vasoactive agents and oxygen to ensure perfusion and oxygenation of vital tissues; *(ii)* Antimicrobial agents and early drainage or removal of purulent foci for bacterial eradication; and *(iii)* Immunotherapy.

### *Hemodynamic Stability and Tissue Oxygenation*

Management of fluid and electrolyte balance is vital in the treatment of sepsis, particularly when shock is present. Every effort to enhance oxygen delivery to the tissues must be made. The increased work of breathing in patients with sepsis syndrome and septic shock can increase tissue oxygen consumption. This problem can be overcome by using assisted ventilation. Extremes of body temperature should be avoided because they increase oxygen

**TABLE—I** *Investigatory Approach to Neonatal Sepsis.*

| |
|---|
| *Evidence for infection* |
| Culture from blood, CSF, urine Demonstration of a micro-organism in tissue, fluid or buffly coat smear, using Gram stain or Acridine orange stain, Antigen detection (CSF). |
| *Evidence for inflammation* |
| Leukocytosis, increased immature/total neutrophil ratio, neutropenia. |
| Pleocytosis in CSF, synovial or pleural fluid. |
| Acute phase reactants: CRP, ESR. |
| Cytokines: IL-6 |
| *Evidence for multiorgan dysfunction* |
| Metabolic acidosis: pH, $PCO_2$ Pulmonary functions: $PO_2$, $PCO_2$ Renal functions: Blood urea, creatinine Hepatic functions: Bilirubin, SGPT, SGOT Disseminated intravascular coagulation: Coagulation profile, fibrin split products. |

requirements(39,40).Infants in shock require above normal oxygenation, ventilation and circulation and management includes supplemental oxygen(41). Breathing support by bag and mask ventilation should be started unless respiration is judged adequate. Slow and shallow respirations are not sufficient in the presence of shock. Frank shock constitutes an indication for controlled assisted ventilation(42).

Common errors in treating shock include the use of a diluted fluid, use of too little fluid or slow administration of fluid. Only those fluids at least isotonic to serum have a role in shock. Isotonic fluids like lactated Ringer's solution and 0.9% normal saline must fill the entire extracellular fluid compartment. More dilute solutions are shared with the intracellular space as well. Bolus therapy is usually given in aliquots of 20 ml/kg rapidly (in 4-5 minutes) (43). If two boluses 'of crystalloid solutions fail, colloid solutions (plasma, albumin or dextran) may be useful.

Dopamine is the initial inotropic agent of choice in septic shock because of its beta adrenergic effects on the myocardium, alpha adrenergic effects on the peripheral vasculature and dopaminergic effects on renal and splanchnic vessels. If myocardial function is decreased and systemic vascular resistance is elevated, the combined use of dobutamine and low doses of dopamine can be helpful.

Electrolyte abnormalities, metabolic acidosis and decreased level of calcium phosphate and glucose may be present and should be corrected to achieve optimal myocardial function. Guidelines for the management of septic shock are summarized in *Fig. 3*.

*Bacterial Eradication*

Prompt administration of antibiotics empirically is important. The choice of initial antibiotics depends on the likely etiologic agent, the microbial susceptibility patterns in the nursery, tissue penetration, toxicity, cost and availability of the antibiotic.

The traditional Western recommendation for initial antibiotics in neonatal sepsis is a combination of ampicillin with an aminoglycoside and may be used in respiratory infections and when sepsis is suspected. However, resistance to ampicillin is frequently observed (31). Third generation caphalosporinss (cefotaxime, ceftazidime) are more useful in Gram negative infections commonly encountered in India. They are not effective against *Listeria* and *Enterococcus*. However, these pathogens have not been reported commonly from India. Aminoglycosides

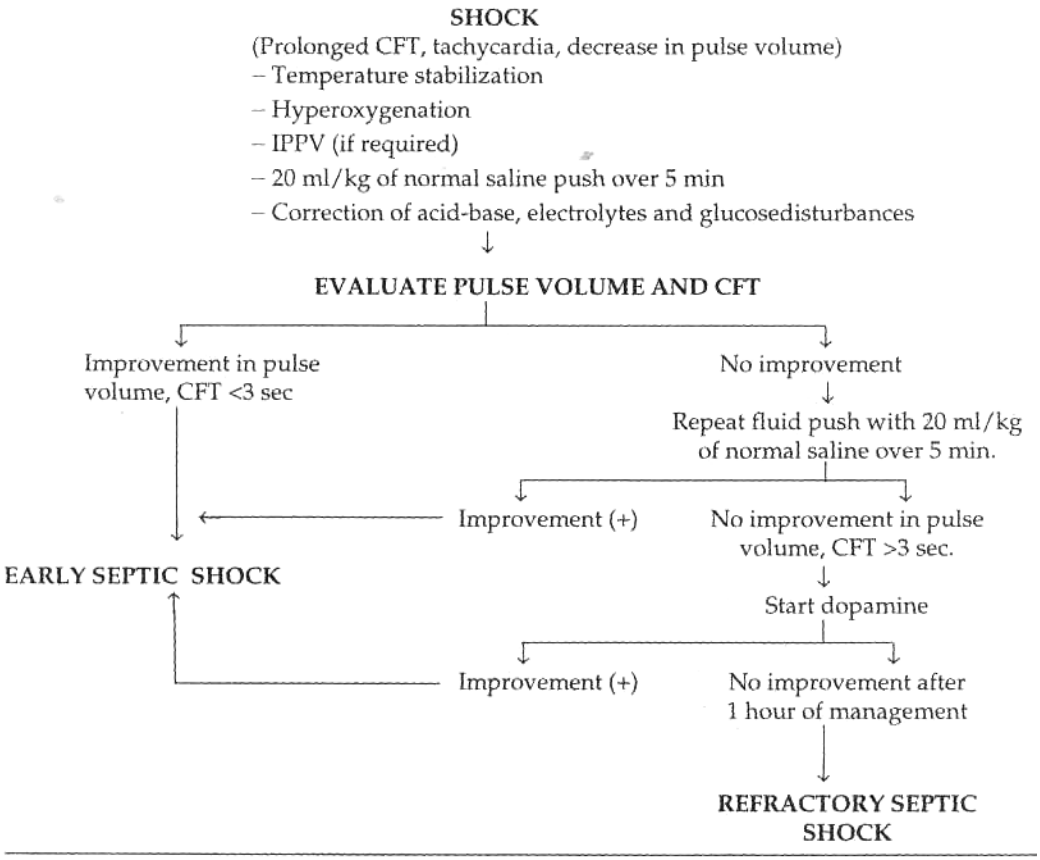


*Fig. 3. Guidelines for the management of septic shock.*

continue to remain useful against E. *coli, Klebsiella* and *Pseudomonas*

The choice of antibiotics should be re-evaluated when results of cultures and susceptibility tests become available and if the patient does not respond clinically. Ciprofloxacin is being used in life threatening sepsis when the organism isolated is resistant to all the other available antibiotics. The duration of therapy depends on the initial response to the antibiotics but should be 7 to 10 days in most infants with sepsis. The minimal duration of therapy is 21 days for infants with meningitis caused by Gram negative enteric bacilli. Any purulent foci or abscesses should be drained.

*Exchange Transfusion*

Theoretic and documented benefits of exchange transfusions in neonatal sepsis include the following(44-50): *(i)* Increase in circulating levels of C3 immunoglobulins, particularly IgM and IgA which may enhance defense mechanisms; *(ii)* Removal of bacteria and bacterial toxins; *(iii)* Improvement in the opsonic activity against the offending organism; *(iv)* Correction of neutropenia with enhanced neutrophil function; *(v)* Improvement in perfusion and tissue oxygenation; *(vi)* Decrease in hemorrhagic complications by correcting the platelet count and plasma coagulation sys tern and removing fibrin degradation products; and *(vii)* Resolution of sclerema

A survey of the outcome of the published reports of exchange transfusion in neonatal sepsis shows that the survival in nine non-randomized predominantly retrospective trials was 62% for infants receiving exchange transfusions and 38% for those in the control group(51-59). Similarly, the survival of septic neonates in six uncontrolled trials of exchange transfusions was also 62% (46,58,60-63) *(Table II)*. Unfortunately none of these studies were randomized and in many instances the controls were not from simultaneous years. In addition to design problems, patient selection and care varied remarkably (35). A recent randomized controlled trial in septic neonates with neutropenia recorded significant improvement in neutrophil count and function. The survival was 65% in the exchange group and 30% in controls (p=0.7)(48).

In summary, exchange transfusion in neonatal sepsis is appealing, particularly in the developing world because it is more readily available and affordable than granulocyte transfusion and IV immunoglobulins. Unfortunately, its effectiveness has not been adequately evaluated. We prefer to do exchange transfusion in neonatal sepsis associated

***TABLE II*** *- Survival of Septic Infants in Relation to Exchange Transfusion*

| Authors | Year | Survival n (%) | |
|---|---|---|---|
| | | Transfused | Not transfused |
| *Controlled trials* | | | |
| Prodhom *et al.*(51) | 1974 | 7/8 (88) | 0/8 (0) |
| Tollner *et al.*(52) | 1977 | 10/10 (100) | 5/10 (50) |
| Pearse *et al.*(53) | 1978 | 13/19 (680 | 7/17 (41) |
| Belohradsky *et al.*(54) | 1978 | 37/74 (50) | 60/132 (45) |
| Courtney *et al.*(55) | 1979 | 23.34 (68) | 4/14 (29) |
| Lemos(56) | 1981 | 8/8 (100) | 0/14 (0) |
| Bossi *et al.*(57) | 1981 | 12/22 (55) | 7/13 (54) |
| Narayanan *et al.*(44) | 1984 | 8/20 (40) | 2/20 (10) |
| Xanthou *et al.*(58) | 1985 | 25/44 (57) | 18/62 (29) |
| Gross *et al.*(59) | 1987 | 7/11 (64) | 8/11 (73) |
| *Randomized controlled trial* | | | |
| Mathur *et al.*(48) | 1993 | 13/20 (65) | 3/10 (30) |
| *Uncontrolled trials* | | | |
| Shigeoka *et al.*(60) | 1978 | 12/15 (80) | |
| Vain *et al.*(46) | 1980 | 7/10 (70) | |
| DeCurtis *et al.*(61) | 1982 | 2/2 (100) | |
| Hall *et al.*(62) | 1983 | 30/41 (73) | |
| Togari *et al.*(63) | 1983 | 7/10 (70) | |
| Xanthou *et al.*(58) | 1985 | 37/76 (49) | |
| Total | | 95/154 (62) | |

with neutropenia, sclerema, earliest evidence of disseminated intravascu-lar coagulation and metabolic acidosis (pH <7.2).

*Granulocyte Transfusion in Neonatal Sepsis*

This adjunct to therapy of neonatal sepsis may be useful, particularly in neutropenia(64). Few studies of transfusion of adult granulocytes have shown promising results(65-71). However, they differ in study design, entry criteria, method of polymorphonuclear collection, dose and frequency of granulocyte transfusion. The number of granulocytes transfused varies from 0.1 to 1.8 x $10^9$. Untoward effects could be graft versus host disease, transmission of hepatitis, cytomegalovirus, leukocyte aggregation, sequestration of leukocytes in lungs and volume overload. Hence this modality should be used with caution in cases not responding to conventional therapy.

*Immunoglobulins*

Intravenous (IV) immunoglobulins have been evaluated for prophylaxis as well as treatment of neonatal sepsis. Recent prophylactic trials have not shown any beneficial effect of IV immunoglobulins in preterm neonates. However, improved survival has been reported with their therapeutic use in prospective randomized trials in cases of established sepsis(72-75). A recent study(73) is particularly relevant in the Indian context as it included cases of neonatal sepsis caused predominantly by Gram negative organisms. In a prospective randomized trial evaluating pentaglobin (Biotest Pharma, Germany), the authors observed a mortality of 3.3% (1/30) in the immunotherapy group as compared to 20% (6/30) in the control group. The dose varies from 250-700 mg/kg and can be given as a single shot(76).

*Other Therapeutic Agents*

Newer agents being evaluated include human monoclonal antibodies, fibronectin, granulocyte-macrophage colony stimulating factor/ vitamin C, levamisole and pentoxifylline (2,77). In the future, agents manipulating the neonate's own defense system are likely to play a major role in the management of severe neonatal sepsis.

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## NOTES AND NEWS

### EXHIBITION ON CLINICAL PEDIATRICS

An exhibition of photographs of clinical pediatric cases is being organized during the National Conference of IAP at Ahmedabad. Two copies of photographic prints of up to post card size (color or B&W) are solicited from IAP members and Post Graduate students from their collection along with a brief summary of the case. Contributions will be gratefully acknowledged. Kindly correspond with: Dr. Hemant A. Joshi, Joshi Children Hospital, Opp. Railway Station, Virar-401 303 (Maharashtra), *Tel:* 0252-382709 or Dr. Niranjan Shendurnikar, B/142, Jagannath Puram, Near Lalbaug Crossing, Baroda 390 001, (Gujarat) Tel.: 0265-446446.

### IMMUNIZATION RECORD

Newer vaccines would be introduced from time to time, and Immunization Schedules may also need some changes from time to time. An 'Immunization record' has been designed to accommodate all such changes. The booklet also has some essential information for the parents. The price of the booklet is Rs. 10/-. For Doctors a packet of 25 copies is available for Rs. 200/- and a packet of 55 copies for Rs. 400/-. The charges include postage. The amount can be sent by a Demand Draft or Money Order to Dr. Yash Paul, A-C-4, Gayatri Sadan, Jai Singh Highway, Bani Park, Jaipur 302 016.