Neonatal Shock

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Abstract

Shock or circulatory collapse is one of the most common emergencies confronted in the Neonatal ICU. Decreased tissue oxygen delivery is the underlying pathology which may result from decreased preload, cardiac contractility/output or imbalance in afterload. Prompt recognition is based on clinical findings suggestive of decreased peripheral or specific organ perfusion. Confirmation by newer methods like Superior vena cava blood flow by Doppler and use of therapeutic targets like Mixed venous oxygen saturation have favourably changed the outcome of management of shock. This review is aimed at highlighting certain facts and clarifying a few controversies confronted during treatment.

Key words: Shock, Sepsis, Newborn, Management.

Introduction

Shock can be defined as an acute state in which the delivery of oxygen is inadequate to meet the demands of the tissues. Normal circulatory function is the prime prerequisite to meet oxygen demand. The sick neonate needs special mention when it comes to shock as he is ill-equipped to handle the major and multiple changes that occur in the perinatal period. It is thus not surprising that nearly 50% of newborns admitted to the neonatal ICU receive some form of treatment for clinically, or otherwise diagnosed, shock.

Etiology, pathophysiology and clinical features

A multitude of factors, most often in combination but sometimes independently contribute to the development of shock(1):

Hypovolemia

This contributes to decrease in preload due to blood loss or reduced venous return. The baby presents with tachycardia, thready pulse, pallor, and no hepatosplenomegaly. It may result from the following causes:

a. Fetomaternal hemorrhage

b. Vasa previa

c. Rupture of umbilical cord seen in precipitate deliveries

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d. Inadequate placental transfusion

e. Severe dehydration

f. Obstruction of venous return due positive pressure ventilation, tension pneumothorax, cardiac tamponade(2).

Cardiogenic causes

The immature myocardium of a preterm neonate and additional insults in the form of hypoxia and infections jeopardise cardiac contractility. The presence of shunts through persistent fetal channels further complicate the estimation of cardiac output by standard methods of measurement. The common causes of cardiogenic shock are:

a. Cardiomyopathy: one of the commonly seen cause of cardiac dysfunction is asphyxia : antepartum or intrapartum, respiratory failure, impaired oxygen transport due to severe anemia or hemoglobinopathy.

b. Metabolic causes like severe hypoglycaemia and hypocalcemia

c. Dysrhythmia

d. Congenital malformation-like complex cardiac anomalies - Any newborn with shock and hepatomegaly, cyanosis, a cardiac murmur, or differential upper and lower extremity blood pressures or pulses should be suspected to have a ductal dependent circulation

e. Inborn errors of metabolism resulting in hyperammonemia or hypoglycemia (may simulate septic shock) and appropriate

laboratory tests should be obtained to rule out these conditions.

Sepsis

Septic shock should be suspected in any newborn with tachycardia, respiratory distress, poor feeding, poor tone, poor colour, diarrhoea, or reduced perfusion, particularly in the presence of a maternal history of chorioamnionitis or prolonged rupture of membranes(2). The sensitivity and positive predictive value of the screening tests can be increased by the number of parameters considered. CRP, IL6, IL8, TNFalpha, procalcitonin are used as markers of early sepsis. Blood culture is the gold standard for diagnosis of sepsis. It is important to distinguish newborn septic shock from cardiogenic shock caused by closure of the patent ductus arteriosus in newborns with ductal-dependent complex congenital heart disease. Newborn septic shock is typically accompanied by increased pulmonary vascular resistance and artery pressures. PPHN can cause right ventricle failure with right to left shunting at the atrial/ductal levels causing cyanosis.

The pathogenesis of septic shock may differ in more than one ways from the others(3). Animal studies have proven that endotoxemia leads to myocardial depression in sepsis and results from global myocardial ischemia caused by reduced coronary blood flow. Endogenous myocardial depressant substances produced in response to sepsis cause direct myocardial damage without affecting coronary perfusion.

Among the most prominent clinical and hemodynamic features of septic shock are low systemic vascular resistance and decreased peripheral use of oxygen and other nutrients. Another is that tissue perfusion is adequate but cellular metabolism is reduced. Vascular imbalances result in the maldistribution of blood flow. Neutrophil margination along with platelet aggregation lead to release of many mediators. Activated leucocytes generate superoxide radicals, that directly damage cells. Apart from important mediators derived from arachidonic acid (prostaglandins and leukotrienes),local mechanism of vascular control is endothelium-derived relaxing factor, or nitric oxide, a potent endogenous vasodilator in the microcirculation

Drugs

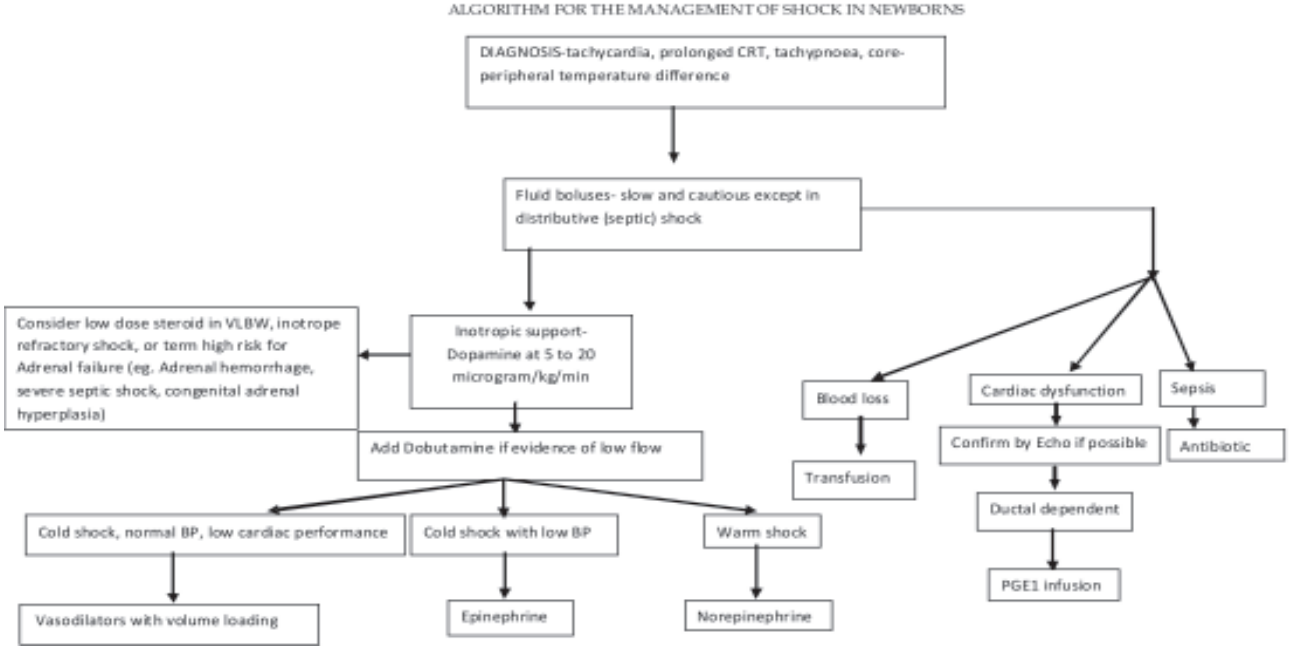
This forms a part of the distributive shock spectrum especially when hypovolemic infants, in whom blood pressure has been maintained by vasoconstriction, are given vasodilators such as PGE, isoproterenol or magnesium.

Delivery results in the removal of the low resistance placental circulation. The sudden workload on an immature myocardium to meet systemic demands which until then was supplied by the placental circulation is one of the first major changes to take place. If a tissue is inadequately perfused, as in hypovolemic or cardiogenic shock, the decrease in oxygen delivery causes a shift from aerobic to anaerobic metabolism, resulting in the accumulation of lactate, the product of anaerobic glycolysis. Hypoperfusion also decreases the intracellular stores of high-energy phosphates. Although many patients with septic shock have elevated blood lactate concentrations, a substantial number (perhaps one third) do not.

Diagnosis

The standard parameters used for the diagnosis of shock are tachycardia, prolonged capillary refill time, oliguria, core-peripheral temperature difference, hypotension, hyperkalemia, and lactic acidosis(1,4). Most if not all of the above have been found to have drawbacks when used in the diagnosis of shock and as therapeutic endpoints during management. A study published in 1997 showed that there was poor correlation between the clinicians' ability to estimate cardiac index and the objectively measured value, although some variation was seen among the various levels of seniority(5).

Capillary refill time (CRT) measured in the hand or foot of a newborn infant in the first 5 days of life is a relatively subjective measurement with an endpoint that is not easy to define and a wide range of values in normal infants(6). Many factors influence the CRT significantly, like environmental, axillary, and skin temperatures. An Australian study demonstrated that core peripheral temperature difference and CRT are imperfect bedside tests for detecting low blood flow in the first day after birth(7). However, these are used by many



clinicians as they are the only non invasive, repeatable assessment parameters available(4)!

Many a time shock (inadequate oxygen delivery) has been considered equivalent to hypotension. It is well recognised that low BP is a late manifestation of shock. But the disadvantages of relying on BP (systolic or mean arterial) are manifold. Invasive and continuous BP monitoring by arterial catheterisation is now being increasingly used in many NICUs. Monitoring of intra-arterial blood pressure through an umbilical or peripheral arterial catheter is widely accepted as the optimum method.[4] To avoid the risks associated with this many methods of non invasive BP monitoring were devised. However , one of the most commonly used- the Dinamp oscillometric method in VLBW babies is less reliable in the lower pressure range and specifically, it tends to overestimate pressure in hypotensive infants(8).

Large numbers of very low birthweight (VLBW) infants receive treatment for hypotension during the first day of life. Normal values of BP for very low birth weight infants have been studied extensively(9,10) and it is well accepted by clinicians that the lower limit of mean BP is equivalent to the gestational age in weeks. It is to be noted that this standard is true only in the first 48 hours of life. The fallacy in the rule of thumb is obvious from the study which showed that for a similar gestational age, small for gestational age infants had lower blood pressure compared to appropriate for gestational age infants(9).

Even if the barriers of accurate BP measurement and objective standards for normal limits are overcome, a well designed study demonstrated that normal blood pressure cannot necessarily be equated with normal systemic flow(11). Echocardiographic assessments of perfusion performed in the first 48 h of postnatal life revealed no evidence of a positive association between blood pressure and volume of blood flow(12). Low blood pressure does not correlate with poor perfusion in the first 48 h of postnatal life in sick preterm infants. Watkins et al found that hypotension was strongly associated with intraventricular haemorrhage, but not with periventricular ischaemic lesions(13). And finally, even if hypotension is related to cerebral haemorrhage, blood pressure management directed at these population-based thresholds alone may not prevent brain injury in this vulnerable population(14).

This lead to the search for an accurate marker of peripheral and brain oxygen delivery. A landmark finding by Kluckow and Evans that measurement of SVC flow (by Doppler) can serve the above purpose(15). Ventricular outputs cannot be used to assess systemic blood

flow in preterm infants and term infants with persistent fetal circulation because they are confounded by shunts through the ductus arteriosus and atrial septum. However, flow measurements in the superior vena cava (SVC) can assess blood returning from the upper body and brain(15,16). In infants born after 36 weeks, median SVC flow rose from 76 ml/kg/min on day 1 to 93 ml/kg/min on day 2; in uncomplicated very preterm infants, it rose from 62 ml/kg/min at 5 hours to 86 ml/kg/min at 48 hours. The lowest SVC flow for the preterm babies rose from 30 ml/kg/min at 5 hours to 46 ml/kg/min by 48 hours (15). This parameter has scope to be used for response to therapy too.

The use of continuous SVC Oxygen percentage(mixed venous oxygen saturation) (17) as a standard therapeutic target has improved outcome(18). Specifically for research purposes and less so for clinical use, oxygen consumption ,energy expenditure and resting metabolic rate are found to have variations with severity of septic shock which can be used for determining improvement or deterioration(19,20).

Biochemically, apart from the usual measurements of serum potassium, arterial blood gas analysis and the lactic acidosis, during critical illness, glucocorticoid secretion markedly increases, but the increase is not discernible when only the serum total cortisol concentration is measured. Measuring serum free cortisol concentrations in critically ill patients with hypoproteinemia may help prevent the unnecessary use of glucocorticoid therapy(21).

Treatment

The determination of the underlying cause and the hemodynamic alterations resulting from it will guide therapy.

Expansion of intravascular compartment:

In post hemorrhagic or hypovolemic shock, immediate re-expansion of blood volume is imperative and lifesaving. Blood, when indicated (PRBC transfusion) as an intervention for poor circulation offers the opportunity to change multiple factors within oxygen delivery without increasing oxygen consumption, and may contribute to protection against early brain injury in premature newborns(22,23). There is evidence to suggest that restrictive transfusion guidelines may be neurologically more damaging to the preterm infant(24).

Controversies regarding the type of fluid to be given for volume expansion are ongoing. Colloids are believed to stay longer in the intravascular compartment because of their high oncotic pressure. However, fluid movement across the capillary wall is not solely related to the net difference in the hydrostatic and oncotic pressure across the capillary endothelium, but also on the permeability of the capillary wall .In sick infants patients with capillary leak syndrome, plasma protein infused intravenously may leak into the interstitial space, resulting in interstitial oedema(25). Isotonic saline is as effective as 5% albumin for treating hypotension in preterm infants, and it has the additional advantage of causing less fluid retention in the first 48 hours(4). Moreover, crystalloid solutions are less expensive than colloid solutions

Several authors have proposed that hypotension in preterm and sick term infants is most often primarily a result of poor peripheral vasoregulation, with myocardial dysfunction or absolute volume depletion being less often the major cause(26). Unless there is clear evidence of hypovolaemia, clinicians should exercise caution when prescribing volume expansion in neonates as this has been found to be associated with increased neonatal deaths(27). The ill effects of unwarranted volume expansion can be patent ductus arteriosus and myocardial dysfunction.

Inotropes

Around 20% of very low birthweight infants admitted to a neonatal intensive care unit become hypotensive within 24 hours of their admission. Standard treatment is either expansion of the circulating volume by the infusion of fluids or by using dopamine to improve cardiac function. Cardiac dysfunction was an important feature in very low birthweight infants with shock. It is speculated that volume expansion may not always be the most appropriate first line treatment for such infants. Observations from a study by Gill et al in 1993 suggest that dopamine should be used

earlier in the treatment of neonate(28). The initial resistance the drug faced was due to the worry of causing intraventricular hemorrhage in preterm infants but cautious use of cardiovascular support to treat early systemic hypotension in low birth weight infants seems to be safe. Moreover, the duration and severity of systemic hypotension per se have been related with altered neurodevelopment(29).

The Cochrane library intervention review indicate that dopamine is more effective than dobutamine in the short term treatment of systemic hypotension in preterm infants(30). There was no evidence of an effect on the incidence of adverse neuroradiological sequelae (severe periventricular haemorrhage and/or periventricular leucomalacia), or on the incidence of tachycardia. Dopamine is more effective than Dobutamine in raising and maintaining MAP above 30 mm Hg; however Dopamine does not increase LV output. On the contrary, dobutamine produces a greater increase in blood flow than dopamine. This finding has been substantiated by the Cochrane review comparing the two for increase in flow(31). Roze et al showed a dose dependent increase in mean arterial blood pressure with dopamine infusions of 5–20 µg/kg/min(32). Range of use of Dobutamine is 5 to 20 microgram/kg/min.

For shock resistant to dopamine and dobutamine: Low-dose epinephrine has been tried and is now frequently used in many centres. It (low dose)does not cause vasoconstriction in the renal or mesenteric circulations during normovolemia or hypovolemia. High doses of epinephrine above 1.6 µg/kg·min may cause renal or mesenteric ischemia, in either the normovolemic or hypovolemic neonate(33). An Indian report reveals good response to adrenaline specifically in septic shock(34). Dopexamine, a relatively new synthetic catecholamine, has been shown to be effective in raising blood pressure and improving arterial pH and urine output(35).

Terlipressin and vasopressin have now found their part in the management of refractory hypotension in newborns(2).

Steroids

Significant association, independent of gestational age and birth weight, exists between serum cortisol and the lowest blood pressure registered in the immediate postnatal period. The empirical use of Hydrocortisone may be as effective as dopamine in treating primary hypotension, but there are no data regarding the long-term safety of steroids used for this indication. There is insufficient evidence to support the routine use of steroids in the treatment of primary or refractory neonatal hypotension.

The findings of Ng et al demonstrate that relatively low-dose hydrocortisone administration improves cardiovascular stability and decreases the need for vasopressor support in hypotensive VLBW neonates(36). Based on the available information, it is reasonable to consider the use of low-dose hydrocortisone in VLBW neonates who remain hypotensive despite vasopressor support or cannot be weaned off vasopressors(37).

Antibiotics

Antibiotic usage protocols are based on the culture positivity and the sensitivity patterns of the specific centre and needs renewal from time to time. Audits held in association with the in-hospital infection control committee will help outline antibiotic guidelines. Third generation Cephalosporins with Aminoglycosides like Gentamicin or Amikacin are usually the initial choice in many centres.

Management of Persistent Pulmonary Hypertension

Inhaled NO therapy is the treatment of choice of uncomplicated PPHN(2). Addition of sodium bicarbonate to the treatment strategy is advantageous as PPHN can reverse when acidosis is corrected .When the cardiac output is reduced due to increased after load, milrinone or inamrinone may be added. ECMO remains the therapy of choice for patients with refractory PPHN and sepsis.

Supportive management

The infant with shock many a time presents as multi organ dysfunction and may need support in the form of blood product

transfusions and coagulation factors, oxygenation and ventilation. Others include renal replacement therapy, anticonvulsants and cerebroprotection measures for asphyxia, antibiotics, thermoneutral temperature and special care of nutritional status and positive energy balance ,to mention a few. It is beyond the scope of this article to deal with each of these problems in detail.

Outcome

Early goal-directed therapy provides significant benefits with respect to outcome in patients with shock(38). Community based studies have clearly demonstrated that management of newborn (and paediatric) septic shock according to the ACCM guidelines has improved survival beyond doubt(39). The use of definite physiological targets of therapy improve outcome(18). Shock in newborns is associated with death or significant sequelae like cerebral palsy, severe developmental delay, hearing impairment, blindness. Permanent damage to other end organs is also known(1). Risk factors for severe after effects are lower gestational age, low birth weight, perinatal asphyxia, acidosis and gram-negative septicaemia(40).

Summary

The prompt and early recognition of neonatal shock is essential to decrease the morbidity and neurological damage. The diagnosis of the underlying problem and the hemodynamic changes associated with each type dictates the management. Fluids, inotropic support, judicious use of steroids and supportive measures are the mainstay of treatment.

References

1. Evans N, Seri I. Cardiovascular compromise in the newborn infant. In Taeusch WH, Ballard RA, Gleason CA. Avery's Diseases of the Newborn. 8th edition, W.B. Saunders, Philadelphia. 2005; 398-409.
2. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine: Crit Care Med 2009; 37(2): 666-688.
3. Parillo JE. Pathogenetic mechanisms of Septic Shock. N Engl J Med 1993; 328: 1471-1478
4. Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. Arch Dis Chld - Fetal and Neo ed 2003; 88: F450-F454.
5. Tibby SM, Hatherill M, Marsh MJ, Murdoch IA. Clinicians' abilities to estimate cardiac index in ventilated children and infants. Arch Dis Chld 1997; 77: 516-518
6. Raju VN. Capillary refill time in the hands and feet of normal newborn infants. Clinic Pediatric 1999; 38(3): 139-144
7. Osborn DA, Evans N, Kluckow M. Clinical detection of low upper body blood flow in very premature infants using blood pressure, capillary refill time, and central-peripheral temperature difference. Arch Dis Chld - Fetal and Neo ed 2004; 89: F168-F173.
8. Diprose GK, Evans DH, Archer LN, Levene MI. Dinamap fails to detect hypotension in very low birthweight infants.Arch Dis Chld 1986; 61: 771-773
9. Lee J, Rajadurai VS, Tan KW. Blood pressure standards for very low birthweight infants during the first day of life. Arch Dis Chld - Fetal and Neo ed 1999; 81: F168-F170
10. Versmold HT, Kitterman JA , Phibbs RH , Gregory GA , Tooley WA . Aortic blood pressure during the first 12 hours of life in infants with birth weight 610 to 4, 220 grams. Pediatr 1981; 67: 607-613
11. Kluckow M,Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation .J Pediatr 1996; 129(4): 506-12.
12. Groves AM, Kuschel CA, Knight DB, Skinner JR. Relationship between blood pressure and blood flow in newborn preterm infants. Arch Dis Chld-Fetal and Neo ed 2008; 93: F29-F32.
13. Watkins AM, West CR, Cooke RW. Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants. Early Hum Dev 1989; 19(2):103-10.
14. Catherine L, Bassan H. Current definitions of hypotension do not predict abnormal cranial ultrasound findings in preterm infants. Pediatr 2007; 120(5): 966-977.
15. Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. Arch Dis Chld - Fetal and Neo ed 2000; 82: F182-F187.
16. Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. Arch Dis Chld - Fetal and Neo ed 2000; 82: F188-F194.

17. Hoeven VMA. Continuous central venous oxygen saturation (ScvO2) measurement using a fibre optic catheter in newborn infants. Arch Dis Chld - Fetal and Neo ed 1996; 74: F177-F181.
18. Oliveira CF, Oliveira DSF, Gottschald AFC, Moura JDG, Costa GA, Ventura AC et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. Int Care Med 2008; 34(6): 1065-1075
19. Kreymann G, Grosser S, Buggisch P, Gottschall C, Matthaei S, Greten H. Oxygen consumption and resting metabolic rate in sepsis, sepsis syndrome, and septic shock. Crit Care Med 1993 Jul; 21(7): 1012-9.
20. Mrozek JD, Georgieff MK, Blazar BR, Mammel MC, Schwarzenberg SJ. Effect of sepsis syndrome on neonatal protein and energy metabolism. N Engl J Med M 2000; 20(2): 96-100.
21. Hamrah AH, Oweni TS, Arafah BM. Measurement of serum free cortisol in critically ill patients. N Engl J Med 2004; 16: 1629-1638.
22. Kirkman HN, Riley HD. Posthaemorrhagic anemia and shock in the newborn. Pediatr 1959; 24: 97-105.
23. Andersen CC, Collins CL. Poor circulation, early brain injury, and the potential role of red cell transfusion in premature. Pediatr 1959; 117: 97-105 .
24. Bell EF, Strauss RG, Widness JA, Mahoney LT. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatr 2005; 115: 1685-1691.
25. So KW, Fok TF, Ng PC, Wong WW, Cheung KL. Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. Arch Dis Chld - Fetal and Neo ed 1997; 76: F43-F46.
26. Short BL, Meurs KV, Evans JR. Summary proceedings from the cardiology group on cardiovascular instability in preterm infants. Pediatr 2006; 117(3): S34-S39.
27. Ewer AK, Tyler W, Francis A, Drinkall D, Gardosi JO. Excessive volume expansion and neonatal death in preterm infants born at 27-28 weeks gestation. Paediatr Perinat Epidemiol 2003; 17(2): 180-6.
28. Gill AB, Weindling AM. Randomised controlled trial of plasma protein fraction versus dopamine in hypotensive very low birth weight infants. Arch Dis Chld 1993; 69: 284–7.
29. Pellicer A, Carmen MB, Madero R, Salas S, Quero J, Cabañas F. Early systemic hypotension and vasopressor support in low birth weight infants: impact on neurodevelopment. Pediatr 2009; 123: 1369-1376.
30. Subhedar NV, Shaw NJ. Intervention Review- dopamine versus dobutamine for hypotensive preterm infants. Cochrane Database of Systematic Reviews, Issue 4, 2009.
31. Osborn DA, Paradisis M, Evans NJ. Intervention Review-the effect of inotropes on morbidity and mortality in preterm infants with low systemic or organ blood flow. Cochrane Database of Systematic Reviews, Issue 4, 2009
32. Roze JC, Tohier C, Maingueneau C, Lefèvre M, Mouzard A. Response to dobutamine and dopamine in the hypotensive very preterm infant. Arch Dis Child 1993; 69: 59–63.
33. Bigam DL, Barrington KJ, Jirsch DW, Cheung PY. Effects of a continuous epinephrine infusion on regional blood flow in awake newborn piglets. Biol Neonate 1998; 73: 198-206.
34. Daga SR ,Gosavi DV, Verma B. Adrenaline for septic shock in the newborn. Indian Pediatr 2000; 37: 799-800.
35. Kawczynski P, Piotrowski A. Circulatory and diuretic effects of dopexamine infusion in low-birth-weight infants with respiratory failure. Intensive Care Med 1996; 22(1): 65-70.
36. Ng PC, Lee CH, Lam CWK, Ma KC, Fok TF, Chan IHS, Wong E. Transient adrenocortical insufficiency of prematurity and systemic hypotension in very low birthweight infants. Arch Dis Child- Fetal and Neo ed 2004; 89: F119-F126.
37. Istvan Seri. Hydrocortisone and Vasopressor-Resistant Shock in Preterm Neonates .Pediatr 2006; 117(2): 516-518.
38. Rivers E, Nguyen B. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345(19): 1368-1377.
39. Han YY, Carcillo JA. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. Pediatr 2003; 112 (4): 793-799.
40. Duchemin KE, Laborie S, Rabilloud M, Lapillonne A, Claris O. Outcome and prognostic factors in neonates with septic shock. Pediatr Crit Care Med 2008; 9(2): 186-91.