Review
Of
Literature
Review of Literature

Respiratory distress presents a major threat to the survival of the newborn and contributes inestimably to morbidity in this age group. S.P. Khatua et al (1979) reported that though the overall incidence of respiratory distress was 6.9 /1000 live birth, it was 30.45 and 5.37 in premature and mature infants respectively. indicating that the incidence in premature was 6 times more common than in term infants. Driscoll & Smith (1962) noted respiratory distress accounting for about half of the neonatal death. Higher incidence of respiratory distress ranging from 2.92% - 3.9% was also noted by other workers.

In an autopsy study of 422 cases, Driscoll & Smith observed lung disorder in 63% cases of which hyaline membrane disease was in 60% cases, pneumonia in 14% cases and massive aspiration in 3% cases. Prenatal mortality study in India by various authors revealed respiratory disorders as the cause of death in 13% -54% cases. In order of frequency, the important causes were pneumonia, pulmonary hemorrhage aspiration and H.M.D.

Prod'hom et al (1974) in their study of 1402 cases of respiratory distress with a birth weight of 2 kg. or less found H.M.D. in 42.2%, transient tachypnea in 30%, aspiration syndrome in 16 % and symptomatic cases like pneumonia, malformation in 10.9% cases.
Hyaline Membrane Disease

Schaffer (1971) found respiratory distress syndrome as the leading cause of respiratory distress limited almost entirely to premature.

Cunningham and Smith (1973) in their study of 137 cases requiring transport to special ward observed 78 cases of respiratory disorder, of which 73% were due to R.D.S. and 23% due to massive aspiration.

H.M.D is more common in male than in female infants (Miller and Futrakul, 1968); it is more common in white than in nonwhite infants (Richardson and Torday, 1994).

At any given gestational age, the incidence is higher for cesarean section without labor than for vaginal delivery (Fedrick and Butler, 1972). There is a significantly increased risk if elective cesarean section is performed before completion of 39 weeks gestation (Morrison et al, 1995).

Most infants of diabetic mothers are large for gestational age, and similarly over nourished infants in the absence of maternal diabetes are also at increased risk (Naeye et al, 1974). When corrected for the important effect of gestational age, the occurrence of HMD is significantly increased in gestational diabetes and in insulin-dependent mothers without vascular disease (Robert et al, 1976).
Early reports in comparatively large infants suggested that the risk is decreased in infants who are small for gestational age (Gluck and Kulovich, 1973); however, in much less mature infants seen, comparisons of appropriate-for-gestational-age and small-for-gestational-age infants, both weight matched and gestation matched, suggest that immature small-for-gestational-age infants do not have this advantage (Pena et al, 1988). In fact, there is some evidence that the risk of RDS at constant gestational age may be increased in small-for-gestational-age infants and that the mortality may be higher (Thompson et al, 1992; Tyson et al, 1995).

Cause of hypoxia in infants is the presence of an open, poorly ventilated lung compartment with extremely low V/Q, representing a significant portion of the lung and producing variable hypoxic vasoconstriction and alterations in right-to-left shunt as the inspired oxygen changes (Corbet et al, 1974).

In preterm infants without RDS, the ductus arteriosus tends to close within 4 days of birth (Reller et al, 1988), whereas in RDS the ductus tends to remain open (Reller et al, 1993) and may become a significant problem by 3 to 4 days of age (Corbet, 1996).

Infants do not grunt with every breath, and those with severe disease grunt most frequently. By maintaining a positive intrapulmonary pressure during most of the respiratory cycle, grunting
probably helps to prevent atelectasis. When not grunting, infants with HMD have small tidal volumes and a rapid respiratory rate.

Jobe et al., showed that the combination of antenatal corticosteroids and surfactant replacement therapy reduced morbidity and mortality rates to very low levels in a group of preterm infants.

Maternal conditions that compromise fetal growth and may produce, decreased risk include pregnancy induced hypertension, chronic hypertension, sub-acute placental abruption, narcotic addiction, and maternal smoking, Tubman and colleagues (1991) found an increased risk for RDS in infants of hypertensive mothers.

Edberg and coworkers (1991) found decreased compliance, increased resistance, decreased lung volume and reduced gas mixing efficiency in very-low-birth-weight infants with RDS.

In infants who die, deMello and associates (1987) has demonstrated the complete absence of tubular myelin and a modest deficiency of lamellar bodies in Type – 2 cells in comparison with controls.

Meconium aspiration syndrome

Meconium staining of the amniotic fluid is found in about 9% of deliveries at term, and at birth 56% of these babies have meconium in their tracheas (Gregory et al, 1974).
S.P.Khatua et al (1979), found that the higher incidence of aspiration syndrome in this study was due to poor antenatal care, higher number of referred cases with prolonged labour, failed medical induction, abnormal labour and accidental hemorrhages, all of which predispose to perinatal asphyxia with aspiration.

Airway resistance is increased in newborn infants and experimental animals with MAP (Tran et al, 1980; Yeh et al, 1982). In addition, dynamic lung compliance is reduced while static lung compliance is unchanged, suggesting that airway obstruction is patchy and located in peripheral airways.

Early data suggested that meconium did not impair surfactant function (Tran et al, 1980), more recent data suggest that meconium does inactivate surfactant (Davey et al, 1993; Moses et al, 1991; Sun et al, 1993a).

Meconium is aspirated into the tracheobronchial tree when the fetus begins to gasp deeply in response to hypoxia and acidosis. Data showing that cord arterial pH is lower in meconium-stained infants with meconium in their tracheas at delivery supports this hypothesis (Yeomans et al, 1989).

According to Cleary GM et al (1990), neonates with meconium aspiration syndrome and umbilical pH ≥7.20 at delivery developed seizures as often as those with pH <7.20 (20.1% vs. 21.1%; P = 1.0).
Normal acid-base status at delivery is present in many cases of severe meconium aspiration syndrome, which suggests that either a preexisting injury or a nonhypoxic mechanism is often involved.

Studies on meconium aspiration syndrome have led to the speculation that asphyxial episodes too brief to decrease pH or Apgar scores may cause the passage of meconium in utero. These conclusions were supported by a study showing that there was no correlation between the consistency of meconium and markers of fetal asphyxia (Trimmer and Gilstrap, 1991).

There is usually slow radiological clearing over 10 days but in some babies the meconium disappears within 2 – 3 days possibly by ciliary action, phagocytosis or enzymatic lysis (Halahakoon and Halliday, 1995).

Studies have suggested that when thick meconium staining has occurred the obstetrician should suck out the mouth as the head crowns, using either a suction catheter or a bulb suction. Gregory et al (1974) found that 56% of meconium stained infants had meconium in the trachea and in 10% there was meconium below the cords despite it being absent from the mouth or pharynx. “Compared with expectant management intubation and suctioning of the apparently vigorous meconium stained infant does not result in a decreased incidence of
MAS or other respiratory disorders. Complications of intubation are infrequent and short lived.”

A large randomized study, showed no benefit of routine endotracheal intubation in these circumstances and indeed the babies whose airways were aspirated had more respiratory problems than the control infants (Linder et al, 1988).

In a study by Zagariya A et al (2004), meconium instillation caused significant expression of inflammatory cytokines TNF, IL-6, and IL-8 (p<0.05) with a peak of 8 hours after meconium instillation. Levels of IL-10 were insignificant (p > 0.05). Also significant increase in necrotic cells and neutrophils (p < 0.05), compared to the control, saline instilled rabbit lungs.

Because meconium must ultimately be removed by phagocytes, respiratory distress and requirements for supplemental oxygen may persist for days or even weeks after birth. Infants who present with a shorter course and with rapid resolution of symptoms are more likely to have had retained fetal lung fluid than MAP.

Transient Tachypnea of Newborn

In 1966, Avery and associates described the clinical and radiographic features of eight babies with transient neonatal tachypnea, a condition that the authors attributed to delayed
absorption of fetal lung liquid. Cells from rabbits that were born prematurely or without prior labor did not exhibit increased Na\(^+\), K\(^+\) - ATPase activity, which is an observation that may help to explain the lung fluid retention often associated with premature birth. Around the time of birth, the long epithelium switches from a predominantly Cl – secreting membrane to a predominantly Na\(^+\) absorbing membrane, with a resultant reversal of the direction of liquid flow.

**Neonatal Pneumonia**

While Benirschke (1960), had shown that apparent or inapparent maternal bacteremia could produce infection. Blane (1961), demonstrated that antenatal infection in these situations resulted from the hematogenous dissemination, the microorganisms being carried on the maternal circulation to the intervillous spaces of the placenta and thence into the blood stream. Their observations has been corroborated by Gotoff and Behrman (1970), as well, who further observed that while this was the usual mode of intrauterine viral infections, bacterial infection of the fetus generally did not follow this route. Listeria monocytogenes and vibrio fetus, however, were the possible exceptions (Gotoff and Behrman, 1970).

Blanc (1959), Benirschke (1959), Pryles (1963), Ramos and Stern (1969), Gotoff and Behrman (1970) and Habel et al (1972),
commented upon the association between the early rupture of membrane, prolonged labour and excessive manipulation infection of amniotic fluid resulting in fetal infection. However, Blanc (1959), gave a comprehensive account of the progress of events leading to whet he termed "Amniotic Infection Syndrome". The process according to him started at the internal OS with or without intact membranes and comprised of polymorphonuclear infiltration of amnion and chorion. The infection then spread to placenta and occasionally involved the umbilical vessels as well. Demonstration of polymorphonuclear infiltration of placental tissue, chorion and gastric aspirate (Blanc, 1961) were all pointers to the fact that the baby was coming from an infected environment.

Wilson (1964), Overbach (1970) therefore advocated routine examination of the placental end of the umbilical cord, as a screening test for evidence of ascending infection.

The strong association of amnionitis with premature birth may be due to a developmental deficiency of bacteriostatic factors in amniotic fluid (Schlievert et al, 1975).

Most cases of amnionitis, however, are not associated with pneumonia in the newborn. In some infants, aspiration of infected amniotic fluid occurs, but the lung parenchyma is not invaded by pathogens. As a result, neutrophils of maternal origin are confined to
the air spaces, fetal neutrophils do not infiltrate the septal walls, and
fibrinous exudate does not occur. Blood culture in these infants is
negative, and the clinical picture is that of fetal asphyxia, with or
without postasphyxial pulmonary edema.

With an increasing latent interval between rupture of membranes
and labor, the incidence of clinical amnionitis also increases (Burchell,
1964) as well as the frequency of bacteremia is cord blood samples
collected at birth (Tyler and Albers, 1966).

S.P.Khatua et al (1979) reported that aspiration syndrome was
the commonest cause of respiratory distress and was found in 57.1%
cases followed by pneumonia in 9.35% and R.D.S. in 8.8% cases.
Incidence of pneumonia was quite high (9.35%) in this series. Two
infants had intra uterine pneumonia and both of them had the history
of prolonged membranes rupture. The rest 15 cases had prenatally
acquired pneumonia and most of them had history of either prolonged
labour or difficult delivery.

A prolonged interval between rupture of membranes and the
onset of labor is a significant independent factor favoring an increased
incidence of amnionitis only for gestation of 37 weeks or more
In fact, infection may be one of the causes of premature labor because amnionitis often occurs in the presence of intact membranes (Naeye and Peters, 1978).

Infants of mothers with active urinary tract infection in the 2 weeks before birth are at increased risk for amnionitis (Naeye, 1979a).

The absence of labor and delivery by cesarean section are associated with a greatly reduced risk of amnionitis and of congenital pneumonia (Avery, 1984). Data also suggest that obstetric digital examinations after rupture of membranes significantly increase the chance of amniotic infection (Schutte et al, 1983). Amnionitis is more common in undernourished populations, perhaps because bacteriostatic factors may be lacking in the amniotic fluid (Naeye and Blanc, 1970).

The pneumonia occurring in infants infected with L. monocytogenes may be transplacental, postamnionitis, or transnatal in type. In transplacental pneumonia, granulomatous disease of the placenta is present. The amniotic fluid in Listeria amnionitis has a greenish or chocolate-brown appearance. The chest radiograph shows a diffuse reticulonodular pattern of pneumonia if the onset is intrauterine. In transnatal pneumonia, the chest radiograph shows a bronchopneumonia pattern (Gordon et al, 1970).
The onset of pneumonia caused by Chlamydia trachomatis is usually delayed until 1 to 3 months of age, it is considered to be a transnatal pneumonia, the pathogen being acquired from the mother’s vagina at delivery (Gilbert, 1986). About 2% to 10% of pregnant women have vaginal colonization with Chlamydia; in a San Francisco study, the rate was 4.7% (Schachter et al, 1986). In infants of colonized mothers, about 35% develop conjunctivitis, and 20% may develop pneumonia (Schachter et al, 1979).

In a study by S Webber et al (1990), all babies admitted to the neonatal unit during a period of 41 months were prospectively studied to find out the incidence, aetiology, and outcome of neonatal pneumonia, and the value of routine cultures of endotracheal tubes. Pneumonia of early onset (before age 48 hours) occurred in 35 babies (incidence 1.79/1000 live births). In 20 (57%) it was caused by group B streptococci. Blood cultures showed the presence of organisms in 16 of the 35 (46%). Endotracheal tube colonisation had occurred in 94% of these, most commonly by Gram negative organisms and Staphylococcus epidermidis. In only one of seven cases with simultaneous bacteraemia was the same organism grown from cultures of the blood. Ten babies with pneumonia of early onset (29%) died; all were preterm infants.
There have been isolated reports of congenital pneumonia caused by Ureaplasma urealyticum (Brus et al, 1991; Panero et al, 1995; Quinn et al 1985; Ursi et al. 1995; Waites et al, 1989) and Mycoplasma hominis (Ursi et al, 1995). Mycoplasma and ureaplasma are commonly associated with amnionitis in the mother; the pneumonia has an early onset, but the specific diagnosis may be made comparatively late in the clinical course. The organisms are cultured only with special media after a period of 3 to 5 days.

Gotoff and Behrman (1970), Xanthau (1972) and Steigbigel et al (1974) reported that WBC count has a wide range of normal values in the newborn period. Leucopenia (< 4000 WBC / cmm) or leukocytosis (> 25000 WBC/cmm) support a diagnosis of infection, but absence of a marked leukopenia, or leukocytosis does not rule out the possibility of septicemia. Boyles et al (1978), have suggested that leukopenia of < 10,000 cells/cmm is associated with infection in first day of life.

Marsh et al (1967), Xanthau (1972), Akanzua et al (1974) observed that change in the ratio of non-segmented to segmented neutrophils in the blood were sensitive index of the severity of the infection than the increase in the granulocyte series. Marce et al (1979) showed that the values of band cells / neutrophil ratio is 0.14 when associated with group B. β haemolyticus streptococcus infection. They documented values up to 0.17 upto first day of life.

Evans et al (1970), reported that M-ESR is a simple inexpensive test requiring only capillary blood and hence ideally suited for newborn infants. ESR is a non-specific indicator of infection. The sedimentation rate is in normal newborn babies for the first five days of the life. This is elevated when infective process is going on in neonate. Adler et al (1975) and Parida et al (1980) also observed similar findings.

Mathai et al (2004), in their study reached a conclusion that CRP level in cord blood of ≥ 6 mg/L was significantly associated with rupture of membranes for more than 24 hours, labour for more than 12 hours and maternal fever. At 24 hours, elevation in CRP levels was significantly associated with primiparity, more than three vaginal examinations after rupture of membranes, meconium staining of amniotic fluid and amniocentesis. When the cut-off CRP level was increased to 12 mg/L, significant association was noted only with maternal fever.

Since CRP levels rise during the initial 24 hours in many babies irrespective of infection or administration of antibiotics, serial determinations in this period may not be of much use in diagnosis but may help in identifying uninfected babies and restricting antibiotic use.
In the study by Mathai et al (2004), they found at 24 hours, CRP levels of 6 mg/L had a negative predictive value of 99%. This level therefore could be used to guide antibiotic therapy when latex agglutination kits are used. Testing samples in further dilutions to establish the actual amount of CRP may not be necessary since increasing levels were not associated with increasing severity or prognosis.

In comparison to leukocyte counts and ratios, CRP levels at 24 h proved to be the single best indicator for diagnosing EOS.

Early onset pneumonia has been estimated to occur in 1.79 per 1000 live births (Webber et al 1990). Nosocomial infection causing pneumonia was found in about 8% of babies in a neonatal intensive care unit (Hemming et al, 1976). Pneumonia as a complication of endotracheal intubation for mechanical ventilation has an incidence of about 30% (Giacoia et al, 1981).

Gotoff and Behrman (1970), in their work noted an increasing trend of listeria monocytogenes infection.

Bhakoo et al (1974), Guha et al (1978), Khatua et al (1980) and Mishra et al (1985), also noted E.coli as the most common organism in the causation of neonatal infection. They also noted an increasing trend of Klebsiella infection. Other organisms reported by these workers were staph aureus, pseudomonas and peptococcus etc.
Sinha et al (1980), however, observed that P. auroginosa is the most common organism in the causation of neonatal sepsis (81.7%).

Mondal et al (1991), observed that staphylococcus was the most common organism in the cases who were born outside the hospital and inside the hospital. Klebsiella was more common than acinobacter among hospital born babies.

Pruthi et al (1983), in their study of 947 neonates reported that usefulness of infection scoring system at birth for predicting neonatal infections.

High risk factors are:

1. Apgar score at 1 min < 6 or frankly meconium stained liquor.
2. Foul smelling liquor at birth or gastric aspirate polymorphonuclear > 20/HPF or respiratory distress at birth.
3. Prolonged labour > 24 hours.
4. Unclean vaginal examination, maternal fever > 38°C within 24 hours of delivery.
5. Birth weight < 2 Kg and or gestational age < 37 weeks.
6. Leaking membranes > 24 hours.

According to a study by S. Misra et al (1991) 44 babies had pneumonia, of which 30 recovered and 14 died. There were 12 babies (28.6%) who did not have tachypnea. Seven of these non-tachypneic babies died (58.3%), while 7 out of 32 babies with tachypnea expired
(21.3%). The difference in mortality between the non-tachypneic and
tachypneic babies was statistically significant) p < 0.01). However, 8 of
these 12 babies without tachypnea were of low birth weight (75%).
The mortality of low birth weight (55.6%) was significantly higher (p <
0.01) than the mortality of normal birth weight neonates with
pneumonia (15.4%).

S. Misra et al (1991) in their study reported that at least one of
the 3 rapid diagnostic tests for infection (i.e. micro-ESR more than 13
mm in first hour, absolute neutrophil count above or below the
reference value for the age of the neonate and C-reactive protein
positivity in the plasma by Rapi-tex) was positive in 31 babies (70.4%).
Among these 31 babies a bacterial etiology of pneumonia could be
established in 22 neonates (71%) by culture and CIEP (counter
immuno electrophoresis) technique. Only 3 babies with positive test
for bacterial infection (culture or CIEP) had all rapid diagnostic tests
negative. Bacterial culture of the blood was positive in 17 babies.
Gram negative and gram positive bacteria were grown from 11 and 10
babies respectively. The various bacteria isolated were Klebsiella
pneumonia (5) Staph epidermis (4). Actinobacter lowfii (3)
streptococcus species (2) Pseudomonas aeruginosa (2).Coagulase
negative staphylococci (1) Escherichia coli (1) Salmonella Group E (1)
Salmonella typhimurium (10) Morganella morgani (10) and Enterobacter (1)

Various investigators have used both direct and indirect methods for studying the bacteriology of neonatal pneumonia. Laryngeal / tracheal aspirates have not been shown to be useful in studying the bacterial etiology of pneumonia beyond 12h of life. Blood culture has been found useful while lung aspiration culture have been shown to be the best method. Pharyngeal - secretion and gastric aspirate culture are almost useless.

In a study by S.Thomas et al (1981) forty infants developed lobar pneumonia or bronchopneumonia. They were mostly term babies. 17 of them had prolonged rupture of membranes (PROM) for more than 24 hours while two had less than 24 hours. Of these 24 were delivered vaginally with vertex presentation and eight were delivered by lower segment caesarian section indicating that there was no significant correlation between the mode of delivery and the development of secondary pneumonia. Similarly there was no correlation between maternal illness and subsequent respiratory infection. The onset of RDS in these cases varied from 0-56 hours (mean 13.1 hr) and the maximum duration was 144 hours (mean 44.8 hr). In all these cases there was evidence of pneumonia radiologically. The organism isolated from blood culture were Klebsiella aeruginosa,
E. coli, pneumococcus staphylococcus aureus, Staphylococcus albus and salmonella typhi.

J.N Misra et al (1985) found that "Blood culture was positive in 36.4 as against 44% reported by Shakunthala et al (1978). Gram negative bacteria was detected in 11(25%) Strep. Pneumoniae antigen in 10 (22.4%) and Staph aureus in 3 (6.4%) babies". In an earlier study Shakunthala et al (1978) isolated Staph. Aureus, Strep. Pneumoniae and Gram negative bacteria from 28, 28 and 2% neonates with pneumoniae respectively. In contrast to studies from the developed countries, beta haemolytic streptococcus was not isolated from any of the cases.

Study by J.N Misra et al (1985) showed a continued high prevalence of streptococcus pneumoniae, an increasing incidence of gram negative bacteria and a falling rate of staph. aureus pneumonia. The changing bacteriology of neonatal pneumonia may be related to antibiotic usage protocol and introduction of intensive care facilities.

Among the bacterial isolates, 23.5% of the Gram negative bacteria and the staphylococci were resistant to gentamicin, while all of them were sensitive to amikacin. All the staphylococci isolated were sensitive to methicillin. Therefore initial antibiotic therapy for neonatal pneumonia should include ampicillin for streptococcal Pneumonias,
and aminoglycoside antibiotic for Gram negative bacteria (amikacin) and cloxacillin for staph. aureus.

S.Thomas et al (1981) found that the duration of onset for aspiration pneumonia was 0-11 hrs. of birth and the R.D.S. persisted for a period varying from 7-36 hours, transient tachypnea started within 0-4 hrs. and lasted for a maximum period of 48 hrs., meconium aspiration syndrome started at 0-8 hours and lasted for 62 hrs.

According to Mathur et al (2002): no significant difference was found in respiratory rate in neonates with pneumonia compared to neonates with respiratory distress due to other causes (p=0.22). Of the 103 cases with pneumonia ,11.6% neonates had respiratory rate less than 60 /min and would have been missed by the WHO definition of pneumonia (respiratory rate greater than 60/min. The fatality in 7 neonates with respiratory rate of less than 50/min was 57.1% which was higher than in those neonates with pneumonia having respiratory rate greater than 50/ min. Earlier studies have also found high mortality (27.7% and 58.3% respectively) in preterm neonates in whom respiratory rate was less than 50/min. In the same study by Mathur et al (2002) bacterial etiology of pneumonia was established in 49 neonates (47.5%) by blood culture. This was slightly higher than that reported earlier. The bacterial isolates are consistent with the earlier studies, which suggest increasing incidence of Klebsiella.
Following findings were established by their study "Pneumonia was the most common cause of respiratory distress in neonates. Clinical features and X-ray chest would miss the diagnosis of pneumonia in neonates in 15% cases and these have to be corroborated with sepsis screen and blood culture, for a definitive diagnosis. The diagnosis of pneumonia based on respiratory rate more than 60 per minute as suggested by WHO would miss the condition in 11.0% cases and fatality in the missed cases is higher."