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Review Article

Factors Associated with Neonatal Pneumonia: A Narrative Review

Manoj Kumar[1], Swati[2], Avinash Kumar[3], Anjali Kumari[3]

[1]Assistant Professor, Department of Pediatrics, All India Institute of Medical Sciences, Deoghar, Jharkhand, India

[2]Assistant Professor, Department of Obstetrics and Gynecology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

[3]Postgraduate Resident, Department of General Medicine, Narayan Medical College and Hospital, Rohtas, Bihar

[3]Senior Resident, Department of Obstetrics and Gynecology, A.N.M.M.C.H, Gaya, Bihar

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Corresponding author: Dr. Manoj kumar
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Abstract

The greatest risk of death from pneumonia in childhood is in the neonatal period. It is estimated that pneumonia contributes to between 750 000–1.2 million neonatal deaths annually, accounting for 10% of global child mortality. The etiology depends on time of onset. Gram negative bacilli predominate in the first week of life, and Gram-positive bacteria after that. Streptococcus pneumonia probably causes about 25% of neonatal pneumonia. Other associated risk factors are malnutrition (40% in India), Indoor air pollution, non-breast feeding, chronic pulmonary disease (obstructive), etc. Strengthening of health care delivery system for early detection and treatment and as well as minimization of preventable risk factors can avert a large proportion of death due to pneumonia. Interventions that would reduce mortality from this condition would have a large range of beneficial effects: improved maternal health, better management of other common neonatal conditions, and reduced long term childhood and adult morbidity.

Keywords: pneumonia, risk factors, burden, mortality

Introduction

Neonatal pneumonia accounts for 6.1% of the total global neonatal mortality. It contributes to 5.1% of neonatal mortality in India and 5.6% in South Asia. [1] There is no international consensus regarding definition, diagnostic criteria and management of pneumonia among new-born babies. [2,3] Recently in India, the neonatal mortality rate (NMR) has declined and now over half of India's under-five deaths occur in the neonatal age group. Seventeen percent of these are attributed to pneumonia, making it the most dreaded neonatal infection. [4]

At present, the epidemiologic pattern of pneumonia is being altered by changes in patient characteristics, such as increased immunosuppression, and by changes in

medical practice. [5] Many bacteria and viruses can cause pneumonia and many of them can be detected by methods available only in research laboratories. [6] Control of pneumonia depends upon an understanding of the relative importance of etiologic agents for recommendations regarding treatment and for the development of vaccines. [7]

In India, there is very little information about neonatal pneumonia. To reduce the high prevalence of neonatal pneumonia and its accompanying mortality, it is critical to identify and eliminate risk factors associated with the disease, as well as to execute effective therapies to increase neonatal survival. The goal of this study was to find risk variables and mortality predictors for newborn pneumonia in the Indian environment.

Classification and Problems in Understanding the Epidemiology of Neonatal Pneumonia

Neonatal pneumonia can be arbitrarily classified as early and late onset. There are various definitions of early onset pneumonia; some authors have used 48 hours as a cut off, others have suggested 7 days. It may be operationally useful to separate the disease classification between the first week of life and the subsequent three weeks. In most series, Gram negative bacteria predominate in the first week and Gram-positive bacteria predominate subsequently. [2]

Intrauterine pneumonia also occurs in the setting of a systemic infection in the mother, such as rubella, cytomegalovirus, Treponema pallidum, Listeria monocytogenes, tuberculosis, and HIV. These infections may be asymptomatic in the mother. Associated features include hepatosplenomegaly, thrombocytopenia, and jaundice. [2]

The literature on the bacterial etiology of neonatal pneumonia is influenced by studies that include nosocomial infection in neonatal intensive care units. [8, 9] Many studies do not report the age of onset. A further difficulty is that blood cultures will underestimate the proportion of pneumonia that is bacterial, and lung puncture studies have rarely been performed on neonates. [10, 11] In Ethiopia, a diagnosis of pneumonia in young infants was negatively associated with bacteremia, compared with the diagnoses of clinical sepsis, ‘‘severe disease’’, or ‘‘eventually fatal sepsis’’. [12] In studies where a high proportion of infants had previously received antibiotics, the highest yield has come from the combination of blood culture, lung puncture culture, and serum and lung aspirate latex agglutination antigens. [13]

Aetiology and Pathogenesis

The epidemiological features of neonatal pneumonia, in general, with their resultant implications for treatment and prevention are sufficiently similar to those of neonatal bacteremia and meningitis, and therefore can be used to understand the etiology of the disease. [2]

The bacterial etiology of neonatal pneumonia is also influenced by nosocomial infection in neonatal intensive care units. In some areas of the world high rates of Streptococcus pneumonia have been detected in late-onset neonatal pneumonia. Also, since lung-derived samples are rarely obtained from neonates, [10, 11] studies pertaining to neonatal pneumonia contain blood culture data which will underestimate the proportion of cases that are bacterial. [2]

Viral neonatal pneumonias can either be associated with intrauterine, early-onset or late-onset pneumonias, and can be acquired from the birth canal [e.g. herpes simplex virus (HSV)]), infected siblings, parents and/or healthcare workers [e.g. respiratory viruses such as respiratory syncytial virus (RSV)] with or without nosocomial involvement. Congenital pneumonia is caused by a mixture of bacteria, viruses and fungi. [14]

Early onset neonatal pneumonia:

Bacterial causes found in studies from developing countries clearly distinguished early from late onset neonatal sepsis and pneumonia. Escherichia coli, group B Streptococcus, Klebsiella spp, Staphylococcus aureus and Streptococcus pneumonia were the most commonly isolated bacteria. [2] In a further study that did not make a clear distinction between early and late causes, among 150 Indian neonates presenting at a median of 164 hours of life with respiratory distress, of whom 103 were diagnosed with pneumonia, blood cultures were positive in 49 cases (48%): Klebsiella in 28, Staph aureus in seven, coagulase negative Staphylococci in seven. [15]

Late onset neonatal pneumonia:

Two lung aspirate studies from India have highlighted the importance of Gram-positive bacteria in neonatal pneumonia: one study found S pneumonia (14 out of 50) and Staph aureus (14 out of 50) to be the most common causes of neonatal pneumonia. [11] A second study found

S pneumonia antigen positive in serum or lung aspirate of 10 of 44 (22%) neonates with pneumonia (but no cultures of S pneumonia were positive), and Gram-negative bacilli were cultured in 11 of 44 (25%). [13]

Atypical pathogens:

Congenital syphilis is still a major cause of neonatal infection in many developing countries, and fatal cases are invariably associated with severe pneumonitis and hypoxemia (pneumonia alba). In a study from Papua New Guinea, [16] congenital syphilis was the cause of death in 13.5% (17 of 126) neonates, and the case fatality rate for congenital syphilis was 33%. [17] Severe hypoxemia was common. [18] In Malawi, independent risk factors for neonatal death included maternal syphilis (hazard ratio 2.4; 95% confidence intervals 1.3 to 4.4), low birth weight, and first pregnancy. [19]

Associated Risk Factors:

In India, poverty, poor immunization status, indoor air pollution, overcrowding and malnutrition/ poor nutritional practices appeared to be the major associated risk factors. The same factors along with very young age, oxygen saturation (SpO2) of <90 per cent or abnormal chest X-ray at presentation also determined the outcome. [20-24]

Malnutrition:

Common bacterial pathogens in such children differ from those reported in children without severe malnutrition with more frequent infections with *Klebsiella pneumonia*, *Staphylococcus aureus*, and *Escherichia coli*. [25] In India, more than 40 per cent of children aged under-3 years are underweight and more than half of all children under 6 months are not exclusively breastfed. [26]

Hygienic practices: Hand and respiratory hygiene are crucial in minimizing the spread of most organisms responsible for acute respiratory infections and pneumonia. Studies have shown that hand washing with soap and water can reduce the incidence of acute respiratory infections and pneumonia by up to 50 percent. [27-29] The recommendations to cover the mouth and nose during coughing/ sneezing as a component of respiratory hygiene/cough etiquette have been based on their plausible effectiveness. [30-32]

Mother's lack of education and inexperience as a caregiver is one more risk factor for childhood pneumonia that may be amenable to public health intervention. [33] Teenage pregnancy and lack of essential support by health services add to the impact from this risk. Fertility rates in South Asia range from 71 to 119 births per 1000 women aged 15-19. [34]

Chronic pulmonary disease(obstructive) : This is a common condition in the region due to the high prevalence of the underlying risk factors, smoking and indoor air pollution.[35, 36] By using the criteria developed by Anthonisen *et al*, an average patient with chronic pulmonary disease suffers 2 or 3 attacks of acute exacerbation each year. [37] And, more than half of the exacerbations are caused by a bacterial infection and about a third by viral. [38, 39]

Social determinants and access to services by the poor: Pneumonia burden is inversely related to access to healthcare. Healthcare resources in the region, especially in India, are not seriously inadequate but unequal distribution of resources has been the major determinant of access to healthcare and disease prevention and control. Only about a fifth of the total health expenditure is borne by the State in high burden countries; the rest comes from the individual or family's 'out-of-pocket' expenses. [40]

Diagnosis and Investigations:

Chest X-rays should be performed in any patient with respiratory abnormalities. Blood should be collected for a complete blood count (CBC), C-reactive protein and culture in all cases of neonatal pneumonia. While the yield from blood cultures is low, blood, if possible, should be collected prior to antibiotic therapy to guide second line treatment in the event of first-line antibiotic failure. Blood cultures collected simultaneously with endotracheal tube aspirates in mechanically ventilated neonates may also assist in determining the significance of endotracheal tube colonization. Pus from empyema or skin pustules should be submitted for Gram staining and bacterial culture. [14] The most useful diagnostic tests for congenital pneumonia facilitate identification of the infecting microorganism. [41]

Bacterial culture:

Conventional bacteriological culture is used most widely and is currently the most helpful test. Aerobic incubation of cultures is sufficient for recovery of most responsible pathogens. Although the foul smell of amniotic fluid in the setting of maternal chorioamnionitis is often attributable to anaerobes, these organisms are seldom shown to be causative.

Blood culture:

Blood culture with at least 1 ml of blood from an appropriately cleaned and prepared peripheral venous or arterial site is essential, since much neonatal pneumonia are hematogenous in origin and others serve as a focus for secondary seeding of the bloodstream. Blood culture samples drawn through freshly placed indwelling vascular catheters may be helpful, but the possibility of contamination rises, the longer the catheter is in place. Multiple cultures of blood from different sites and/or drawn at different times may increase culture yield, but limited circulating blood volume precludes this as the standard of care in neonates**.**

Urine culture:

During the first 3 days of life, urine culture is unlikely to be helpful because most urinary tract infections seen at this age are hematogenous in origin.

Culture of specimens from endotracheal aspiration:

Culture and Gram stain of an endotracheal aspirate obtained by aseptic technique as soon as possible after intubation may be useful. Under typical circumstances, airway commensals take as long as 8 h to migrate down the trachea. At least one study demonstrated that culture of endotracheal aspirates obtained within 8 hours of birth correlates very well with blood culture results and probably reflects aspirated infected fluid. The longer the tube has been in place, the greater the likelihood that recovered organisms represent colonizers rather than invasive

pathogens; nonetheless, recovery of a single recognized pathogen in large quantities may be helpful in the selection of antibiotic therapy, especially if culture results from normally sterile sites are negative.

Culture from other respiratory sites:

In the presence of radiographically visible pleural fluid, careful positioning of the infant and cautious thoracentesis after sterile preparation of the sampling site may yield diagnostic findings on Gram stain, direct microscopy and/ or culture. Sonography may reveal smaller fluid pockets and facilitate safer sampling under direct visualization. Although data from neonates are insufficient to draw conclusions, studies in older populations suggest a very high correlation with culture of lung tissue and/or blood.

Serological tests:

They have limited use but may offer some insights. Serological tests for syphilis may suggest or confirm the presence of pneumonia alba, particularly in high-risk population. The value of assessing antibody responses in acute and convalescent sera from infants using flora recovered from endotracheal aspirates has been suggested as being useful.

Prevention and Control:

Relatively inexpensive and simple, yet safe and effective measures have been available and are also emerging for both prevention and control of pneumonia or acute lower respiratory infection in all age groups. Reducing risk factors, improving case management at the household, community and facility levels, ensuring regular supervision and reliable logistics, and sound monitoring and evaluation are the most effective ways of reducing morbidity and mortality from pneumonia. Providing effective referral care for cases with severe pneumonia requiring oxygen, second-line antibiotics, and other supportive management will contribute further to reduce mortality. Lack of public health focus and commitment has allowed the burden to remain high. Bringing pneumonia back to the main focus is also crucial to achieve the MDG-4, and national public health programmes can do so by taking the following steps. [3]

Surveillance and disease burden estimation:

Reliable estimation of pneumonia burden and region/ country/ or locale-specific risk factors is still lacking in the region especially from the remote areas inhabited by socioeconomically weak and marginalized populations and tribal groups. A focused active surveillance system at the community level and integrated well with the national integrated disease surveillance system is imperative to determine the true burden, seasonality and trend of this important disease in all age groups. [3]

Research, monitoring and evaluation:

Re-focusing on this forgotten priority in the peripheries of health services means finding ways to scale-up implementation of the available interventions for prevention and case management. Implementation of available interventions for prevention and control has encountered known and unknown barriers in many parts of the Region and therefore there is a need for the researchers to focus on identifying the barriers and the means to remove them for scaling up. [3]

Mobilizing national and international response:

Data generated through reliable surveillance and research studies, especially on the burden size and remediable risk factors and control measures, can be used to mobilize response from the national and international partners and stakeholders through effective advocacy. [3]

Prevention:

The etiology of childhood community-acquired pneumonia is varied and establishing its etiology is complex. *S. pneumonia* was the most frequently identified agent. *S. pneumonia* was also found to be associated with death in children with pneumonia [42]. Pneumococcal polysaccharide vaccines have been recommended since 1985, for children older than 2 years who are at high risk of invasive disease (for example asplenic children). These vaccines have not been recommended for younger children and infants because of poor antibody response before 2 years of age [43].

Pneumonia can also be an invasive disease but secondarily because the initial contamination route is the respiratory airway [44]. Serotype b is more likely to invade the bloodstream from the lung than NST strains [45]. It is believed that *H. influenzae* pneumonia is usually due to serotype b because of results from blood cultures [46].

Preventive Measures Shown to be Effective:

Active management of preterm rupture of membranes:

Antibiotic administration after preterm rupture of membranes is associated with a delay in delivery and a reduction in major markers of neonatal morbidity (neonatal infection, use of oxygen therapy, and abnormal cerebral ultrasound scans). [47]

Promotion of basic newborn care in communities:

Early and exclusive breast feeding has been shown to decrease the risk of pneumonia in infants outside the neonatal period, and there is every reason to expect a similar or greater protective effect against late onset neonatal pneumonia. [48, 49]

Regional Burden:

The estimated incidence of pneumonia in children under five years of age in the South-East-Asian-Region (SEAR) is 0.36 episodes per child year while the world average is 0.26 and the average for the developing countries 0.29. For further comparison, incidence in developed countries is 0.05 episodes per child year. Of the 156 million yearly new cases of childhood pneumonia worldwide, 61 million cases occur in the SEAR. Of the estimated 3.1 million annual deaths among the under-five population in SEAR countries, 19 per cent are attributable to pneumonia and this does not take into account the pneumonia cases among neonatal infections/sepsis. [50]

India needs a special mention in the context of childhood pneumonia. In the numerical term, with 43 million new cases every year, India tops the list of 15 countries across the world with high disease burden. [50] Morbidity rates tend to vary between 0.2 to 0.5 episodes per child-year and approximately 10 to 20 per cent of these episodes tend to be severe. [51-55] Among the high burden countries, India has a mortality rate of 322 per 100 000 under-five population compared to China's 86. [50]

Middle-income countries contribute to around 151 of the annual 156 million under five pneumonia cases. India is the largest contributor to global pneumonia deaths, accounting for around 43 million cases per year. Neonatal pneumonia differs from childhood pneumonia in many ways and is classified as 'early onset' or 'late onset', corresponding to the two major environments from which the infectious agent may be contracted: the intrauterine environment and birth canal; and the external environment. [56] Moreover, differences in infective agents result in a number of characteristic variants of neonatal pneumonia. [57] The likelihood of occurrence can be augmented by risk factors and determinants. In India, economic compromise, poor immunization

status, malnutrition and indoor air pollution are some of the major risk factors for developing pneumonia. [58]

Taking note of the regional burden, the 63rd Regional Committee of the South-East Asia Region once again adopted the resolution on the coordinated approach to prevention and control of acute diarrhea and respiratory infections in September 2010. Improved breastfeeding practices, appropriate complementary feeding, expanded immunization coverage, hand washing and respiratory hygiene, improved air and water quality at homes, improved community sanitation practices, and zinc supplements to children have been identified as the core preventive strategies. [59,60]

Conclusion:

The global burden of neonatal pneumonia is huge. Efficient interventions must be targeted at all levels of the health services and communities. Unlike for pneumonia in older infants and children, where effective interventions against two bacteria (S pneumonia and H influenzae) will substantially reduce disease prevalence, the etiology of neonatal pneumonia is more complex.

Management and prevention strategies for neonatal pneumonias cross multiple levels of the population and healthcare provision and have broader based effects that are sometimes difficult to measure.

The growing prevalence of antibiotic resistance to common and affordable antibiotics will eventually impact morbidity and mortality rates for neonates, especially in the developing world, and emphasize the importance of continuing to develop universal maternal and preventative health programmes.

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