PREDICTORS OF MORTALITY IN SUBJECTS HOSPITALIZED WITH ACUTE LOWER RESPIRATORY TRACT INFECTIONS

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Objective: *To identify the predictors of mortality due to acute lower respiratory tract infection (ALRI).* ***Design:*** *Prospective cohort study. Setting: Urban tertiary care teaching hospital.* ***Methods:*** *201 cases with ALRI between 2 weeks to 5 years of age were prospectively enrolled and followed up to determine outcome. Detailed history and clinical evaluation were recorded on a pretested proforma. Significant independent predictors of mortality were determined by comparison of dead subjects (n=21) with surviving children (n=180) in a multiple logistic analytic framework. Results: The case fatality rate (CFR) was 10.45%. Significant independent predictors of mortality were (OR, 95% CD age less than 1 year (23.1,2.7-197.5), inability to feed (6.2,1.3-30.7), associated loose stools (5.1,1.2-27.3), weight for age Z score <-3 (3.9,1.01-9.7), short duration of fever (1.2,1.0-1.5) and bandemia (1.1,1.05-1.2). The WHO guidelines identified 91% of children diagnosed as ALRI by clinical and investigative criteria. The CFR was related to severity of WHO classification ("pneumonia"-0%, "severe pneumonia"-8.7% and "very severe pneumonia"-47.0%). However, 2 of the 18 subjects with a diagnosis of "no pneumonia" expired (CFR 11.1% and 10% of total mortality).* ***Conclusion:*** *Even in settings of high case fatality, predictors of mortality can be identified in under five children suffering from ALRI. In this context, age below 1 year, inability to feed, presence of loose stools and severe malnutrition merit attention for interventional purposes.*

Key words: *Acute lower respiratory tract infection, Mortality, Predictors, Pneumonia.*

ACUTE lower respiratory tract infections (ALRI) are being increasingly recognized as a major cause of childhood mortality, being associated with a third of all under five deaths in developing countries. Pneumonia was estimated to account for 3.1 million under-five deaths in the third world annually(l). While mortality due to major killers in children like diarrhea, measles, tetanus and whooping cough has decreased substantially over the past decade, a similar trend in mortality due to pneumonia has not been observed(2). In recognition of this fact, the World Health "Organization (WHO) initiated the Acute Respiratory Infection (ARI) Control Programme in 1983. This has at it's centerpiece a case management approach, wherein the critical decisions as regards antimicrobial therapy, supportive measures and referral have to be taken by the health personnel. Four objective signs (fast breathing, chest indrawing, central cyanosis and inability to drink) associated with increasing severity of ALRI(3), constitute the core of the management protocol of a child with

cough. Studies reveal that the application of standardized case management protocols can produce upto 50% reduction in mortality due to childhood ALRI in the developing countries(4-ll). The success of the programme depends on detection of high risk cases and timely referral to hospitals with secondary and tertiary level care.

In an attempt to target appropriate cases for early intensive intervention, several workers have evaluated simple predictors of mortality in ALRI. However, many of these reports have several lacunae(12-19). Most studies have evaluated limited factors; either host factors have been studied or only clinical signs evaluated. The study designs have been non-uniform precluding a ready interstudy comparison. Further, the data has been invariably analyzed in a univariate manner. The present study was, therefore, designed to address these shortcomings while identifying the risk factors associated with mortality due to ALRI in hospitalized children.

Subjects and Methods

The study was conducted during the period September 1993 to May 1994. Children in the age group 2 weeks to 5 years, admitted in the Pediatric Emergency Room with symptoms suggestive of ALRI were screened. Children with clinical or radiological features consistent with acute laryngo-tracheo-bronchitis, acute laryngitis, bronchiolitis and pneumonia based on standard case definitions were enrolled in the study(3,20).

Acute laryngitis was defined as an acute infective condition comprising hoarseness of voice associated with a brassy or barking cough, without stridor. Lower respiratory tract signs like tachypnea, chest wall retractions and crepitations were absent. The presence of stridor along with hoarseness of voice and brassy or barking cough comprised the syndrome of acute laryngo-tracheo-bronchitis. Chest X-rays in both the above conditions were normal. Bronchiolitis was diagnosed in infants presenting with cough and first or second episode of tachypnea with respiratory distress; auscultation revealed wheeze with or without crepitations. There was no significant response to bronchodilators. Chest radiographs usually revealed only hyperinflation, though scattered areas of infiltration or atelectasis did not negate the diagnosis. Pneumonia was a condition characterized by presence of fever and tachypnea, with or without chest wall retractions. Crepitations were present on auscultation and bronchial breathing in case of consolidation. For labelling the child as tachypneic, the WHO guidelines were followed (age <2 months: respiratory rate >60/min; age 2-12 months: respiratory rate >50/min; age >1yr: respiratory rate >40/min). The respiratory rate was counted over 1 minute. Children who did not have tachypnea, but other clinical and radiological features were suggestive of pneumonia were also included in the study, as were children with no radiological findings but having clinical features suggestive of pneumonia. Subjects with a clinical diagnosis of bronchial asthma (based on wheeze, history of repeated similar episodes, positive family history of bronchial asthma and rapid response to bronchodilator therapy) were excluded from the study.

Recruitment to the study and clinical evaluation of the subject was done by a single investigator (VS). A detailed history of the relevant symptomatology such as fever, cough, rapid breathing, decreased feeding, lethargy, irritability and wheezing was taken. Details of treatment prior to hospitalization were also obtained. Socio-economic history regarding the age and education of parents, parental smoking, family size and

family income were also recorded. Other pertinent information such as birth order, birth history, immunization status, feeding practices especially breastfeeding and past medical history of the child were also recorded.

A detailed examination of each child including anthropometry (height, weight and mid arm circumference) was carried out. During the general physical examination, emphasis was laid on assessing the general condition of the child, respiratory and pulse rate (counted over one minute), severity of respiratory distress, presence of fever and other signs such as cyanosis, pallor and signs of vitamin deficiency. Detailed systemic examination of the respiratory, cardiovascular and central nervous systems was done. The presence of underlying congenital anomalies such as congenital heart disease and Down's syndrome were recorded. The child was assessed for associated illnesses such as diarrhea, septicemia and meningitis. Investigations were carried out and treatment instituted by the admitting unit as per their usual protocol.

This cohort of subjects was kept under follow up during their hospital stay to determine the final outcome. For analytic purposes, children who died during the course of hospitalization served as cases while those discharged were taken as controls. A total of 209 children were enrolled in the study, of which 8 were subsequently dropped from analysis. Of these, 2 were proven to have illness of tubercular etiology and 2 had only acute exacerbation of bronchial asthma. Four children who left against medical advise (LAMA) were also excluded after ensuring that they did not significantly affect the assessment of risk factors.

Analysis was carried out on a computer using the statistical packages Epi Info version 5 and Statistix PC, DOS version 2.0 (1987). Nutritional status (Z scores) was calculated in comparison to National Center for Health Statistics reference population by Epi Info software. All the socio-economic, infant care, clinical and investigative variables were compared in cases and controls by univariate analysis. Relevant statistical tools included Chi square test, Fisher's exact test and Student's "t" test. Significant ($p < 0.05$) factors on univariate analysis and clinically important features were subsequently subjected to stepwise multiple logistic regression analysis to determine the independent predictors of mortality due to ALRI.

Results

Of the 201 children analyzed (117 males and 84 females), 16 were below 2 months of age, 89 were between 2 to 12 months of age and 96 were between 12 to 60 months of age. Mortality was inversely related to age, case fatality rate (CFR) being 31.25% in children less than 2 month of age, 14.6% in children 2 to 12 months of age and 3.12% in children 12 to 60 months of age. Overall, there were 21 deaths while 180 children improved, CFR being 10.45%. CFR in males was 12.8% and 7.1% in females; this difference was not statistically significant.

In accordance with the study criteria, 182 were diagnosed as pneumonia, 18 as bronchiolitis and one as acute laryngotracheo-bronchitis. When classified as per WHO guidelines for the diagnosis of ALRI, these simple criteria identified 91% of the children, who had been diagnosed to have ALRI on detailed clinical and radiological examination. The severity of the illness was also adequately assessed as evidenced by the increasing CFR with increasing grades of illness (pneumonia, severe pneumonia, very severe pneumonia) as shown in *Table I.* However, notably 2 of the 18 subjects with a diagnosis of "no pneumonia" as per WHO guidelines expired (CFR

TABLE I–*Diagnosis by WHO Criteria and Mortality*

Diagnosis by WHO criteria	Controls (Alive=180)	Cases (Dead=21)	Case fatality rate (%)
No pneumonia	16	2	11.1
Pneumonia	45	0	0
Severe pneumonia	104	10	8.7
Very severe pneumonia	9	8	47.0
Wheezing	6	0	0
Severe croup	0	1	100

11.1% and 10% of total mortality).

Table II lists the various variables subjected to univariate analysis. None of the socio-economic variables evaluated, proved to be statistically significant. Of the biological variables, only age was a significant univariate predictor of mortality. Subjects below 1 year age comprised a little over half of the study group (105 out of 201 children) while they accounted for 86% of the deaths (18 of the 21 cases). Of the infant care factors, duration of exclusive breastfeeding and total duration of breastfeeding were protective factors. A history of any immunization was statistically comparable in both group (69% controls vs 48% cases). However, a history of measles immunization amongst the eligible subjects had a significant protective efficacy. Absence of fever, on history, in children less than 2 months of age was found to be significant, as was inability to feed in children between 2-12 months of age. Of the 29 children who had associated loose stools, 7 died, which was statistically significant. The mean duration of all symptoms considered were observed to be shorter in cases as compared to controls; of which cough, fever, fast breathing and lethargy were statistically significant. On clinical examination, general condition of the child, absence of fever, cyanosis, presence of respiratory distress, grunt, an obtunded sensorium and underlying congenital heart disease were observed to be significant predictors of mortality. Twenty children had an underlying congenital heart disease, the majority being left to right shunts. Of these 6 children died, CFR being 30%. A weight for age Z score (WAZ) below-3 was a significant predictor of mortality in children below 1 year of age. On multivariate analysis, the significant ($p < 0.05$) independent predictors of mortality *(Table III)* were age less than 1 year (OR 23.1), inability to feed (OR 6.2), presence of loose stools (OR 5.1), WAZ <-3 (OR 3.9), shorter duration of fever (OR 1.2) and bandemia (OR 1.1**).**

Discussion

The case fatality rate in the present series was substantial (10.45%) but well within the reported range of 3.5%(13) to 16.6%(21) from similar settings. An important contributor to the relatively high case fatality was the age distribution of the cohort (51% subjects <1 year). A younger age (<1 year) was documented to be the most important independent predictor of mortality in children with ALRI in the present study (OR 23.1). An inverse relationship between ALRI mortality and age has been documented in most of the earlier reports(13,15,18,19) with a few exceptions (12,17,21). It may be prudent to consider subjects below 1 year of age as a high risk

TABLE II–*Variables* Subjected to Univariate Analysis

Socio-economic		
Maternal age	Maternal education	Family size
Paternal age	Paternal education	Family income
Biological		
Birth order	Sex	Age*
Infant care		
Duration of exclusive breastfeeding*	Measles Immunization*	
Total duration of breastfeeding*		
Clinical		
Historical		
Previous ALRI	Cough	Lethargy*
Absence of fever*	Fast breathing	Irritabiity*
Inability to feed*	Post measles state	Loose stools*
Treatment prior to hospitalization		
Examination		
General condition*	Absence of fever*	Wheezing
Respiratory distress*	Cyanosis*	Stridor
Pallor	Obtunded sensorium*	Grunt*
Hepatomegaly	Associated congenital* heart disease	
Anthropometry (Z scores)		
Weight for age*	Height for age	Weight for height
Investigations		
Hemoglobin	Total leucocyte count	
Bandemia*	Differential leucocyte count	

* Statistically significant (p <0.05)

TABLE III– *Significant (p <0.05) Independent Predictors of Mortality in ALRI*

Predictor	Odds ratio (OR)	95% Confidence intervals (CI)
Age < 1 year	23.1	2.7-197.5
Inability to feed	6.2	1.3-30.7
Presence of loose stools	5.1	1.2-27.3
Weight for age (Z score <-3)	3.9	1.01-9.7
Short duration of fever	1.2	1.0-1.5
Bandemia	1.1	1.05-1.2

group in ALRI to be targeted for appropriate referral and intensive intervention instead of the currently suggested(3,22) cut off point of *2* months.

Other important significant independent predictors of mortality in the current series were inability to feed (OR 6.2), presence of loose stools (OR 5.1) and severe malnutrition (weight for age <-3 SD; OR 3.9). Earlier studies have also documented failure to feed(17,18), concurrent illness like diarrhea, septicemia or meningitis(15,19) and malnutrition (12,13,15,17-19) to be significant risk factors for mortality in ALRI. Immune deficiency and impairment of host

responses in malnourished children predisposes them to severe infection and complications of ALRI with consequently higher mortality(23).

Bandemia and short duration of fever were the other significant independent factors associated with mortality in the current study. However, these are unlikely to be of considerable clinical significance since the OR's were low (1.1 and 1.2, respectively). A shorter duration of fever is probably a reflection of the fulminant nature of the disease. Earlier studies(17,18) have reported grunting and nasal flaring, which are indicators of severity of illness, to be strong predictors of mortality. These two factors were not significant as independent predictors in the present series and were replaced by an identical indicator, namely, inability to feed. Similarly, an assessment of the general condition of the child by the investigator was an important predictor of mortality; 86% of the children who died had been labelled as "very sick" in this manner. However, an assessment of the general condition of the child by the investigator in view of the subjective nature of such assessment, this factor was not included in the analytic framework.

The reported strong association between parental education, maternal age, family income and breastfeeding(14,24,25) and risk of death from ALRI was not evident in the multivariate model of the present study. These differences are related to the factors included in the final multivariate analytic model. While the current study identified direct markers of the severity of illness, the former reports(14,24,25) were largely restricted to social factors. The social factors are underlying determinants which influence either the health seeking behavior of severity of illness, thereby indirectly contributing to the mortality. Once direct markers of mortality are available in the analytic model, the underlying determinants may cease to attain statistical significance.

An important reassuring aspect of the study was the documentation of the substantial utility of simple guidelines of WHO(3) for case management of ARI. However, a disturbing finding was the occurrence of death in 2 of the 18 cases who were classified as "no pneumonia" as per the WHO guidelines. This finding only reinforces the clinical experience that the simplified criteria are not totally infallible and serve as a reminder for the need for constant refinement of such guidelines.

It is concluded that even in settings of high case fatality, predictors of mortality can be identified in under five children suffering from ALRI. In this context, age below 1 year, inability to feed, presence of loose stools and severe malnutrition deserve special emphasis. Early identification of subjects with these factors for close monitoring and appropriate referral and therapy may be important for reducing ALRI related mortality.

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