RESEARCH PAPER

Tachypnea and Other Danger Signs *vs* Pulse Oximetry for Prediction of Hypoxia in Severe Pneumonia/Very Severe Disease

VARUN ALWADHI, POOJA DEWAN, *RAJEEV KUMAR MALHOTRA, DHEERAJ SHAH AND PIYUSH GUPTA

*From Departments of Pediatrics, and *Biostatistics and Medical Informatics, University College of Medical Sciences and GTB Hospital, Dilshad Garden, Delhi, India.*

Correspondence to: Dr Piyush Gupta, Professor of Pediatrics, Department of Pediatrics, University College of Medical Sciences, Delhi 110 095, India. prof.piyush.gupta@gmail.com

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Objectives: To compare the performance of respiratory rate and other clinical signs against pulse oximetry for predicting hypoxia in children with Severe pneumonia/Very severe disease as per Integrated Management of Neonatal and Childhood Illness (IMNCI) classification.

Design: Cross-sectional study.

Setting: Pediatric emergency department of a tertiary-care hospital in Delhi, India.

Subjects: 112 hospitalized children (2 mo - 5 y) with Severe pneumonia/Very severe disease as per IMNCI classification.

Methods: Respiratory rate was recorded at enrolment, along with other clinical signs and symptoms. Oxygen saturation (SpO_2) was measured by a pulse oximeter. Clinical predictors of hypoxia (SpO_2 <90%) and their combinations (index test) were evaluated for their sensitivity, specificity, positive predictive value and negative predictive value for diagnosis of hypoxia, against pulse oximetry (reference test).

Results: Hypoxia was present in 57 (50.9%) children. Presence of tachypnea, head nodding, irritability, inability to drink/breastfeed, vomiting, and altered sensorium was significantly associated with hypoxia (P<0.05). Multiple logistic regression revealed that age-specific tachypnea (RR≥70/min for 2-12 mo, and RR ≥60/min for ≥12 mo), head nodding, and inability to drink/breastfeed were independent predictors for hypoxia with sensitivity of 70.2%, 50.9% and 75.4%, respectively; and specificity of 88.9%, 96.4%, and 90.9%, respectively. When all three predictors were used in conjunction, the sensitivity increased to 91.2% and specificity was 81.8%.

Conclusions: No single clinical sign can perform as well as pulse oximetry for predicting hypoxia in children with severe pneumonia. In settings where pulse oximetry is not available, combination of signs, age-specific tachypnea, head nodding, and inability to drink/breastfeeding has acceptable sensitivity and specificity.

Keywords: *Acute respiratory infection, Integrated Management of Neonatal and childhood illness, Monitoring Oxygen Therapy.*

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Pneumonia continues to be the leading cause of childhood mortality, accounting for 15% of all under-five deaths, worldwide [1-5]. To reduce child mortality, it is pertinent to reduce the mortality due to pneumonia. In a recent systematic review, hypoxia (oxygen saturation <90%) was identified as one of the most important risk factors for death in lower respiratory tract infections [6]. Hypoxia can be easily identified by pulse oximetry. According to a recent estimate, pulse oximetry has the potential to avert up to 1,48,000 deaths if implemented across selected countries [7]. However, non-availability of pulse oximetry in resource-poor settings is a major impediment in the early diagnosis of hypoxia and most health workers use clinical algorithms as proposed by Integrated Management of Neonatal and Chilhood (IMNCI) to identify children with severe pneumonia. The limited utility of clinical features alone to identify hypoxia in children with acute lower respiratory tract infection has been demonstrated in a few studies [8,9]. We conducted this study to ascertain whether clinical signs can compare with pulse oximetry to identify hypoxia amongst under-five children with severe pneumonia/Very severe disease, diagnosed as per the IMNCI algorithm adapted from WHO guidelines [10,11]. The primary objective was to determine the sensitivity and specificity of clinical signs and symptoms and their combinations against pulse oximetry for predicting hypoxia in children aged 2 months to 5 years.

METHODS

This study was carried out from December 2013 to January 2015 in the Pediatric emergency department of Guru Teg Bahadur Hospital, a tertiary-care Public hospital. All consecutive children, aged 2 months to 5 years, with cough or difficult breathing and with any of the following signs – any general danger sign (convulsions, lethargy/unconsciousness, inability to drink/breastfeed, or vomiting), chest indrawing, or stridor in a calm child –

were classified as having Severe Pneumonia or Very Severe Disease as per IMNCI guidelines [10,11] and enrolled. Children with history of recurrent nebulization (≥3 episodes), congenital heart disease, severe palmar pallor, cold skin with capillary refill time (CRT) longer than 3 seconds and weak and fast pulse, axillary temperature <36ºC, meningitis, severe dehydration, severe anemia (hemoglobin <7g/dL), and those needing ventilatory support were excluded. A child, once enrolled in the study, was not included again if presenting with another episode in subsequent days/months.

A detailed clinical history was obtained at enrolment including the sociodemographic profile and symptomatology. Socioeconomic status was determined by using modified Kuppuswami scale [12]. Anthropometry including weight, length/height and mid upper arm circumference was recorded using standard techniques [13]. Weight-for-height and height-for-age Z-scores were derived using WHO Anthro software [14]. This software uses WHO reference standards for growth in under-5 children [15]. Stunting and severe stunting were defined as height-for-age *Z*-score (HAZ) <-2SD and HAZ <-3SD, respectively. A child was considered to have severe acute malnutrition in presence of weight for height/length <-3SD or mid upper arm circumference <115 mm [16]. Physical examination included recording of vital signs (temperature, heart rate, respiratory rate, and blood pressure), assessment of chest indrawing, stridor, wheezing and other signs of respiratory distress (*e.g.* head nodding, nasal flaring, grunting, and cyanosis), and chest auscultation for crepitation/wheezing. Respiratory rate was counted for a full minute. The counting was done when the child was quiet. Fast breathing/tachypnea was defined as per WHO cut-offs [17]. Oxygen saturation was measured at admission using a pulse oximeter (OhmedaBiox 3700e pulse oximeter, BOC Health Care), with an appropriate-sized probe on a finger or toe, in room air. Hypoxia was defined as oxygen saturation <90% in room air determined using pulse oximetry [10]. Participants were categorized as having hypoxia or not having hypoxia. Children presenting with wheeze and fast breathing or chest indrawing were given a trial of rapid acting inhaled bronchodilator for up to three times 15-20 minutes apart, in accordance with the WHO recommendations and unpublished IMNCI algorithm being revised in the country [Revised IMNCI Chart book (2016); Personal communication from Norway India Partnership Initiative (NIPI)]. The child was assessed again for fast breathing and chest indrawing, and was then classified accordingly.

Children were managed as per Indian Academy of Pediatrics (IAP) Guidelines for treating Severe Pneumonia [18]. Children with oxygen saturation <90% were administered oxygen [10]. Outcome was recorded as survived/died.

Prior data indicated that the prevalence of hypoxia in Indian under-five children with cough and rapid respiration or difficulty in breathing was 25.7% and respiratory rate as predictor of hypoxia had sensitivity and specificity of 82.1%, and 51.8%, respectively [8]. Using sensitivity of 82.1% with ±15% relative precision on either side and α error of 5%, the sample size was estimated to be 98.

Statistical methods: All data were entered in the SPSS 20 software (IBM corp, Armonk, NY, USA). Differences in proportion were compared by Chi square test and Fisher's exact test. Differences between means were compared by unpaired Student's t-test where data was normally distributed and Mann-Whitney U test for non normally distributed data. A probability below 0.05 was regarded as statistically significant. The strength of association of clinical risk factors with hypoxia was determined by calculating odds ratio (OR) with their 95% confidence intervals (CIs). A uni-variate logistic regression analysis was used to identify the clinical predictors of hypoxia in children with pneumonia. Thereafter, independent predictors were identified using multivariable logistic regression (MLR) and co-variates significant at $P<0.15$ level in univariate analysis were included in the MLR. The sensitivity, specificity, negative and positive predictive values for different symptoms and signs were determined taking presence of hypoxia and non-hypoxia as gold standard. The 95% confidence intervals of these diagnostic indices were calculated using the exact binomial method (Clopper and Pearson method).

RESULTS

One hundred twelve children (median (7-21) age 7 months; IQR 7-21 months; 77 boys) with diagnosis of Severe pneumonia/Very severe disease were enrolled. Most of the children (99, 88.4%) were from the semi-urban slums, and all of them belonged to lower socioeconomic strata. Only 72 (64.3%) children received exclusive breastfeeding, and 62 (55.4%) were fully immunized for age. Wasting and stunting were present in 75 (67%) and 66 (58.9%) children, respectively.

Fifty-seven (50.9%) children were detected to have hypoxia. The sex and age distribution among the hypoxic and non-hypoxic children were comparable (***Table* I**). The prevalence of fast breathing, head-nodding, inability to drink/breastfeed, vomiting everything, and altered sensorium was significantly higher among the hypoxic children. The prevalence of abnormalities on chest

TABLE I CHARACTERISTICS OF THE UNDER-FIVE CHILDREN WITH PNEUMONIA

[‡]*Characteristic*	*Hypoxic (n=57), No. (%)*	*Non-hypoxic (n=55), No. %*	*P value*	*OR (95% CI) (unadjusted)*
Gender	40 (71.2)	37 (67.3)	0.74	1.15 (0.52, 2.55)
Age (mo)[‡]	7.0 (3.0 to 21.5)	7.0 (4.0 to 18.0)	0.77	1.00 (0.98, 1.03)
*Age-specific tachypnea	57 (100)	46 (87.3)	0.006	[#]
[$]Age-specific tachypnea	51 (89.5)	29 (52.7)	<0.001	7.62 (2.81, 20.67)
[†]Age-specific tachypnea	40 (70.2)	5 (9.1)	<0.001	23.53 (7.99, 69.31)
Grunt	4 (7.3)	0	0.12	[#]
Chest indrawing	57 (100%)	54 (98.2)	0.49	[#]
Head nodding	29 (50.9)	2 (3.6)	<0.001	27.45 (6.10, 123.53)
Nasal flaring	36 (63.2)	29 (52.7)	0.26	1.54 (0.72, 3.27)
Bronchial breathing	7(12.3)	4 (7.3)	0.37	1.79 (0.49, 6.48)
Crackles in chest	57 (100)	55 (100)	1.00	[#]
Rhonchi	47 (82.5)	43 (78.2)	0.57	1.31 (0.51, 3.34)
Irritability	19 (33.3)	30 (54.5)	0.02	0.42 (0.19, 0.89)
Inability to drink	43 (75.4)	5 (9.1)	<0.001	30.71 (10.23, 92.22)
Vomit everything	27 (47.4)	9 (16.4)	<0.001	4.60 (1.90, 11.13)
Altered sensorium	28 (49.1)	2 (3.6)	<0.001	25.59 (5.69, 115.62)
Convulsions	0	1 (1.8)	0.49	[#]
[@]Radiological pneumonia	50 (90.9)	43 (78.2)	0.18	1.99 (0.72, 5.51)
Outcome (Died)	4 (7.1)	0	0.12	[#]

**Respiratory rate ≥50/min and ≥40/min in children aged 2-12 months and ≥12 months, respectively; [$]respiratory rate ≥60/min and ≥50/min in children aged 2-12 months and ≥12 months, respectively; [†]respiratory rate ≥70/min and ≥60/min in children aged 2-12 months and ≥12 months, respectively; [‡]Median (IQR); [#]Odds ratio cannot be computed; [@]radiological pneumonia data were not available for two hypoxic subjects and for one non-hypoxic subject.*

radiograph was similar in both groups. Overall, 29 children (25.9%) had severe acute malnutrition as defined by WHO. The prevalence of SAM in the hypoxic group was 36.45 (20/55) against 15.8% (9/57) in the non-hypoxic group. Four children had a fatal outcome (3.6%), all of them had hypoxia at presentation, and two of them had severe acute malnutrition.

After logistic analysis, head-nodding, age-specific tachypnea (respiratory rate ≥70/min and ≥60/min in children aged 2-12 months and ≥12 months, respectively) and inability to drink/breastfeed were found to be significant independent risk factors for hypoxia (***Table* II**). Sensitivity, specificity, positive predictive value, and negative predictive value of the different signs and symptoms to predict hypoxia is shown in ***Table* III**. Overall, combination of the three independent predictors had the best sensitivity of 91.2% for predicting hypoxia, and the specificity was 81.8%.

DISCUSSION

We found that hypoxic under-five children with severe pneumonia had significantly higher chances of having age-specific fast-breathing, head nodding, irritability, inability to drink/breastfeed, vomiting and altered sensorium; all of which are also recognized by the IMNCI for identifying a child with severe pneumonia. Head nodding, age-specific tachypnea (respiratory rate ≥70/min and ≥60/min in children aged 2-12 months and ≥12 months, respectively) and inability to drink/breastfeed were found to be significant independent risk factors for hypoxia.

TABLE II RESULTS OF LOGISTIC REGRESSION TO IDENTIFY INDEPENDENT PREDICTORS OF HYPOXIA IN UNDER-FIVE CHILDREN WITH PNEUMONIA

Predictor	*Adjusted OR (95% CI)*	*P value*
[*]Age-specific tachypnea	9.2 (2.3, 35.9)	0.001
Head nodding	7.5 (1.3,44.3)	0.025
Inability to drink	17.8 (4.9,64.1)	<0.001

[*]Respiratory rate ≥70/min and ≥60/min in children aged 2-12 months and ≥12 months, respectively.

TABLE III SENSITIVITY, SPECIFICITY, POSITIVE AND NEGATIVE PREDICTIVE VALUE OF CLINICAL MARKERS FOR PREDICTING HYPOXIA IN UNDER-FIVE CHILDREN WITH SEVERE PNEUMONIA

Characteristics	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
*Age-specific tachypnea	100	12.7	54.3	100
$Age-specific tachypnea	89.5	47.3	63.7	81.2
†Age-specific tachypnea	70.2	88.9	88.9	74.6
Grunt	7.0	100	100	50.9
Chest indrawing	100	1.8	51.4	100
Head nodding	50.9	96.4	93.5	65.4
Nasal flaring	63.2			
Bronchial breathing	12.3	92.7	63.6	50.5
Accessory muscle use	10.5	100	100	51.9
Rhonchi	82.5	21.8	52.2	54.5
Inability to drink	75.4	90.9	89.6	78.1
Vomit everything	47.4	83.6	75.00	60.5
Altered sensorium	49.1	96.4	93.3	64.6
Irritability	33.3	45.5	38.8	39.7
†Age-specific tachypnea + Inability to drink	89.5	81.8	83.6	88.2
†Age-specific tachypnea + Head Nodding	82.5	90.9	90.4	83.3
†Age-specific tachypnea Head nodding +Inability to drink	91.2	81.8	83.9	90.0
Radiological evidence of pneumonia	90.9	20.4	53.8	68.8.

*NPV: Negative predictive value, CI: Confidence interval, OR: Odds ratio, PPV: Positive predictive value; *respiratory rate ≥50/min and ≥40/min in children aged 2-12 months and ≥12 months respectively; $respiratory rate ≥60/min and ≥50/min in children aged 2-12 months and ≥12 months respectively; †respiratory rate ≥70/min and ≥60/min in children aged 2-12 months and ≥12 months respectively.*

The limitations of our study include its hospital-based design and that hypoxia was determined based on pulse oximeter readings and not on arterial blood gas analysis. In addition, our study population included only children with severe pneumonia and very severe disease; children with acute lower respiratory tract infection managed on ambulatory basis in the community were not evaluated. There were only 10 children of less than 3 months age and only 29 cases of severe acute malnutrition. In a study in Nepalese children with pneumonia [9], the clinical predictors significantly associated with hypoxia were lethargy, grunting, nasal flaring, cyanosis, and inability to breastfeed/drink; chest indrawing was found to be the best clinical predictor of hypoxia in children aged 2 months to 5 years presenting with pneumonia with 68.9% sensitivity and 82.6% specificity. The variance in results as compared to our study may be due to a difference in the altitude of the two study places. Another reason could be that we enrolled children with IMNCI classification of severe pneumonia.

Our study had severe acute malnutrition in only about 25% participants which may account for lack of significant association between chest indrawing and hypoxia. Malnourished children tend to have reduced serum potassium, magnesium and calcium levels, which may contribute to the reduced strength of accessory respiratory muscles and have generalized muscle wasting and hypotonia [19,20]. Thus, malnourished children may be unable to exhibit chest indrawing, a clinical sign often regarded as ominous in children with pneumonia. However, Chisti, *et al*. [21] found chest indrawing to be a good clinical predictor for hypoxia in malnourished Bangladeshi children with pneumonia. They explained that the rapid breathing and lower chest wall indrawing observed in malnourished children was due to hyperventilation in an effort to eliminate the excess CO_2 from the pulmonary circulation in children with severe pneumonia. The present study had only 29 malnourished cases making it difficult to draw a reasonable conclusion.

We observed that hypoxia was present in 50.9% of children with severe pneumonia, which is much higher than 25.6% reported from another study from Delhi among under-five children severe pneumonia [8]. The difference stems from the fact that the definition of severe pneumonia used in our study is based on IMNCI

WHAT IS ALREADY KNOWN?

- Clinical signs are surrogate markers to predict hypoxia in children with pneumonia ≥2 months of age.

WHAT THIS STUDY ADDS?

- No single clinical sign is appropriate to predict hypoxia in children presenting with pneumonia; combination of clinical signs improves the ability to predict hypoxia.

guidelines, which uses a syndromic approach to identify sick children unlike the WHO algorithm used by Lodha, *et al*. [8].

We found that the conventional WHO cut-offs to define tachypnea had a 100% sensitivity but an unacceptable specificity of 12.7% to predict hypoxia in children with IMNCI classification of severe pneumonia/ very severe disease. However, increasing the WHO cut-offs for fast breathing by 20 (defined as "respiratory rate ≥70/min and ≥60/min in children aged 2-12 months and ≥12 months, respectively) increased the specificity to 88.9% while sensitivity was 70.2%. We also found that inability to drink/breastfeed and head-nodding were independent predictors of hypoxia in these children. When all the three clinical signs were combined, the sensitivity was 91.2% and specificity was 81.8%, which seems acceptable to diagnose hypoxia in children with severe pneumonia in resource-poor settings. However, using a combination of clinical signs to identify sick children may be more cumbersome and would require training of health workers. In addition, none of the three signs (tachypnea, inability to drink/breastfeed, and head nodding) is specific for hypoxia, and may be seen in a variety of clinical conditions like metabolic acidosis due to renal failure, dehydration and neurological illnesses.

Pulse oximetry was able to correctly identify hypoxia in 10-20% more children with severe pneumonia than with clinical signs alone. Pulse oximetry has the potential to delineate severe from non-severe pneumonia with greater precision and will help optimize the usage of antibiotics and oxygen in children with pneumonia. While, age-specific fast breathing cut-offs and presence of danger signs continue to be acceptable as surrogate markers for severe pneumonia, use of pulse oximetry in the standard care of children presenting with pneumoniawill help us accelerate our efforts to improve child survival. In settings where pulse oximetry cannot be performed for any reason combination of signs, age-specific tachypnea (respiratory cut-offs of ≥70/min and ≥60/min in children aged 2-12 months and ≥12 months respectively), head nodding, and inability to drink/ breastfeed can be used for admission and oxygen therapy.

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