

Predictors of hypoxaemia in hospital admissions with acute lower respiratory tract infection in a developing country

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Abstract

Since oxygen has to be given to most children in developing countries on the basis of clinical signs without performing blood gas analyses, possible clinical predictors of hypoxaemia were studied. Sixty nine children between the ages of 2 months and 5 years admitted to hospital with acute lower respiratory tract infection and an oxygen saturation (SaO_2) < 90% were compared with 67 children matched for age and diagnosis from the same referral hospital with an SaO_2 of 90% or above (control group 1), and 44 unreferred children admitted to a secondary care hospital with acute lower respiratory infection (control group 2). Using multiple logistic regression analysis, sleepiness, arousal, quality of cry, cyanosis, head nodding, decreased air entry, nasal flaring, and upper arm circumference were found to be independent predictors of hypoxaemia on comparison of the cases with control group 1. Using a simple model of cyanosis or head nodding or not crying, the sensitivity to predict hypoxaemia was 59%, and the specificity 94% and 93% compared to control groups 1 and 2, respectively; 80% of the children with an SaO_2 < 80% were identified by the combination of these signs. Over half of the children with hypoxaemia could be identified with a combination of three signs: extreme respiratory distress, cyanosis, and severely compromised general status. Further prospective validation of this model with other datasets is warranted. No other signs improved the sensitivity without compromising specificity. If a higher sensitivity is required, pulse oximetry has to be used.

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Hypoxaemia is the most serious manifestation of severe pneumonia in children. The case fatality rate of pneumonia is inversely related to the arterial haemoglobin oxygen saturation (SaO_2).¹ As respiratory infections are one of the main causes of death in children in developing countries,^{2,3} and the delivery of oxygen to hypoxaemic children may improve the outcome, the detection of hypoxaemia is important. The most reliable way to do this is an

arterial blood gas analysis or the determination of the arterial haemoglobin SaO_2 by pulse oximeter. However, machines to make these measurements are expensive, need constant maintenance, and are not widely available in developing countries. To help health professionals decide which children are hypoxaemic and might benefit from oxygen treatment, we have studied the signs and symptoms indicating hypoxaemia in children with pneumonia.

Methods

PATIENTS

The study was performed in the paediatric ward of the Royal Victoria Hospital (RVH) in Banjul, the only tertiary paediatric referral hospital in the Gambia, and in the hospital of the Medical Research Council (MRC) in Fajara, a primary and secondary care institution serving a predominantly periurban population. Children between 2 months and 5 years of age were included if they presented with an acute lower respiratory tract infection and had no signs of congenital heart disease or meningitis. The case children had an arterial haemoglobin SaO_2 of < 90%, measured by pulse oximeter. This SaO_2 is generally considered to reflect severe hypoxaemia. Control group 1 comprised children who were referred to the ward of the RVH with the same diagnosis and exclusion criteria as the cases but who had an SaO_2 of 90% or above. These children were matched to the case children for age and for the clinical diagnosis of bronchiolitis or pneumonia. As they were matched controls, their status of having an SaO_2 of 90% or above was known to the investigator. Therefore, a second control group was enrolled: control group 2 comprised of unreferred patients with acute lower respiratory tract infection who presented to the outpatient department of the MRC laboratories. These children were examined without knowledge of the SaO_2 . The children in control group 2 were enrolled as part of an evaluation of the World Health Organisation (WHO)/Unicef sick child algorithm and comprised children in this group with a diagnosis of acute lower respiratory tract infection. According to the severity of the condition, children were admitted or treated as outpatients. Children with a SaO_2 below 90% and children who were not admitted were excluded from the analysis.

A history was obtained from the caretaker. First, the complaints and duration of complaints were asked for in an open manner. Then

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Table 1 Patient characteristics

		Cases	Control group 1 RVH	Control group 2 MRC
No		69	67	44
Age (months)	Median (25%, 75%)	12 (6, 19)	12 (6, 18)	17 (7, 23)
Sex	Female/male (% female)	33/36 (48%)	37/30 (55%)	18/26 (41%)
Sao ₂	Median (25%, 75%)	82 (72, 85)	96 (94, 98)	96 (95, 98)

specific questions about the history of the child were asked. The physical examination documented the general status of the child, specific respiratory findings, vital signs, and anthropometric measurements. The categories of the signs are shown together with the results in the tables. Head nodding is a movement of the head synchronous with each breath, which is caused by increased use of auxiliary muscles of respiration and therefore indicates severe respiratory distress. All observations were done by a single observer (MWW). Weight for age was calculated using the United States National Center for Health Statistics (NCHS) standard as comparison. If possible, a chest radiograph was obtained, which was read in a blinded manner by one of us (EKM). Parenchymal changes were classified in the following way: (a) none; (b) minor—consistent with pneumonia in the presence of supportive physical findings; (c) major—diagnostic of pneumonia by itself, but no lobar consolidation; (d) lobar consolidation. The presence of pleural changes, pneumothorax, and hyperinflation was also noted.

Verbal consent was obtained from the caretaker and all explanations were given by a field assistant who spoke the appropriate language. The study was approved by the Gambian Government/MRC ethics committee.

STATISTICAL ANALYSIS

Comparisons between continuous normally distributed data were made using the *t* test after application of Bartlett's test for homogeneity of

variance, while non-normally distributed data were compared using the Wilcoxon test. Discrete data were compared using the χ^2 with Yate's correction or Fisher's exact test if the frequencies were small.

The predictors of hypoxaemia were determined using multiple logistic regression models. Models were compared between one another using changes in deviance with the corresponding changes in degrees of freedom which follow a χ^2 distribution (likelihood ratio test). Analyses were performed using SPSS for Windows, SAS for Windows, and Epi-Info software packages.

Results

Sixty nine children with an acute lower respiratory tract infection and hypoxaemia, together with 67 controls with an Sao₂ of 90% or above, were seen at RVH. Eighty three unreferral children with a diagnosis of acute lower respiratory tract infection were seen at the MRC hospital. Of those seen at the MRC hospital, three had an Sao₂ below 90% and were excluded from the study, 36 were treated as outpatients and, as the disease was much milder in these cases, not considered in this analysis, and 44 were admitted to the ward. A clinical diagnosis of bronchiolitis was made in nine of the cases (13%), in eight (12%) of the children in control group 1, and in four (9%) of the children in control group 2. Six of the cases, but none of the controls, had measles as concurrent diagnosis. The characteristics of the patients in the three groups are listed in table 1, the findings on examination of the chest radiographs in table 2.

The median (25%, 75% quartiles) duration of illness was four days (3, 7) for the cases, three days (3, 4) for control group 1, and three days (3, 5) for control group 2 ($p = 0.1$ for cases *v* control group 1, $p = 0.5$ for cases *v* control group 2).

VOLUNTEERED COMPLAINTS

Rashes were significantly more common in the cases than in control group 1 (10% *v* 0%, $p = 0.01$), cough more common in cases than in control group 2 (71% *v* 50%, $p = 0.04$), and abdominal pain more common in control group 2 than in the cases (16% *v* 0%, $p = 0.001$). Otherwise, there was no significant difference between the groups in volunteered complaints.

SYMPTOMS ON DIRECT QUESTIONING

Moderate or severely reduced feeding was present in 29 (42%) of the cases, in 15 (22%) of children in control group 1, and in five (11%) of children in control group 2 ($p = 0.02$ for cases *v* control group 1, $p = 0.001$ for cases *v* control group 2).

Convulsions were reported in 10 (15%) of the cases, in two (3%) of children in control group 1, and in seven (16%) of children in control group 2 ($p = 0.04$ for cases *v* control group 1, $p = 1$ for cases *v* control group 2); abnormal sleepiness in 29 (42%) of cases, in 15 (22%) of children in control group 1, and in seven (16%) of children in control group 2 ($p =$

Table 2 Chest radiograph findings. Percentages in brackets

Sign	Categories	Oxygen cases	Control group 1 RVH	Control group 2 MRC	<i>p</i> Value cases <i>v</i> control group 1	<i>p</i> Value cases <i>v</i> control group 2
No of x rays obtained		60 (87%)	58 (87%)	36 (82%)		
Quality	Fair Poor Unreadable	56 (93) 2 (3) 2 (3)	52 (90) 5 (9) 1 (2)	35 (97) 1 (3)		
Consolidation	None Minor Major Lobar	6 (10) 13 (22) 29 (50) 10 (17)	9 (16) 20 (35) 14 (25) 14 (25)	4 (11) 7 (19) 13 (36) 12 (33)	0.06	0.3
Pleural involvement	None Effusion Pyopneumothorax	51 (88) 5 (9) 2 (3)	52 (91) 5 (9)	35 (97) 1 (3)	0.8	0.25
Hyperinflation	Present	17 (29)	21 (37)	3 (8)	0.5	0.04

Table 3 Physical signs reflecting the general status of the child. Percentages in brackets

Sign	Categories	Oxygen cases	Control group 1 RVH	Control group 2 MRC	p Value cases v control group 1	p Value cases v control group 2
Appearance	Normal	4 (6)	4 (6)	10 (23)	<0.0001	0.002
	Sick	34 (49)	54 (81)	26 (59)		
	Very sick	31 (45)	9 (13)	8 (18)		
Arousal	Normal	21 (30)	52 (78)	Not done	<0.0001	—
	Lethargic	43 (62)	15 (22)			
	Unresponsive	5 (7)	0 (0)			
Attentiveness	Engages	19 (28)	48 (72)	29 (66)	<0.0001	<0.0001
	Decreased	44 (64)	19 (28)	15 (34)		
	Dull	6 (9)	0 (0)	0 (0)		
Movement	Spontaneous	44 (64)	63 (94)	41 (93)	<0.0001	0.005
	Stimulation	20 (29)	4 (6)	3 (7)		
	Pain	2 (3)	0 (0)	0 (0)		
	None	3 (4)	0 (0)	0 (0)		
Ability to feed	Normal	20 (29)	45 (67)	27 (61)	<0.0001	0.001
	Decreased	38 (55)	20 (30)	16 (36)		
	Not able	11 (16)	1 (1)	1 (2)		
	Not interested	0 (0)	1 (1)	0 (0)		
Quality of cry	Vigorous	20 (29)	45 (67)	29 (66)	<0.0001	<0.0001
	Weak	36 (52)	21 (31)	14 (32)		
	Hot	13 (19)	1 (1)	1 (2)		
Consolability	Quiets down	37 (54)	47 (70)	25 (57)	0.001	0.005
	Irritable	16 (23)	13 (19)	17 (39)		
	Continues crying	1 (1)	6 (9)	2 (5)		
	Does not cry	15 (22)	1 (1)	0 (0)		
Tone	Normal	57 (83)	65 (97)	43 (98)	0.02	0.048
	Hypertonic	1 (1)	0 (0)	0 (0)		
	Hypotonic	11 (16)	2 (3)	1 (2)		

0.02 for cases *v* control group 1, $p = 0.007$ for cases *v* control group 2). Irritability was inversely related to hypoxaemia; it was reported in 28 (41%) of cases, in 38 (57%) of children in control group 1, and in 28 (64%) of children in control group 2 ($p = 0.09$ for cases *v* control group 1, $p = 0.03$ for cases *v* control group 2).

Cough, difficulty in breathing, fast breathing, noisy breathing, and diarrhoea were reported with similar frequency in cases and controls.

EXAMINATION FINDINGS

General observations on the status of the children are presented in table 3. The findings on examination of the respiratory system are shown in table 4.

The nutritional status of the cases was significantly worse than in the controls. The weight for age (Z score, mean (SD)) was -2.17 (1.3) for the cases, -1.26 (1.6) for control group 1, and -1.08 (1.4) for control group 2 ($p = 0.0003$ for cases *v* control group 1, $p = 0.001$ for cases *v* control group 2). Children with measles were not significantly more malnourished than other children in the case group. Forty two of the cases (61%) had a weight for age of below 80% of the NCHS standard, but only 22 (33%) of the children in control group 1 and 16 (36%) of the children in control group 2. The mean (SD) upper arm circumference was 12.0 (1.7) cm for cases, 13.0 (1.5) cm for control group 1, and 13.6 (1.3) cm for control group 2 ($p = 0.0001$ for both comparisons).

The mean (SD) temperature was $38.3(1.2)^{\circ}\text{C}$ for the cases, $38.7(1.1)^{\circ}\text{C}$ for control group 1, and $38.8(1.0)^{\circ}\text{C}$ for control

group 2 ($p = 0.07$ for cases *v* control group 1, $p = 0.02$ for cases *v* control group 2).

The heart rate was not significantly different between groups.

MULTIPLE LOGISTIC REGRESSION

Using multiple logistic regression independent predictors of hypoxaemia when comparing the cases with control group 1 were sleepiness, arousal, quality of cry, cyanosis, head nodding, decreased air entry, nasal flaring, and upper arm circumference. When cases were compared with control group 2, difficulty in breathing as a volunteered complaint, sleepiness as a complaint, cyanosis, crepitations, respiratory rate, head nodding, upper arm circumference, and liver size were independent predictors.

SENSITIVITY AND SPECIFICITY OF DIFFERENT SIMPLE MODELS

Using a small number of variables from both comparisons above, the following model gave the best sensitivity combined with a reasonable specificity: presence of cyanosis, or head nodding, or not crying at all during examination. This model predicted the presence of hypoxaemia with a sensitivity 59% and a specificity of 94%, compared with control group 1, and a sensitivity of 59% and a specificity of 93%, compared to control group 2. Changing these criteria to *weak or absent* cry, or head nodding, or cyanosis increased the sensitivity to 84%, but lowered the specificity to 62% and 63% for control groups 1 and 2, respectively. Replacing the 'ability to cry' in above model with 'not feeding at all', being hypotonic, or being unresponsive to stimuli gave sensitivities of 59%, 58%, and 56%, respectively, whereas the specificities remained above 90%.

The WHO criteria for giving oxygen^{4,5} of cyanosis, inability to drink, severe chest indrawing, or a respiratory rate over 70 breaths per minute predicted hypoxaemia with a sensitivity of 62% and specificities of 76% and 82% for control groups 1 and 2, respectively. Leaving out the respiratory rate in the WHO model increased the specificity to 96% and 95%, respectively, and lowered the sensitivity to 52%. A respiratory rate of > 70 or grunting or severe indrawing for children under 12 months and a respiratory rate of > 60 for older children as a single predictor of hypoxaemia, as proposed in a study from Kenya,¹ gave a sensitivity of 71% and specificities of 47% and 61% for control groups 1 and 2, respectively.

Thirty children had an SaO_2 of $< 80\%$. For this subgroup of the most severe cases, the model of absence of crying or head nodding or cyanosis had a sensitivity of 80%, the WHO model with respiratory rate had a sensitivity of 80%, the WHO model without respiratory rate had a sensitivity of 77%, and the model based on the two cut off points for respiratory rate proposed in the study from Kenya had a sensitivity of 80%.

Table 4 Observed respiratory signs of the children. Percentages in brackets

Sign	Categories	Oxygen cases	Control group 1 RVH	Control group 2 MRC	p Value cases v control group 1	p Value cases v control group 2
Cough	Heard	63 (91)	49 (73)	33 (75)	0.01	0.04
Nasal flaring	Present	49 (71)	31 (46)	18 (41)	0.006	0.003
Nasal discharge	Present	25 (36)	21 (31)	19 (43)	0.5	0.6
Cyanosis	Present	27 (39)	0 (0)	0 (0)	<0.0001	<0.0001
Hyperinflation of thorax	Visible	13 (19)	13 (19)	1 (2)	1.0	0.008
Respiratory rate	Mean SD	62.6 14.0	61.3 12.1	54.7 13.2	0.6	0.003
Supraclavicular indrawing	None	17 (25)	37 (55)	34 (77)	0.001	<0.0001
	Mild	27 (39)	22 (33)	10 (23)		
	Moderate	21 (30)	8 (12)	0 (0)		
	Severe	4 (6)	0 (0)	0 (0)		
Intercostal indrawing	None	24 (35)	46 (69)	35 (80)	<0.0001	<0.0001
	Mild	18 (26)	14 (21)	3 (7)		
	Moderate	24 (35)	7 (10)	6 (14)		
	Severe	3 (4)	0 (0)	0 (0)		
Lower chest wall indrawing	None	18 (26)	25 (37)	27 (61)	0.1	0.002
	Mild	17 (25)	22 (33)	8 (18)		
	Moderate	29 (42)	18 (27)	8 (18)		
	Severe	5 (7)	2 (3)	1 (2)		
Grunting	None	36 (52)	41 (61)	25 (57)	0.2	0.5
	Occasional	23 (33)	22 (33)	16 (36)		
	Every breath	10 (15)	4 (6)	3 (7)		
Head nodding	Present	18 (29)	3 (4)	3 (7)	<0.0001	0.006
Crepitations	Present	64 (93)	59 (88)	27 (61)	0.3	<0.0001
Wheeze	Present	15 (22)	12 (18)	5 (11)	0.4	0.4
Rhonchi	Present	7 (10)	10 (15)	9 (20)	0.7	0.1
Decreased air entry	Present	12 (17)	2 (3)	2 (5)	0.03	0.2

Discussion

We could show in our study that a simple model of cyanosis, or head nodding, or absence of crying on examination could predict hypoxaemia ($\text{SaO}_2 < 90\%$) with a sensitivity of 59% and a high specificity. A number of physical signs were highly significantly associated with hypoxaemia, but the sensitivity of each sign alone was low. Cyanosis has long been known to be associated with hypoxaemia,^{6,7} but the difficulty of its detection, especially in children with dark pigmentation of the skin, makes it an insensitive marker. In our study, the respiratory rate was a poor predictor of hypoxaemia, as found in other studies.^{8,9} Irritability as a sign for hypoxaemia is based on observations in England, where a small number of children, mainly with bronchiolitis, became irritable when they were disconnected from oxygen.¹⁰ Other observers did not find this a helpful sign.⁷ In our series, irritability was inversely related to the presence of hypoxaemia, that is, hypoxaemic children tended to be more lethargic than irritable. The higher proportion of children with bacterial pneumonia might account for this finding. The influence of malnutrition on the severity of acute respiratory tract infection has been described before,^{11,12} but it had not been shown, to our knowledge, that it is associated with hypoxaemia. As control group 1 was matched to the cases by

age, we could not evaluate the effect of age. Unpublished observations in the RVH indicate that younger children are at higher risk for hypoxaemia, and the children in control group 2 tended to be older, though the difference in age was not statistically significant. The influence of age will have to be evaluated in future studies. Our study was performed at sea level. It has been shown that altitude influences physical signs.^{13,14}

However, no single sign was sufficiently sensitive and specific to be used as a single predictor. Only a combination of several independent highly specific markers was able to improve sensitivity without compromising specificity overmuch. We have restricted the final model of prediction of hypoxaemia to three elements that were consistent in both comparisons. Quality of cry and head nodding have the additional advantage that they can be taught easily to health professionals with a limited amount of training. Cyanosis is often difficult to detect, although when present it is highly specific for the presence of hypoxaemia. The combination of the three signs doubled the sensitivity of each individual sign, whereas it did not decrease the specificity substantially.

The weakness of the comparison of cases with control group 1 is the possibility of observer bias, as the allocation of the children to the control group was known to the observer. Therefore the findings in the comparison with control group 2 lend additional weight to the observations. However, control group 2 had a higher number of bronchiolitis cases and no child in the control groups had measles. This difference might have affected the results.

Comparing our results to other published suggestions, we found that the WHO guidelines^{4,5} had a similar sensitivity but were slightly less specific. As only a minority of pneumonia cases will be hypoxaemic, this fall in specificity will result in overtreatment with oxygen, which does not matter where oxygen is available and cost considered negligible. However, in developing countries, indiscriminate oxygen treatment will make it unaffordable. In a setting where 15% of pneumonia cases are hypoxaemic, as in RVH (unpublished observations), a fall in specificity from 94% to 76% means that the number of children who receive oxygen but do not actually require it (false positives) quadruples. Two out of three children who receive oxygen in this scenario do not need it. Leaving the respiratory rate out of the WHO model resulted in a considerable increase in specificity and lost only 10% in sensitivity. The model based on cut off points in respiratory rate, as suggested from Kenya,¹ did not perform as well as our model or the WHO guidelines. All three models showed a better sensitivity in the subgroup of children who were most profoundly hypoxaemic. A recent study from Papua New Guinea developed a model to increase the sensitivity of a combination of four clinical signs (cyanosis, grunting, reduced consciousness, respiratory rate above 90/min) to 67%, but the specificity of this model fell to 70%.¹⁵

The retrospective fitting of models to data maximises the predictive value of variables. To make best use of the variables we selected, they will have to be validated prospectively. Head nodding in particular has not been documented widely in studies. The attraction of the sign is the ease of recognition without undressing the child and the ease with which it can be taught to health professionals, provided it is validated in other studies.

Using only a limited number of physical signs, hypoxaemia will be missed in certain children, or oxygen will be wasted on children who do not really need it. Especially in a setting where oxygen has to be bought in cylinders, a pulse oximeter might be a cost effective purchase, as it allows children in need of oxygen to be identified, and the amount of oxygen given can be titrated to the actual need of the patient, thus avoiding wastage. In a more peripheral setting, where children will be screened by using physical signs as an aid for possible referral to bigger hospitals with a supply of oxygen, the teaching of signs predicting hypoxaemia will enable health professionals to refer the majority of patients in need of supplemental oxygen.

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