

Hypoxaemia in acute respiratory and non-respiratory illnesses in neonates and children in a developing country

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Arch Dis Child 2002;86:108–112

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Accepted for publication 13 November 2001

Aims: To determine, in sick neonates and children requiring admission to a hospital in the highlands of Papua New Guinea: (1) the incidence and severity of hypoxaemia; (2) the proportion with hypoxaemia who do not fulfil criteria for acute lower respiratory infection (ALRI); and (3) the power of clinical signs to predict hypoxaemia, according to age and disease category.

Methods: Age dependent normal values for transcutaneous oxygen saturation (SpO_2) were established in 218 well neonates and children in Goroka. A total of 491 sick neonates and children were then studied on presentation to the paediatric department at Goroka Hospital.

Results: A total of 257 sick neonates and children (52%) were hypoxaemic. Hypoxaemia was present in 179/245 (73%) with clinical criteria for ALRI; 79/246 (32%) with non-ALRI illnesses (including meningitis, septicaemia, severe malnutrition, low birth weight, birth asphyxia, and congenital syphilis) were also hypoxaemic. For children aged 1 month to 5 years with ALRI, the clinical signs best predicting hypoxaemia were cyanosis, respiratory rate >60 , poor feeding, or reduced spontaneous activity; in those without ALRI the best predictors were cyanosis, respiratory rate >60 per minute, and inability to feed, but the positive predictive value was much lower than for children with ALRI. For neonates cyanosis was predictive of hypoxaemia, but tachypnoea or inability to feed were not.

Conclusions: Hypoxaemia is an under recognised complication of non-ALRI illnesses in children and in sick neonates in developing countries. Use of algorithms with high sensitivity for the recognition of hypoxaemia, and protocols for administration of oxygen to neonates, and to children with non-ALRI illnesses, might substantially reduce case fatality.

Acute lower respiratory infections (ALRI) are one of the commonest causes of death in children in developing countries. Most ALRI deaths are from pneumonia, the major fatal complication of which is hypoxaemia.¹ The haemoglobin oxygen saturation (SpO_2), measured using a pulse oximeter, has been shown to predict outcome in children with ALRI.² The World Health Organisation (WHO) has developed guidelines for giving supplemental oxygen to children with ALRI in health facilities in developing countries.¹ Several clinical symptoms or signs have been found to predict hypoxaemia in children with ALRI. These include inability to feed, reduced activity, cyanosis, fast respiratory rate, failure to resist examination, grunting, and head nodding.^{3–6} Most studies on the incidence and clinical signs that predict hypoxaemia have been done in infants over 3 months of age with ALRI. There are few published data on the incidence, significance, or clinical predictors of hypoxaemia in sick children who do not have ALRI, or in neonates. Worldwide there are more than 2 million deaths from perinatal causes annually, and non-ALRI conditions such as meningitis, syphilis, tetanus, and septicaemia cause more than half a million deaths in the under 5s each year; therefore the global burden of hypoxaemia in these groups may be very large.⁷

To address this issue we conducted a study of the incidence and clinical predictors of hypoxaemia in neonates and children in all diagnostic categories admitted to a hospital in the highlands of Papua New Guinea. We established normal values for oxygen saturation among well neonates and children in the highlands so that an altitude appropriate age matched comparison with sick children could be done.

We aimed to determine: (1) normal values for SpO_2 at 1600 m above sea level for neonates and children; (2) the incidence and severity of hypoxaemia in age and diagnostic specific cat-

egories; and (3) clinical signs that predict hypoxaemia, and their age specific predictive power.

METHODS

This study was done at Goroka Hospital, a base hospital in the Eastern Highlands of Papua New Guinea located at an altitude of 1600 m above sea level. The hospital serves a mixed rural and periurban population of 380 000; about 3000 children and neonates are admitted to the 85 bed paediatric department each year. Children are referred from aid posts and rural health centres, or come directly from villages.

To establish normal values of haemoglobin oxygen saturation, children from 1 month to 5 years were recruited from the outpatient immunisation clinic, and neonates (28 days of age or less) were recruited from the postnatal ward. They were eligible if they were assessed as being healthy, based on history and examination by two of the investigators (AJB and JLB). SpO_2 of resting children (before immunisation) was measured using a pulse oximeter (Nelcor Puritan Bennet-3930 with Dura-Y infant sensor) attached to the finger or toe. Recordings were taken after stabilisation of the pulse oximetry reading for one minute. Age, weight, and current province of residence of the child were also recorded.

For the ill child portion of the study, children were recruited at the time of presentation to the children's ward. The children

Abbreviations: ALRI, acute lower respiratory infection; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SpO_2 , transcutaneous oxygen saturation; WHO, World Health Organisation

Table 1 ALRI, non-ALRI and diagnosis specific oxygen saturation in children aged 1 month to 5 years

Principal diagnosis	Number	Median (IQR) SpO ₂	Number (%) with clinical ALRI	% with SpO ₂ <88%	Difference from normal children: p value
Normal children	151	96 (95–97)	0	3 (2)	
All sick children	359	86 (76–93)	223 (62)	200 (56)	<0.0001
ALRI	223	82 (72–88)	223 (100)	162 (72.6)	<0.0001
Sick children, no ALRI	136	93 (86–96)	0	38 (27.9)	<0.0001
Meningitis	40	86 (78–93)	3 (7.5%)	21 (53)	<0.0001
Septicaemia	10	79 (57–94)	1 (10.0)	6 (60)	<0.0001
Diarrhoeal disease/dysentery	35	95 (91–96)	7 (20)	3 (8.6)	0.0003
Marasmus or kwashiorkor	21	94 (88–96)	4 (19)	5 (23.8)	0.007
Malaria	5	95 (92–96)	1 (20)	0	0.57
Typhoid	4	94 (85–97)	0	1 (25)	0.12

Table 2 ALRI, non-ALRI and diagnosis specific oxygen saturation in neonates

Principal diagnosis	Number	Median (IQR) SpO ₂	Number (%) with clinical ALRI	% with SpO ₂ <86%	Difference from normal neonates: p value
Normal	67	94 (92–95)	0	1 (1.5)	
Sick neonate	132	88 (66–94)	22 (16.7)	57 (43.2)	<0.0001
ALRI	22	72 (52–85)	22 (100)	17 (77)	<0.0001
Sick neonate, no ALRI	110	90 (72–96)	0	40 (36.4)	0.0002
Septicaemia	34	87 (59–93)	7 (20.6)	15 (44.1)	<0.0001
Low birth weight	33	89 (75–96)	0	10 (30.3)	0.02
Birth asphyxia	25	74 (39–93)	0	15 (60)	<0.0001
Congenital syphilis	4	56 (12–72)	0	4 (100)	0.0008

were not selected for severity of illness or particular diagnostic groups, but represented all children admitted by two of the investigators (TD and SS) over 12 month and four month periods, respectively. Diagnoses were assigned according to the presenting clinical features and the results of relevant investigations. Multiple diagnoses were recorded if present. Children were evaluated for the presence of ALRI: this included children with the WHO definitions of mild, moderate, severe, or very severe pneumonia, measles, and pertussis.¹ We also included children with pulmonary tuberculosis in this group with ALRI. We recorded the presence or absence of the following clinical symptoms or signs: inability to feed, reduced activity, cyanosis, fast respiratory rate, failure to resist examination, grunting, and head nodding. These signs were recorded before measuring the SpO₂, which was done with the child breathing room air, as described above. Age and weight of the child were also recorded.

Logistic regression analysis was used to determine the best independent combinations of clinical signs predicting hypoxaemia, and these are presented as odds ratios (95% confidence intervals), sensitivity, specificity, and positive (PPV) and negative (NPV) predictive value. For combination algorithms the area under the receiver operating characteristics curve (ROC) was calculated.⁸ An ROC curve plots sensitivity versus 1-specificity. An algorithm or test with perfect predictive power, that is 100% sensitivity and 100% specificity, will have an area under the ROC curve of 1.0. An algorithm that predicts no better than chance has an area under the ROC curve of 0.5; 0.6–0.7 is considered to be poor prediction, 0.8 is moderate prediction, and 0.9 excellent prediction.

The study methods were approved by the Papua New Guinea Medical Research Advisory Committee as part of a larger study of severe pneumonia in children.

RESULTS

Normal values of haemoglobin oxygen saturation

A total of 218 well children were studied: 67 neonates (aged <28 days) and 151 older children (1–60 months). The overall

mean and median SpO₂ were 95.0% (range 75–100%). The mean SpO₂ for children was lower for neonates than older children: 93.3% (SD 3.4%) compared to 95.7% (SD 2.7%) ($p < 0.0001$).

To determine the proportion of children in age and diagnostic groups with hypoxaemia, we defined hypoxaemia as SpO₂ more than 2SD below the mean for age. For neonates this value was 86.5%, so hypoxaemia was considered to be present if the SpO₂ was less than 86%. In older children this value was 90.3 and hypoxaemia was considered to be present if the SpO₂ was less than 88%. We believe these levels reflect when it is feasible to give supplemental oxygen in children in many resource poor settings in developing countries. It is most unlikely that small hospitals in developing countries can afford, or have the facilities to provide, supplemental oxygen for all children with SpO₂ 88–90% (see discussion).

Hypoxaemia in sick children and neonates with and without ALRI

A total of 491 sick children were evaluated: 132 neonates and 359 between 1 month and 5 years. Tables 1 and 2 show the oxygen saturation values at the time of presentation according to age group and diagnostic categories. Of 245 patients with ALRI, 179 (73%) had hypoxaemia. In addition, 79 (32%) of the 246 patients who did not fulfil criteria for ALRI illnesses were hypoxaemic. Of the 136 (28%) children 1 month to 5 years who did not fulfil criteria for ALRI, 38 (28%) were hypoxaemic. Outside the neonatal period, common non-ALRI conditions associated with hypoxaemia were meningitis, septicaemia, and severe malnutrition. Although many children with these diagnoses also fulfilled the criteria for ALRI, and probably had pneumonia as a coinfection, these 38 children between 1 month and 5 years with hypoxaemia had no evidence of associated ALRI. Diarrhoeal disease, malaria, and typhoid were not commonly associated with hypoxaemia, although the number of cases evaluated was small.

Forty of 110 neonates (36%) who did not fulfil criteria for ALRI were hypoxaemic. The common non-ALRI causes of

Table 3 Predictive value of clinical signs for hypoxaemia (SpO₂ <88%) in the sick children (1 month to 5 years)

Sign	Number with sign/number recorded	Odds ratio (95% CI)	p value	Sensitivity	Specificity	PPV	NPV
Not feeding	119/349	2.3 (1.4–3.7)	<0.001	41.9	76.2	69.7	50.0
Cyanosis	78/356	31.5 (9.7–102.3)	<0.001	37.9	98.1	96.2	55.8
Reduced activity	128/336	1.7 (1.1–2.7)	0.02	43.5	69.2	65.6	47.6
Respiratory rate >60	180/359	5.0 (3.2–7.8)	<0.001	67.0	71.1	74.4	63.1
Failed to resist examination	100/346	1.0 (0.6–1.6)	0.96	29.0	44.3	56.0	44.3
Head nodding	27/356	3.0 (1.2–7.7)	0.02	10.7	96.2	77.8	46.5
Grunting	64/358	1.8 (1.0–3.2)	0.04	21.6	86.8	67.2	46.9

Table 4 Predictive value of clinical signs for hypoxaemia (SpO₂ <86%) in the sick neonates

Sign	Number with sign/number recorded	Odds ratio (95% CI)	p value	Sensitivity	Specificity	PPV	NPV
Not feeding	75/130	1.9 (0.95–4.0)	0.07	66.7	49.3	50.7	65.4
Cyanosis	49/132	21.5 (8.4–54.6)	<0.0001	71.9	89.3	83.7	80.7
Reduced activity	55/132	4.4 (2.1–9.2)	<0.0001	61.4	73.3	63.6	71.4
Respiratory rate >60	41/132	1.2 (0.57–2.53)	0.62	33.3	70.7	46.3	58.2
RR <30	7/132	8.7 (1.0–74.5)	0.048	10.5	98.7	85.7	59.2
Failed to resist examination	35/126	3.7 (1.6–8.4)	0.002	42.6	83.3	65.7	65.9
Head nodding	2/132			3.5	100	100	57.6
Grunting	19/132	3.4 (1.2–9.6)	0.021	22.8	92.0	68.4	61.1

neonatal illness associated with hypoxaemia were septicaemia, low birth weight, birth asphyxia, and congenital syphilis.

Clinical signs predicting hypoxaemia

Tables 3 and 4 show the predictive value of individual clinical signs for hypoxaemia in sick children and neonates. For children over the age of 1 month, respiratory rate greater than 60 was the single most useful sign. Cyanosis was much more specific, but if used alone would have failed to detect more than 60% of children with hypoxaemia. Failure to resist examination was not a significant predictor, and head nodding and grunting, although specific for hypoxaemia, were rare signs with very low sensitivity. Reduced activity and inability to feed had moderate specificity, but still failed to detect most children with hypoxaemia.

We attempted to design clinical algorithms to guide health workers in giving supplemental oxygen. Table 5 shows several models based on variables that had independent predictive power. Model 1 uses inability to feed, the symptom recommended by the WHO as an indication for use of supplemental oxygen in children with pneumonia; model 2 uses reduced activity. The two models have comparable predictive power in children with ALRI, but not in sick children without ALRI (where reduced activity was a poor predictor of hypoxaemia, and inability to feed was a better predictor). The PPV of the two models was much higher for sick children with ALRI than those non-ALRI conditions; more than 50% of children with non-ALRI illness receiving oxygen based on these algorithms would not require it, compared with less than 20% of children with ALRI.

The predictive models for hypoxaemia in older children performed less well when applied to neonates. Although model 1 was highly sensitive (inability to feed or tachypnoea or cyanosis), application of this model would mean that almost 50% of neonates given oxygen would not require it. Cyanosis or reduced activity or tachypnoea (model 2) performed better, but was still poorly specific for hypoxaemia.

Tachypnoea was not predictive of hypoxaemia in neonates (table 4); no threshold for respiratory rate greater than 60 per minute was significant. Bradypnoea, which we defined as a respiratory rate less than 30, was predictive of hypoxaemia. Neonates with bradypnoea had a mean SpO₂ of 47% (SD 11.5%), while neonates with a respiratory rate greater than 60 had a mean SpO₂ of 74% (SD 3.8%) (p = 0.01). This reflects the reduced respiratory drive of young infants in response to severe hypoxia. Although specific for hypoxaemia, bradypnoea was relatively uncommon and therefore an insensitive sign (table 5). However, it is important to teach health workers that a neonate who has an abnormally slow respiratory rate has a much more urgent need of oxygen than one with an increased respiratory rate. This would be the only reason to include respiratory rate in a model of hypoxaemia prediction for neonates, as without bradypnoea the combination of cyanosis or reduced activity (model 5) was just as good at detecting any hypoxaemia. Model 4, which incorporated abnormally fast and slow respiratory rate, did not enhance predictive power.

Although cyanosis was the best independent predictor of hypoxaemia in neonates (table 4) the two signs of altered arousal (reduced activity and failure to resist examination) and grunting remain important to record and teach, as they predicted death better than the sign of cyanosis.

Hypoxaemia as a predictor of death in ALRI and non-ALRI illness

Twenty nine of the sick patients in the study died (5.9%). Of the 245 neonates and children with ALRI, four died (1.6%); all were hypoxaemic at presentation. Of the 246 neonates and children without ALRI, 25 died; 18 (72%) of these had hypoxaemia. The odds ratio for death in non-ALRI illness if hypoxaemia was present was 6.0 (2.0–15.1; p < 0.001).

For sick neonates overall hypoxaemia was associated with an increased risk of death: odds ratio 3.1 (1.1–8.8). Importantly this applied to neonates with non-ALRI illness: odds ratio 4.6 (1.6–13.4). None of the 22 neonates with ALRI

Table 5 Predictive models using minimal number of independently predictive variables for age and ALRI specific diagnoses

Predictive models	Odds ratio (95% CI)	Sensitivity	Specificity	PPV	NPV	Area under ROC
Children 1–60 months with ALRI						
Model 1 RR >60 or Cyanosis or Not feeding	4.3 (2.2–8.7) p<0.001	81.9	49.0	82.4	48.1	0.65
Model 2 RR >60 or Cyanosis or Reduced activity	5.2 (2.6–10.4) p<0.001	83.2	51.0	83.2	51.0	0.67
Children 1–60 months, no ALRI						
Model 1	6.7 (2.5–18.1) p<0.001	82.8	58.2	46.8	88.5	0.71
Model 2	2.1 (0.9–4.9) p=0.09	71.4	45.6	36.7	78.3	0.59
Neonates, all diagnostic categories						
Model 1	3.9 (1.5–10.5) p=0.007	89.1	32.3	50.5	79.3	0.61
Model 2	5.0 (2.1–11.6) p<0.001	83.6	49.3	55.4	80.0	0.66
Model 3 RR <30 or Cyanosis or Reduced activity	7.3 (3.3–16.4) p<0.0001	78.2	67	64.2	80.3	0.73
Model 4 RR >70, <30 or Cyanosis or Reduced activity	6.2 (2.6–14.5) p<0.001	83.6	54.8	58.2	81.6	0.69
Model 5 Cyanosis or Reduced activity	8.0 (3.5–18.0)	78.2	69.0	66.2	80.3	0.74

died, so it is not possible to evaluate predictive power in this subgroup.

DISCUSSION

Studies of children with ALRI have shown that hypoxaemia is a strong risk factor for mortality,^{2,9} and that the use of supplemental oxygen reduces mortality from ALRI. This current study shows that: hypoxaemia complicates many common illnesses not classified as ALRI; in non-ALRI illnesses hypoxaemia greatly increases the risk of death; the power of clinical signs to predict hypoxaemia are age and diagnosis dependent; and clinical algorithms have low predictive power.

There are several reasons why children with non-ALRI illnesses have hypoxaemia. In meningitis, for example, upper airway obstruction may occur from retained secretions or increased or decreased upper airway tone; bradypnoea or apnoea may occur because of the brain injury, or from chest wall rigidity during convulsions; and pulmonary aspiration or collapse may occur. Coexistent bacterial pneumonia is common in meningitis and the standard clinical signs of ALRI may not be as clear in the setting of brain injury. In septicemia, hypoxaemia may occur from intrapulmonary shunting of blood, pulmonary hypertension, or pulmonary congestion. In developed countries neonatal respiratory distress syndrome associated with prematurity is a common cause of hypoxaemia. In developing countries very low birth weight is more commonly caused by intrauterine growth restriction rather than prematurity,¹⁰ although the mortality from prematurity is much higher than that from intrauterine growth restriction.¹¹ In developing countries a high proportion of babies are born in

a suboptimal environment outside hospitals, where cold stress, hypoglycaemia, sepsis, and pulmonary aspiration complicate low birth weight. In these settings hypoxaemia may be more commonly caused by apnoea or bradypnoea. Apnoea also occurs in other major neonatal diagnoses: meningitis, pneumonia, birth asphyxia, and syphilis. Congenital syphilis is associated with very low birth weight, and generalised syphilitic septicaemia with pneumonitis is present in severe cases from the first hours after birth.

That hypoxaemia is common in severely ill neonates and in non-pneumonic illnesses in older children may also reflect the low sensitivity of currently defined clinical diagnostic criteria for pneumonia in newborn infants, especially those with low birth weight, and in older infants and children when several diseases coexist.

It is not surprising that some clinical signs of hypoxaemia are age and diagnosis dependent. Head nodding,³ for example, was only seen in 3% of hypoxaemic neonates; it is unlikely to be a useful sign because of the lack of head control, even in well newborns. Poor feeding also proved to be less specific in neonates than in older children (tables 3 and 4): almost any insult will cause a newborn to feed poorly, whereas older infants will seek out the breast for comfort unless severity of respiratory distress or reduced conscious state preclude this.

The practical importance of defining a cut off point for Sp_o, when testing clinical signs of hypoxaemia is that it should reflect the feasible threshold for giving supplemental oxygen. We chose the cut off for clinical signs of <88%, because it is most unlikely that small hospitals in developing countries can afford, or have the facilities to provide, supplemental oxygen

for all children with SpO_2 88–90%. This is despite these children being hypoxaemic by the definition of having an SpO_2 more than 2 standard deviations below the mean. In our cohort of sick children outside the neonatal period, giving oxygen when the SpO_2 was 88–90% would mean a 22% increase in the number of children using oxygen (an additional 44 children). Because of the limited supply and high cost of oxygen in developing countries, it may not even be possible to give supplemental oxygen to all children with an SpO_2 <88%. In Goroka we use an SpO_2 cut off for giving supplemental oxygen of 85% for children and neonates with pneumonia, and 90% for children of any age with an acute brain injury (such as meningitis). This reflects resource allocation, and the likely severity of hypoxaemia that is limiting to survival or rate of recovery. Such “safe” levels of hypoxaemia are currently poorly defined, but the use of pulse oximetry can help ration a scarce and expensive resource. Hypoxaemia may be more frequent and more severe in children who live at higher altitude, because of reduced partial pressure of atmospheric oxygen. Goroka is at an altitude of 1600 m above sea level. Observations in normal children at altitudes between 1000 and 2000 m above sea level have a range of SpO_2 values between 88.7% and 96.9%.^{5 6 12 13} Without further evaluation our threshold of SpO_2 85% for giving oxygen should not be applied directly to children living at sea level, where baseline SpO_2 will be >95%.

No model based on clinical signs could predict hypoxaemia very well: in models with high sensitivity, 20% of hypoxaemic children would be missed and 17–50% of children given supplemental oxygen would not need it. This further emphasises the value of pulse oximetry, which may be a cost effective intervention in small and moderate sized hospitals in developing countries.^{2 14} The cost effectiveness of pulse oximetry will be enhanced by its application to children who do not have ALRI and to neonates. It was only in the group of children with ALRI that the PPV of any clinical algorithm was greater than 80%; in children with non-ALRI illness the maximum PPV of an algorithm was 47% and for neonates the maximum PPV was 66%. Therefore using only clinical criteria for the rationing of supplemental oxygen to children with non-ALRI illnesses and to neonates will result in a relatively greater level of “wastage” of oxygen by patients who do not have hypoxaemia. By extending the use of pulse oximetry to these groups there would be a relatively greater saving of oxygen and costs.

An even higher priority will be the provision of adequate supplies of oxygen, or oxygen concentrators in smaller health facilities. Finally, it will be critical to teach health workers that hypoxaemia occurs not only in ALRI, but also in sick newborn infants and children with non-ALRI illnesses, and that prompt intervention can reduce mortality.

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