

When should oxygen be given to children at high altitude?

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First published online: 16 September 2008

The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:

http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *When should oxygen be given to children at high altitude?*

INTRODUCTION

Each year pneumonia causes more than 3 million deaths in children under 5 years of age (including neonates), and results in 11-20 million hospitalizations.^{1,2} 98% of deaths from pneumonia in children occur in developing countries.³ Hypoxaemia is a significant risk factor for mortality,⁴⁻⁶ and a strong predictor of radiographic pneumonia.^{5,7,8} The recognition of hypoxaemia among children with pneumonia is crucial in management, may assist in diagnosis and helps determine prognosis.

Currently the World Health Organization (WHO) recommends clinical signs to guide the starting and stopping of oxygen therapy. Where pulse oximetry is available, WHO recommends an arterial oxygen saturation measured by pulse oximetry (SpO₂) of 90% as the threshold for oxygen administration.⁹ The latter approach may only be implementable in settings where oxygen supplies are not limited. At high altitudes, where normal oxygen saturation levels are lower than at sea level, a threshold of 90% may be less relevant. A clearer definition of the lower limit of normal SpO₂ among children at different altitudes would enable protocols for oxygen therapy to be adapted to local conditions, and enable resources to be appropriately applied.

To assist in the identification and management of hypoxaemia, this study aimed to use the published literature to define normal values of SpO₂ in children and to propose a model for defining hypoxaemia at varying altitudes.

METHODS

Search strategy and inclusion criteria

A review was conducted using OVID Medline (1950-August week 2 2007) and Embase (1980-2007 week 33). The abstracts of potentially relevant publications were reviewed, and the complete texts of studies addressing the inclusion criteria (outlined below) were obtained. References cited by these

articles, as well as the link option 'Find similar' in OVID and Embase were then used to widen the search.

Studies were included if they reported SpO₂ of healthy, awake children aged 1 week to 12 years, permanently residing in the study location. In order to ensure that study data used in the analysis provides a reasonable estimate of the normal SpO₂ of the populations it represents, we set the cut-off for sample size as greater than 30 children. Studies including SpO₂ measurements of preterm, hospitalised, anaesthetised or chronically ill children were excluded. Only papers in English were reviewed, and no attempts were made to obtain unpublished data.

The inclusion criteria were designed to include the largest sample of children for whom such data are available, but it was considered important to exclude studies that described normal episodes of desaturation during the foetal-neonatal transition throughout the first hours of life. Although recovery to adult SpO₂ levels has been previously demonstrated within 15 minutes after birth,¹⁰ a minimum age of one week was set to ensure that such normal fluctuations were not represented.

Data extracted from studies were age, sample size, mean (standard deviation) SpO₂, oximeter type, and altitude above sea level. Where the standard deviation (SD) was not reported, either the 95% confidence interval (CI) or the standard error (SE) was extracted, depending on the information reported. Missing standard errors and standard deviations were then derived from available statistics using standard methods.¹¹ All altitudes less than 100 metres above sea level were considered to be equivalent to sea level (0 metres). If a study reported SpO₂ for different age categories without providing overall summary data, one subgroup was chosen to be included in the analysis, on the basis of the greatest number of subjects and avoiding a sub-group which included the neonatal period.

We defined hypoxaemia as any SpO₂ value at or below the 2.5th centile for a population of healthy children at a given altitude. If the values of SpO₂ are normally distributed, this definition corresponds to a SpO₂ reading of more than 2 standard deviations below the mean.

Statistical analysis

Data were entered into Microsoft Excel, and analysed using Stata version 10.¹² The 2.5th centile of the distribution of SpO₂ values could not be estimated directly, as only one study in the literature reported this statistic.⁶ For this reason, the hypoxaemia threshold was estimated by predicting mean SpO₂ based on altitude, and subtracting two standard deviations from the prediction. The prediction equation was obtained using a linear random effects meta-regression, which was implemented using the user-contributed Stata command "metareg".¹³ The between-studies variance was estimated using restricted maximum likelihood.

Table 1: Studies reporting normal SpO₂ in children aged 0–5 years

Study location	Altitude (m) above sea level	Study population age (n)	Oximeter	Mean SpO ₂ (SD)
Chennai, India ¹³	0	1–60 months (626)	Larsen and Toubro, Stellar P Model	99.0 (1.2)
Lima, Peru ²⁴	0	2–60 months (162)	Nellcor N-10	98.7 (1.5)
Lima, Peru ⁷	0	2–60 months (189)	Nellcor N-10	98.7 (1.1)
	3750	2–60 months (153)		88.9 (2.9)
Utah, USA ¹⁶	1500	2–23 months (80)	Healthdyne 930	98.9 (1.0)†
Goroka, Papua New Guinea ³²	1584	0–2 months (302)	Nellcor N-25	97.1 (2.7)*
Goroka, Papua New Guinea ¹⁸	1600	1–60 months (151)	Nellcor Puritan Bennet-3930	95.7 (2.7)
Denver, USA ³³	1610	1 month (100)	Ohmeda Biox 3700	93.4 (2.0)†
Nairobi, Kenya ⁵	1670	7 days–36 months (87)	Nellcor N-10	95.7 (1.6)
Bogota, Colombia ²³	2640	0–24 months (189)	Nellcor N-10	93.3 (2.1)
San Marcos, Guatemala ¹⁷	2600	0–18 months (55)	Nellcor N-20	93.2 (3.0)
Addis Ababa, Ethiopia ²⁸	2800	0–60 months (150)	Not reported	92.0 (2.0)
Summit County, CO, USA ⁴¹	2800	2 days–22 months (72)	Ohmeda 3740	91.7 (2.1)
El Alto, Bolivia ²⁰	4018	0–60 months (152)	Nellcor N-10	87.8 (3.8)*

*Indicates that a standard deviation was not reported, being instead calculated from the mean, confidence interval and sample size reported; †indicates that a standard deviation was not reported, being instead calculated from the standard error and sample size provided. SD, standard deviation.

Inspection of the summary statistics reported in Table 1 indicates that the distribution of SpO₂ values for many studies is negatively skewed rather than normally distributed; adding two standard deviations to the mean produces a value exceeding the theoretical maximum of 100% for the six studies at 1600m of altitude or less. We required the outcome to be normally distributed, both to satisfy the assumptions of the analysis method, and because we wished for the mean minus 2 SD to correspond to the 2.5th centile. For these reasons, meta-regression was performed on the log-transformed scale. A prediction equation for hypoxaemia threshold was derived by subtracting two standard deviations from the predicted mean SpO₂ on the transformed scale, and back-transforming the resulting equation to the natural scale.

RESULTS

24 studies fulfilled the selection criteria.^{5-7,14-34} Eleven studies were subsequently excluded. These included a study in Peru of a 6 to 18 year old population which did not meet the age criteria²², and one in Nepal of children presenting with cough and coryza.¹⁵ An additional 6 studies did not report a mean SpO₂ value and appropriate measure of variation,^{6,16,20,26,27,35} and 3 studies were excluded due to having a sample size less than^{28,30,31,32}

Mean SpO₂, altitude, sample size and an appropriate measure of variation were reported in the remaining 13 studies (Table 1). Of these 13 studies, 9 reported a standard deviation, 2 a standard error and the remaining 2 a 95% confidence interval. One study examined two populations living at different altitudes⁷, reporting summary statistics separately. Each population was treated as a separate population for the purpose of the meta-regression. In total therefore, the analyses of SpO₂ values included 14 data points from 13 studies.

Very strong evidence was found for an association between study altitude and the study's mean SpO₂ value ($p < 0.001$). The equation obtained for predicting mean SpO₂ at a given altitude was:

$$\text{Mean SpO}_2 (\%) = 100.5 - 1.374e^{0.590 \times \text{altitude (km)}}$$

The equation obtained for predicting the hypoxaemia threshold at a given altitude was:

$$\text{SpO}_2 (\%) = 100.5 - 1.374e^{(0.590 \times \text{altitude (km)} + 0.563)}$$

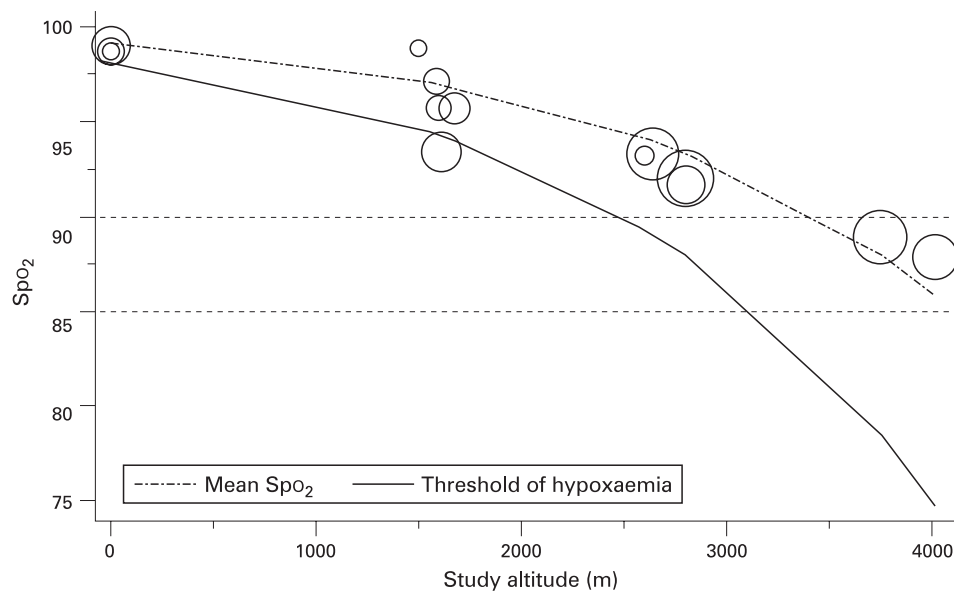
Both prediction equations are graphically depicted in Figure 1. At an altitude of approximately 2500 metres above sea level, the 2.5th centile of the distribution of SpO₂ in normal, healthy children is 90%. This decreases to 85% at approximately 3200 metres above sea level.

DISCUSSION

Oxygen therapy has been shown to improve outcomes in pneumonia.^{4,36} Ensuring a reliable and efficient system for detecting hypoxaemia and supplying oxygen and having clear and simple guidelines for its use is therefore vital to good quality paediatric care. This is particularly so in developing countries given the magnitude of the burden of pneumonia. And yet, such systems are often of poor quality or non-existent where they are most needed, where oxygen administration is often dictated more by availability than by need.

There have been many hurdles to implementing effective systems for oxygen therapy in developing countries: the cost and scarcity of cylinder oxygen and the unreliability of clinical signs in predicting hypoxaemia. In recent times, the introduction of pulse oximetry in developing country health facilities has been advocated for its accuracy in detecting hypoxaemia and cost-effectiveness in limiting oxygen wastage.^{37,38}

Figure 1: Estimated threshold of hypoxaemia at different altitudes. Study estimates are plotted as circles, with size proportional to the precision of the transformed study estimate



If pulse oximetry is to be widely used and understood by health workers, consensus as to the SpO₂ level below which oxygen supplementation should be given is needed.

There are physiological and 'safe practice' arguments for maintaining SpO₂ above 90% at sea level, to ensure that the relationship between SaO₂ and Po₂ is on the flat segment of the oxygen dissociation curve. While SpO₂ levels below 90% at sea level indicate severe respiratory pathology, in high altitude locations such levels are found in normal local children owing to the low barometric pressure. Despite this, the oxygen balance in these children remains adequate in health due to several physiological adaptations, including hyperventilation, polycythemia, enhanced alveolar growth and increased capillary proliferation.^{39;40} For ill children living at such high altitudes, the aim of oxygen supplementation should not therefore be based on normal levels at sea level, but should aim to achieve an adjusted expected normal SpO₂ for that setting. Our study quantifies the expected reduction in SpO₂ levels with increasing altitudes. The strong association found between study altitude and a study's average SpO₂ value suggests that a lower threshold for giving oxygen may be appropriate at very high altitude if supplies are limited.

Figure 1 suggests that at altitudes above 2500 metres, using an SpO₂ threshold of 90% to administer oxygen is conservative, and may result in oxygen supplementation to some children with SpO₂ in the normal range. In facilities with limited oxygen supplies located at these altitudes, therefore, a lower level of SpO₂ can be used, and an approximation could be an SpO₂ <85%. Above 3200 metres, even this lower definition is conservative, and may become too sensitive as a screening test for oxygen need. Such guidelines are based on statistical definitions, and their clinical relevance needs to be further studied. The use of thresholds of hypoxaemia below 90% to indicate oxygen therapy at altitude has been reported in the literature^{7;19;20}, but clearly, in addition to locally-relevant thresholds of SpO₂, oxygen therapy should be based on the overall clinical picture of each child, as well as a careful consideration of resource availability.

In many health facilities, the scarcity of oxygen means that health workers are faced not with the question of which children need oxygen, but which children need it most. It is optimal practice to cohort children requiring oxygen together in a high dependency area of the ward, allowing for regular observation and monitoring. This necessitates the accurate identification of the proportion of sick children requiring such attention. Oxygen saturation by pulse oximetry can be used to facilitate this process and to indicate the severity of respiratory disease^{4;5;41}. In high altitude settings, consideration of the normally lower levels of SpO₂ and being able to approximate these quantitatively, will be useful in informing clinical decisions.

It should be emphasized that ultimately what is important in maintaining adequate tissue oxygenation is the oxygen content in the blood, not the oxygen saturation. This is given by the equation $(1.30 \times \text{Hb} \times \text{SaO}_2) + 0.003 \text{ PaO}_2$. Children with severe anaemia or infants in their physiological nadir of haemoglobin concentration may be hypoxic despite having an SpO₂ level within the normal range. Ideally, oxygen therapy needs to be guided by pulse oximetry as well as measurement of the haemoglobin concentration. However, in the absence of an immediate measure of Hb, emphasis may be placed on identifying the clinical signs of anaemia or identifying children in their nadir of Hb, in whom more liberal thresholds for giving oxygen would be appropriate.

Previous studies have used the mean SpO₂ minus 2 SD to define hypoxaemia in children, and assumed normally distributed saturation levels.^{5;7;18;19} Our study has taken into account the skewed distribution of normal SpO₂, and has weighted each study estimate by its precision. We have also attempted to include the largest number of relevant studies that reported results in a format which would allow a pooled analysis of the data. Our findings suggest that the definition of hypoxaemia as mean SpO₂ minus 2 SD may not accurately capture the lowest 2.5% of values at low and moderate altitudes. We recommend that future studies check distributional assumptions and explicitly report centile values such as the 2.5th centile and/or median.

There are a number of limitations to the study design we used. Where children were selected on grounds of ethnic background, the normal SpO₂ reported may not be representative of unstudied populations of children living at comparable altitudes. In addition, variations between study findings could be due to differences in sampling, ethnicity and age ranges studied, as well as the use of different oximeters and/or protocols for measuring SpO₂. Also, there was no way of controlling for either the precision or the accuracy of the oximeters used in each study. The statistical model employed assumes reliable estimates of study means and standard deviations, as well as assuming that the transformation applied would have resulted in an approximately normal distribution for study populations at all altitudes. Ideally, had raw data been available, summary statistics would have been calculated on an appropriate scale rather than estimated.

SUMMARY

Above altitudes of 2500 metres, giving oxygen for SpO₂ less than 90% may be too liberal for facilities with limited oxygen supplies. There is evidence that for altitudes greater than 2500 metres a threshold of SpO₂ of 85% can be used to identify children most in need of oxygen. A balance needs to be achieved between using accurate altitude-specific definitions of hypoxaemia, and ensuring simple and safe indications for oxygen that can be taught to and used by health workers. We hope the model proposed for predicting normal SpO₂ and the definition of hypoxaemia at different altitudes will be useful for clinicians in determining when to give oxygen.

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