Childhood Anemia at High Altitude: Risk Factors for Poor Outcomes in Severe Pneumonia

WHAT'S KNOWN ON THIS SUBJECT: Pneumonia is the leading cause of death in young children worldwide. Anemia, widely prevalent globally, is not routinely assessed when treating pneumonia. The effect of anemia and high altitude on outcome of pneumonia is not well described.

WHAT THIS STUDY ADDS: Anemia at high altitude increases the risk of poor outcome with severe pneumonia. Children with severe pneumonia at high altitude present with more severe hypoxemia and have a longer time to recovery than children at low altitude.

abstract

BACKGROUND: Pneumonia is the leading cause of mortality in young children globally, and factors that affect tissue delivery of oxygen may affect outcomes of pneumonia. We studied whether altitude and anemia influence disease severity and outcomes in young children with World Health Organization–defined severe pneumonia.

METHODS: We analyzed data from the SPEAR (Severe Pneumonia Evaluation Antimicrobial Research) study, a World Health Organization– and USAID-sponsored multinational randomized controlled trial of antibiotics for severe pneumonia among children aged 2 to 59 months in resource-poor settings. The trial enrolled 958 children in 8 sites at varying elevations, classified as high (≥ 2000 m) or low (< 2000 m) altitude. We compared illness severity and assessed the effect of anemia on treatment outcome at high and low altitudes, adjusting for potential confounders and study site.

RESULTS: Children at high altitudes had significantly lower oxygen saturation on presentation, more cyanosis, lower systolic blood pressure, and higher hemoglobin. After adjusting for potential confounders, anemia predicted treatment failure in children living at high altitude (relative risk: 4.07; 95% confidence interval: 2.60–6.38) but not at low altitude (relative risk: 1.12; 95% confidence interval: 0.96–1.30). Children at high altitude took longer to reach normoxemia than did children at lower altitudes (5.25 vs 0.75 days; $P < .0001$).

CONCLUSIONS: Children at high altitude present with more severe disease, and children with anemia at high altitude are at greater risk of poor outcome when being treated for severe pneumonia. Given the high global prevalence of anemia among young children, prevention and treatment of anemia should be a priority in children living at high altitude and could improve outcomes of pneumonia. *Pediatrics* 2013;132:e1156–e1162

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KEY WORDS

pneumonia, anemia, high altitude, international child health

ABBREVIATIONS

CI—confidence interval

LMIC—low and middle-income country

RR—relative risk

SPEAR—Severe Pneumonia Evaluation Antimicrobial Research

SpO₂—oxyhemoglobin saturation

V/Q—ventilation-perfusion

WHO—World Health Organization

Dr Moschovis conceptualized and designed the study, carried out the data analysis, and drafted the initial manuscript; Dr Banajeh implemented the study, coordinated and supervised data collection, and critically reviewed the manuscript; Dr MacLeod managed and coordinated the data, carried out the data analysis, and critically reviewed the manuscript; Drs Saha and Mino coordinated and supervised data collection and critically reviewed the manuscript; Dr Hayden carried out the data analysis and critically reviewed the manuscript; Dr Christiani contributed to the interpretation of the data and critically reviewed the manuscript; Drs Santosham, Thea, and Qazi conceptualized and designed the study and critically reviewed the manuscript; Dr Hibberd conceptualized and designed the study and drafted the initial manuscript; and all authors approved the final manuscript as submitted.

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Pneumonia is the leading cause of mortality in children under 5 years of age and is responsible for ~1.2 million early-childhood deaths annually.^{1,2} The burden of illness is disproportionately borne by low- and middle-income countries (LMICs); of 156 million new cases of pneumonia, 151 million are in LMICs, and >99% of pneumonia deaths are in LMICs.^{1,3–5} Children who die of pneumonia ultimately die of respiratory failure, unable to deliver sufficient oxygen to vital organs. As pneumonia progresses, hypoxemia ensues from ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. In many cases, these children are at increased risk of respiratory failure because of underlying comorbidities or other risk factors.³

Nearly 140 million people live at high altitude, many of them in LMICs.⁶ The hypoxia caused by low oxygen tension at high altitude is well tolerated in healthy individuals, but in patients with lung disease, the combination of low alveolar partial pressure of oxygen with $\dot{V}/\dot{Q}$ mismatch can be fatal.⁶ Pneumonia, the most common lung disease in children and adults, is more common and more severe at high altitude. At higher altitudes there is a higher incidence of childhood pneumonia,⁷ a higher rate of hospitalization for pneumonia,⁸ and an increase in mortality in children with viral and bacterial pneumonia.^{9,10}

Anemia is widely prevalent among young children in LMICs, affecting 45% of preschool children worldwide and >65% of preschool children in Africa and Southeast Asia.¹¹ In many cases, anemia is a marker for underlying malnutrition or comorbidities that increase the severity of pneumonia and risk of poor outcome. Anemia increases the risk of pneumonia^{12,13} and the risk of hospitalization for pneumonia.¹⁴ With the combination of hypobaric hypoxia, reduced oxygen-carrying capacity, and $\dot{V}/\dot{Q}$ mismatch, children with

anemia living at high altitude might be at greater risk of adverse outcomes from pneumonia. We hypothesized the following in young children with severe pneumonia: (1) children living at high altitude present with greater clinical severity, (2) children with anemia who live at high altitude are at greater risk of adverse outcomes, and (3) children at high altitude have more prolonged hypoxemia during treatment of pneumonia. Therefore, we evaluated the effect of altitude and anemia on poor outcomes in young children with World Health Organization (WHO)-defined severe pneumonia¹⁵ by using data from the previously completed Severe Pneumonia Evaluation Antimicrobial Research (SPEAR) study.¹⁶

METHODS

Study Design

The SPEAR study enrolled 958 children aged 2 to 59 months who were hospitalized with severe pneumonia between August 2000 and April 2004. The study was conducted at 8 sites in 7 LMICs at varying elevations, ranging from sea level to moderately high altitude: Dhaka, Bangladesh (4 m); Guayaquil, Ecuador (4 m); Multan, Pakistan (122 m); Chandigarh, India (350 m); Rawalpindi, Pakistan (500 m); Lusaka, Zambia (1300 m); Sana'a, Yemen (2250 m); and Mexico City, Mexico (2420 m). These sites were classified as either high altitude (≥ 2000 m) or low altitude (< 2000 m).

The eligibility criteria have been described previously.¹⁶ In brief, inclusion criteria were age 2 to 59 months and WHO-defined severe pneumonia¹⁵ (reclassified from the previous WHO definition of “very severe pneumonia,” defined as cough or difficulty breathing plus ≥ 1 of the following: [1] central cyanosis; [2] inability to breastfeed or drink; [3] convulsions, lethargy, or unconsciousness; and [4] severe respiratory distress, including grunting

or very severe chest indrawing). Children were excluded if they had a history of asthma or recurrent wheezing, current illness > 10 days, or treatment with an injectable antibiotic > 24 h before enrollment.

Patients enrolled in the trial underwent physical examination, laboratory tests (including complete blood count), blood culture, and chest radiography. They were randomly assigned to treatment with parenteral chloramphenicol or injectable ampicillin plus gentamicin. Patients were hospitalized until discharge was clinically appropriate, and follow-up evaluation was performed at 10 to 12 days and 21 to 30 days after discharge.

The primary outcome was treatment failure over the course of the study (determined at 48 hours, at 5 days, at the 10- to 12-day visit, or at the 21- to 30-day visit). Treatment failure at 48 hours or 5 days was defined as follows:

1. new development or persistence of ≥ 2 of the following: inability to drink, tachypnea (≥ 50 breaths per minute for age 2–11 months, ≥ 40 breaths per minute for age 1–5 years), and abnormally sleepy or difficult to wake;
2. development of bacterial meningitis, empyema, septic shock, renal failure, or newly diagnosed comorbid conditions;
3. serious adverse drug reaction;
4. modification of antibiotic treatment;
5. voluntary withdrawal or absconding; or
6. death.

Treatment failure at 10 to 12 days and 21 to 30 days was defined as the above plus relapse (hypoxemic pneumonia). Anemia was defined according to the WHO standards for children under 5 years of age as hemoglobin ≤ 11 g/dL.¹⁷ Oxygen saturation was measured at fixed intervals (4 times per day while the

subjects were hospitalized and at each follow-up visit) by using pulse oximetry while the patient was breathing room air.

Statistical Methods

Statistical analyses were performed in SAS version 9.3 (SAS Institute Inc, Cary, NC). Baseline characteristics of children at high altitude versus low altitude were compared by using Pearson's χ^2 for dichotomous variables, Student's *t* test for normally distributed variables, and the Wilcoxon rank sum test for variables with a skewed distribution. For patients in whom hematocrit was measured instead of hemoglobin, hemoglobin was calculated on the basis of the age-adjusted prediction formula reported by Quintó et al¹⁸: hemoglobin = (hematocrit – 0.22 × age)/(3.27 – 0.02 × age). Univariate analyses were conducted in PROC GENMOD using binary regression.

We examined effect modification of the association between anemia and treatment failure by formally testing the interaction term (anemia × altitude) in a multivariate model. Once interaction was assessed, the effect of anemia at high and low altitudes was assessed by constructing separate models for high- and low-altitude sites by using PROC GENMOD, which included treatment group, anemia, known confounders as main effects, and study site as a repeated effect assuming exchangeable correlation within sites. Hemoglobin was also evaluated as a continuous variable in a similar multivariate model.

Among hypoxemic patients, we evaluated time to resolution of hypoxemia in the high-altitude and low-altitude sites, constructing time-to-event curves by using the Kaplan-Meier method. We also compared rates of resolution of hypoxemia by using a multivariate Cox proportional hazards model that included age, gender, treatment group,

anemia, baseline oxygen saturation, heart rate, systolic blood pressure, weight, and treatment site as a random effect. Resolution of hypoxemia was defined as a persistent oxyhemoglobin saturation (SpO₂) >90% during the course of the study. A sensitivity analysis was also performed by using lower thresholds for normoxemia (SpO₂ >88% or >85%) for the patients at high altitude.

P < .05 was considered significant for all hypothesis testing. Based on the fixed sample size of 955 (3 had missing data on treatment outcome) in which 26 of 193 patients failed treatment at high altitude and 143 of 762 patients failed treatment at low altitude, our study had 95% power to detect a relative risk (RR) of treatment failure of 1.7.

Ethics

Families of patients who participated in the SPEAR study provided informed consent after reviewing the risks and benefits of participation. The SPEAR study was approved by the institutional review boards of all hospitals participating in the study, the WHO, the Boston University School of Public Health, and

the Johns Hopkins University Bloomberg School of Public Health. The present analysis has been evaluated and exempted by the Human Research Committee of Partners Healthcare and approved by the SPEAR Steering Committee.

RESULTS

A total of 193 (20%) children were living at the 2 high-altitude sites (Sana'a, Yemen, and Mexico City, Mexico), and 765 patients were living at the remaining 6 low-altitude sites (Dhaka, Bangladesh; Guayaquil, Ecuador; Multan, Pakistan; Chandigarh, India; Rawalpindi, Pakistan; Lusaka, Zambia).

The baseline characteristics of the patients are summarized in Table 1. Patients at high altitude were slightly older, more likely to be female, had lower weight for age, and had lower rates of being up to date with immunizations but were less likely to be classified as anemic (by using the WHO standard of 11 g/dL). The median hemoglobin in patients at high altitude was 10.3 vs 10.0 g/dL at low altitude (*P* < .0001). The most notable differences in severity of presentation were in prevalence of severe hypoxemia and

TABLE 1 Baseline Characteristics of Study Participants

	High Altitude	Low Altitude	<i>P</i> for Difference
Male gender	106/193 (55)	482/765 (63)	.04
Age, mo	7 (3–12)	5 (3–9)	<.0001
Temperature, °C	37.7 ± 0.8	37.7 ± 0.9	.99
Heart rate, beats per minute	155 ± 18	161 ± 23	.0003
Systolic blood pressure, mm Hg	86 ± 12	93 ± 14	<.0001
Respiratory rate, breaths per minute	71 ± 15	69 ± 11	.04
SpO ₂ , %	74 (67–78)	89 (86–92)	<.0001
Weight-for-age z score	–1.7 ± 1.2	–1.3 ± 1.5	<.0001
Breastfed per WHO recommendations	96/192 (50)	426/762 (56)	.14
Immunizations up to date	103/190 (54)	542/749 (72)	<.0001
Antibiotics in 24 h before admission	64/193 (33)	257/757 (34)	.84
Hemoglobin, g/dL	10.3 (9.5–11.5)	10.0 (8.8–10.8)	<.0001
Anemic (hemoglobin ≤11 g/dL)	117/192 (61)	600/762 (79)	<.0001
Unable to drink	140/193 (73)	762/765 (99.6)	<.0001
Abnormally sleepy	29/193 (15)	138/765 (18)	.32
Dehydration	18/193 (9)	97/765 (13)	.20
Cyanosis	182/193 (94)	60/765 (8)	<.0001

Data represent numbers of patients (*n*/*N* [%]), means ± SD, and medians (interquartile range) (for age, SpO₂, and hemoglobin), as appropriate. *P* values are from Pearson's χ^2 for categorical variables, Student's *t* test for normally distributed continuous variables, and the Wilcoxon rank sum test for skewed variables (age, SpO₂, and hemoglobin).

cyanosis, which were both much more frequent in patients at high altitude. At high altitude, 86% of patients had an $\text{SpO}_2 < 80\%$, compared with 11% of patients at low altitude (RR: 7.7; 95% confidence interval [CI]: 6.3–9.5; $P < .0001$; see Fig 1). Other notable differences in disease severity included lower systolic blood pressure and a higher respiratory rate in patients at high altitude (despite being, on average, older).

On univariate analysis, no association was found between altitude and treatment failure (RR: 0.72; 95% CI: 0.47–1.09) nor between anemia and treatment failure (RR: 1.34; 95% CI: 0.94–1.92). When anemia, high altitude, and their interaction were examined in a multivariate model that adjusted for potential confounders and study site, a significant interaction was observed between high altitude and anemia (P for interaction < 0.0001).

On the basis of the finding of interaction between altitude and anemia, separate models were constructed stratifying by altitude (see Table 2). After adjusting for potential confounders, anemia on presentation was found to be a strong independent predictor of treatment failure at high altitude (RR: 4.07; 95% CI: 2.60–6.38). At low altitude, anemia did not predict treatment failure (RR: 1.12; 95% CI: 0.96–1.30).

The effect of hemoglobin was also evaluated as a continuous variable. For each 1-g/dL increase in hemoglobin, the risk of treatment failure decreased by 35% (RR: 0.65; 95% CI: 0.50–0.86). At high altitude, a dose-response effect of hemoglobin on treatment failure was observed, with the greatest effect in the lowest quartile of hemoglobin (RR: 3.70; 95% CI: 1.84–7.4). No dose-response relationship was observed at low altitude (see Fig 2).

When the specific subtypes of treatment failure were examined, a significant difference was found in rates of persistent

FIGURE 1

Distribution of oxygen saturation by altitude. The solid curved line represents a fitted normal density curve based on the observed pulse oximetry values.

TABLE 2 Predictors of Treatment Failure at High- and Low-Altitude Sites

	High Altitude		Low Altitude	
	RR	(95% CI)	RR	(95% CI)
Anemia	4.07	(2.60–6.38)	1.12	(0.96–1.30)
Treatment with chloramphenicol	1.43	(0.89–2.27)	1.42	(0.86–2.35)
Age (months)	0.98	(0.97–0.99)	0.99	(0.96–1.01)
Gender (male)	0.48	(0.31–0.74)	1.00	(0.78–1.28)
Heart rate (per 10 beats per minute)	0.98	(0.81–1.19)	1.03	(0.96–1.09)
Systolic blood pressure (per 10 mm Hg)	0.90	(0.76–1.06)	0.83	(0.74–0.93)
SpO_2 (per 10 %)	0.69	(0.55–0.86)	0.74	(0.66–0.82)
Weight-for-age z score	0.80	(0.65–0.98)	0.81	(0.71–0.93)
Dehydration	4.58	(3.34–6.28)	1.56	(1.00–2.44)
Immunized appropriately	0.45	(0.21–0.98)	0.95	(0.80–1.13)
Breastfed per WHO standards	2.34	(2.33–2.35)	0.94	(0.67–1.32)

Generalized estimating equation multivariate model diagnostics: high-altitude model, area under the receiver operating characteristic curve of 0.834; low-altitude model, area under receiver operating characteristic curve of 0.745.

hypoxemia (RR: 4.8; 95% CI: 2.1–10.8). On the basis of this finding, we evaluated the course of recovery of normoxemia (defined as persistent $\text{SpO}_2 > 90\%$) in patients at high and low altitudes. The median time to normoxemia at low altitude was 0.75 days, whereas the median time to normoxemia at high

altitude was 5.25 days (Fig 3). In a multivariate Cox proportional hazards model adjusting for age, gender, treatment group, anemia, baseline oxygen saturation, heart rate, systolic blood pressure, weight, and site (as a random effect), high altitude was associated with a significantly lower rate of

FIGURE 2

RR of treatment failure by hemoglobin quartile, adjusted for treatment group, age, gender, heart rate, systolic blood pressure, SpO_2 , weight-for-age, dehydration, immunization, breastfeeding, and treatment site. ref, reference. Dotted gray line represents $RR = 1.0$.

FIGURE 3

Time to normal oxygen saturation ($SpO_2 > 90\%$) by altitude. HR, hazard ratio.

normoxemia compared with low altitude (HR: 0.48; 95% CI: 0.34–0.68; $P < .0001$). Recognizing that the threshold for normoxemia is lower at higher altitudes, a sensitivity analysis was performed by using $SpO_2 > 88\%$ and $> 85\%$ as thresholds for defining normoxemia at high altitude; similar results were obtained (HRs [95% CI]: 0.69 [0.52–0.93] and 0.62 [0.50–0.76],

respectively) (Supplemental Figs 4 and 5).

DISCUSSION

In a large clinical trial in young children treated for WHO-defined severe pneumonia across 8 sites in 7 low-resource countries, children at high altitude presented with significantly more severe hypoxemia and cyanosis than

children at low altitude and took longer to recover from hypoxemia. Furthermore, children with anemia at high altitude had a significantly increased risk of poor outcome. This effect was not observed at low altitude, indicating that in young children with severe pneumonia, the combination of high altitude and anemia is of particular concern.

For healthy individuals living at high altitude, low ambient oxygen tension is reflected in a lower blood oxygen content, activating hypoxia-inducible transcription factors that increase erythropoietin and drive bone marrow hematopoiesis.¹⁹ This process depends on the availability of iron and other substrates required for hemoglobin synthesis. Children with nutritional iron deficiency, hemoglobinopathies, chronic inflammatory states, and malaria are unable to mount a sufficient response to the demands of high altitude.

Widely prevalent throughout many low-income nations, both anemia and underlying micronutrient deficiencies are particularly concerning at high altitude²⁰; and as was observed in our study, young children in high-altitude settings are at higher risk of malnutrition. A high prevalence of undernutrition and anemia has been documented in many high-altitude locations,^{21–23} including Nepal, where according to the 2011 Nepal Demographic and Health Survey, $> 70\%$ of children under 18 months are anemic and 40% of children under age 5 years are stunted.²⁴ In addition to nutritional factors, some ethnic groups living at high elevations (eg, Yemen, a site for this study) have a high prevalence of hemoglobinopathies, which may worsen the degree of anemia.²⁵

In many ways, pneumonia is a “stress test” for patients with hypobaric hypoxia and underlying anemia, revealing significant gaps in the spectrum of prevention and treatment. Clinical and

research priorities should include strategies for the prevention of anemia²⁶ (especially in those with respiratory infection), appropriate triage of children with severe pneumonia,¹⁵ and increasing the availability of supplemental oxygen to children with respiratory illnesses.²⁷ Although prevention and treatment of anemia are clearly important, many questions regarding the optimal timing and method of treatment remain unanswered, as well as the relationship of anemia to incident infections.^{28–30}

Our findings must be interpreted in the context of the study design, which highlights some of the limitations of the study. First, it is difficult to separate the effect of altitude from the effect of the unique characteristics of each treatment site. Whereas clinical protocols were standardized across sites, some differences likely remain. To address this concern, potential confounders were included in the model adjusting for variation in demographic, nutritional, and clinical characteristics, and the multivariate generalized estimating equation model accounted for site as a repeated effect.

Second, the effect of altitude on presentation and outcome of pneumonia likely reflects several different components that are difficult to study separately. Because individuals cannot be

randomly assigned to high- or low-altitude sites, it is difficult to study the effect of altitude in isolation. Differences between high- and low-altitude populations may reflect differences in nutritional patterns, exposure to indoor and outdoor air pollution, microbial epidemiology, and genetic risks for disease. There is evidence that among patients living at high altitude, the effect of anemia is greater in those who are exposed to air pollution.¹⁴ Furthermore, individuals living at high altitude are at risk of pulmonary hypertension,³¹ and exacerbation of underlying pulmonary hypertension may contribute to poor outcomes in young children at altitude with pneumonia. Regardless of the underlying mechanism of these differences, the findings of the current study highlight the need for special attention to this population. The complex interplay of chronic hypoxia, anemia, and underlying pulmonary hypertension renders some children unable to appropriately respond to respiratory infections, and these children represent a particularly vulnerable population in need of further study.

Third, the SPEAR trial included patients primarily at low (<500 m) and high (~2500 m) altitudes, making it impossible to study the effects of altitude across a broad range of elevations. In addition, the trial was limited to

children with severe pneumonia. Further studies are needed to understand the intersection of anemia and altitude at a variety of elevations and clinical severity.

CONCLUSIONS

This study reveals that young children with severe pneumonia living at high altitude present with significantly more severe hypoxemia than do children at low altitude, that children at high altitude take longer to recover from hypoxemia, and that anemia at high altitude increases the risk of poor outcome. Prevention and treatment of anemia should be a high priority in young children living at high altitude, and addressing this risk factor could reduce morbidity and mortality from severe pneumonia. Further study is needed to determine the optimal strategies for preventing and treating anemia in the setting of pneumonia.

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