

Hypoxaemia in children with severe pneumonia in Papua New Guinea

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SUMMARY

OBJECTIVES: To investigate the severity and duration of hypoxaemia in 703 children with severe or very severe pneumonia presenting to Goroka Hospital in the Papua New Guinea highlands; to study the predictive value of clinical signs for the severity of hypoxaemia, the predictive value of transcutaneous oxygen saturation (SpO₂) and other variables for mortality.

DESIGN: Prospective evaluation of children with severe or very severe pneumonia. SpO₂ was measured at the time of presentation and every day until hypoxaemia resolved. Children with a SpO₂ less than 85% received supplemental oxygen. By comparing with a retrospective control group for whom oxygen administration was guided by clinical signs, we evaluated whether there was a survival advantage from using a protocol for the administration of oxygen based on pulse oximetry. We determined normal values for oxygen saturation in children living in the highlands.

RESULTS: In 151 well, normal highland children, the mean SpO₂ was 95.7% (SD 2.7%). The median SpO₂ among children with severe or very severe pneumonia was 70% (56–77); 376 (53.5%) had moderate hypoxaemia (SpO₂ 70–84%); 202 (28.7%) had severe hypoxaemia (SpO₂ 50–69%); and 125 (17.8%) had very severe

hypoxaemia (SpO₂ <50%). Longer duration of cough or the presence of hepatomegaly or cyanosis predicted more severe degrees of hypoxaemia. After 10, 20 and 30 days from the beginning of treatment, respectively 102 (14.5%), 38 (5.4%) and 19 (2.7%) of children had persistent hypoxaemia; 46 children (6.5%) died. Predictors of death were low SpO₂ on presentation, severe malnutrition, measles and history of cough for more than 7 days. The mortality risk ratio between the 703 children managed whose oxygen administration was guided by the use of pulse oximetry and the retrospective control group who received supplemental oxygen based on clinical signs was 0.65 (95%CI 0.41–1.02, two-sided Fisher's exact test, *P* = 0.07).

CONCLUSION: There is a need to increase the availability of supplemental oxygen in smaller health facilities in developing countries, and to train health workers to recognise the clinical signs and risk factors for hypoxaemia. In moderate sized hospitals a protocol for the administration of oxygen based on pulse oximetry may improve survival.

KEY WORDS: severe pneumonia; oxygen; hypoxaemia; pulse oximetry; developing countries

ACUTE RESPIRATORY INFECTIONS cause more than 2.7 million child deaths world-wide each year; most of these are pneumonia, and 99% occur in developing countries.^{1–3} Although tissue hypoxia is the main fatal complication of severe pneumonia, there are few published data on the severity of hypoxaemia, no published data on the duration of hypoxaemia, and limited data on the predictive value of hypoxaemia for mortality, in children with severe or very severe pneumonia. Hypoxaemia can be detected using clinical signs, particularly cyanosis, or by pulse oximetry, which uses a transcutaneous sensor to measure the percentage of arterial haemoglobin that is saturated with oxygen. This report describes a study that investigated the severity and duration of hypoxaemia in 703 chil-

dren with severe or very severe pneumonia in Highlands Papua New Guinea (PNG), and evaluated whether there is a survival benefit from monitoring with pulse oximetry.

METHODS

Eligibility criteria

The study was approved by the Papua New Guinea Medical Research Advisory Committee as part of an ongoing randomised comparison of two antibiotic regimens in children with severe or very severe pneumonia. Children were eligible for enrolment if they were aged over 28 days and less than 5 years, and had clinical symptoms and signs of pneumonia (cough or

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Article submitted 3 July 2000. Final version accepted 8 January 2001.

difficulty breathing), with moderate-severe chest indrawing. Eligibility also required one or more of the following signs: 1) cyanosis, 2) inability to feed, 3) apnoea, or 4) signs of heart failure (tachycardia and hepatomegaly). Tachycardia was defined as a heart rate >160 /min. Hepatomegaly was said to be present if the liver was palpable 3 cm or more below the right costal margin. Children with wheeze or clinical bronchiolitis were excluded. The above signs are a combination of the diagnostic criteria for severe pneumonia in PNG,⁴ and what the World Health Organization (WHO) now classifies as very severe pneumonia. The respiratory rate threshold for tachypnoea is higher using the PNG criteria, and the WHO does not include signs of heart failure.⁵ Children who had this clinical diagnosis of severe pneumonia were screened for hypoxaemia using a pulse oximeter (Nelcor [Sydney, Australia] NPD-190 with Dura-Y digital sensor, or Ohmeda [Sydney, Australia] Biox 3700 with Flex II digital sensor). If the SpO₂ was less than 85%, the child was eligible for enrolment. Children were not eligible if they had evidence of structural heart disease, renal or liver dysfunction or meningitis, or if they had received parenteral antibiotic treatment for 24 hours or more in the previous 7 days.

Management protocol and oxygen administration

All children were treated with either chloramphenicol or a combination of benzylpenicillin and gentamicin for 10–14 days. All received oxygen by nasopharyngeal catheter at a flow rate of 0.25–2 L/min. The flow rate was adjusted to achieve a SpO₂ of 85% or more. If the SpO₂ was $<80\%$ on maximum flow oxygen given by intranasal catheter, oxygen was also given by face mask using a second oxygen source at a flow rate of 4–8 L/min. No mechanical ventilation was available. Each day children were examined for changes in clinical status and their SpO₂ was measured while breathing room air for 15 minutes, to assess whether supplemental oxygen was still required. Trials on room air were not done if children required more than one source of oxygen or if they were considered to be too unwell. During daily trials off supplemental oxygen patients were monitored carefully to avoid any adverse complications of hypoxaemia. If severe hypoxaemia (SpO₂ $<70\%$), apnoea or severe respiratory distress occurred children were immediately restarted on oxygen. Children received supplemental oxygen until their SpO₂ on air was 85% or greater. On any given day, if the SpO₂ was 85% or more, they remained off oxygen, and the SpO₂ was rechecked one hour later. After 5 completed days of antibiotic treatment an assessment was made of the response to treatment, and changes were made to antibiotic therapy if the child was not improving. At 5 days the SpO₂ was measured after breathing room air for 30 minutes, unless any of the above contraindications existed or complications occurred. Children were not discharged until their

SpO₂ had been stable at 90% or more while breathing room air for at least 24 hours, until other clinical features of pneumonia had resolved, and they had completed at least 5 days of parenteral antibiotics.

The trials of supplemental oxygen were designed to provide oxygen to those who needed it most. At the beginning of the study we had only six piped oxygen outlets in the 80-bed ward. These outlets were connected to a bank of oxygen cylinders with a safety manifold and alarm that signalled low oxygen source. During the busiest eight months of the year more than 20 children with SpO₂ $<85\%$ were in the ward at any one time and required supplemental oxygen. Because of the high demand and limited supplies, many children initially either shared a piped oxygen source with another patient (with oxygen tubing connected by a Y-connector) or received oxygen from free-standing cylinders. Unfortunately free-standing oxygen cylinders often became empty overnight or when no staff were in attendance. The unwitnessed depletion of oxygen in free-standing cylinders was associated with several serious complications, including very severe hypoxaemia, prolonged apnoea and respiratory arrest, and contributed to two deaths early in the study period. Because of these adverse events, and to avoid the potential for nosocomial transmission of infection from a shared oxygen tubing, we installed another 15 piped oxygen outlets connected to the safety manifold during the course of the study.

Prior to beginning the study, children with pneumonia received oxygen only if they were cyanosed or unable to drink. No pulse oximetry was used.

Outcome definitions and data collected

Mortality associated with the index episode of pneumonia was defined if death occurred 1) at any time during the initial admission, or 2) at any time during readmission to hospital in which the child represented within 30 days of initial hospital discharge. Death occurring during a hospital admission when the child had represented more than 30 days after the initial date of discharge was considered a late death.

Grades of severity of hypoxaemia were defined as follows: mild SpO₂ 85–90%; moderate SpO₂ 70–84%; severe 50–69%; very severe hypoxaemia $<50\%$. Children with the above definition of severe pneumonia but only mild hypoxaemia on presentation were not included in the study. Clinical variables were recorded to determine those that predicted mortality, more severe hypoxaemia (thus identifying those children who should preferentially receive oxygen) and prolonged hypoxaemia. These clinical variables, measured on presentation, were percentage of expected weight for age, duration of cough, respiratory rate, heart rate, temperature, presence of cyanosis, inability to feed, hepatomegaly and co-existence of other conditions such as measles.

To determine whether there has been a difference

in mortality since the oxygen management protocol using pulse oximetry was introduced, admission data were reviewed for the 12 months prior to the introduction of pulse oximetry (1 March 1997–28 February 1998). Data were retrieved on children in whom the discharge and admission diagnoses were severe pneumonia (PNG definition⁴), who did not have coexistent meningitis or congenital heart disease, and for whom a discharge disposition (discharged or died) was recorded. These were compared with the outcome data for the 703 children reported in this study. The mortality in our current prospective cohort was also compared with that in other published studies of very severe and severe pneumonia in which pulse oximetry monitoring was not used. To do this a Medline search was performed on the key words 'severe pneumonia', 'children' and 'mortality', for papers published between 1966 and 1999.

Normal oximetry values

A group of well, normal children aged one month to 5 years was studied to determine normal values for oxygen saturation in the Eastern Highlands. This was done to determine the lower limit of normal for SpO₂ in highland children at 1600 m, as no published data existed. These children were recruited from the out-patient immunisation clinic, and the oxygen saturation was measured at rest prior to immunisation.

Statistical analyses

Normally distributed data are presented as mean (standard deviation [SD]); non-normal data are presented as median (interquartile range [IQR]). The Mann-Whitney test was used to compare independent groups with non-normally distributed data. Logistic regression analysis was used to determine the predictive power of SpO₂ and other clinical variables for mortality. Predictive power of variables for severity of hypoxaemia, duration of hypoxaemia and death are presented as odds ratios (OR), 95% confidence intervals (95% CI), sensitivity, specificity, positive and negative predictive power, and area under the receiver operating characteristics (ROC) curve.⁶ The ROC curve plots the sensitivity of a test versus one minus the specificity. A test with perfect predictive power, i.e., 100% sensitivity and specificity, will have an area under the ROC curve of 1.0; a test that predicts an outcome no better than chance has an area under the ROC curve of 0.5.

RESULTS

Oximetry values in well highland children

In 151 well children the mean SpO₂ was 95.7% (SD 2.7%); therefore the lower limit of SpO₂ among normal children was 90.3% (mean minus 2 SD).

Children with severe pneumonia

Between June 1998 and September 1999, 703 children were recruited into the study. The median age (IQR) was 6.3 months (3.8–10.3 months). Median weight was 7.1 kg (5.8–8.2), mean percentage of expected weight-for-age was 89.8% (SD 20.6%), and 33 (4.5%) children had marasmus (weight <60% of expected weight-for-age). Median duration of cough was 5 days (3–7). A total of 528 (82.5%) had inability to feed, 451 (71%) were cyanosed at presentation, and 338 (48.4%) had hepatomegaly; 45 children (6.5%) presented with apnoea. The mean (SD) heart rate was 160.2 (21.3).

Severity of hypoxaemia

The median SpO₂ at the time of presentation was 70% (56–77); 376 (53.5%) had moderate hypoxaemia (SpO₂ 70–84%), 202 (28.7%) had severe hypoxaemia (SpO₂ 50–69%), and 125 (17.8%) had very severe hypoxaemia (SpO₂ <50%).

Children with any of the following: presence of hepatomegaly, cyanosis or longer duration of cough, were at increased risk of more severe hypoxaemia. Compared to children with only moderate hypoxaemia (defined as SpO₂ 70–84%), cyanosis (OR 4.91; 95% CI 3.33–7.22) or hepatomegaly (OR 2.13; 95% CI 1.58–2.88) predicted the presence of severe or very severe hypoxaemia. Cough >7 days (OR 1.55; 95% CI 1.01–2.36) was a weak predictor of very severe hypoxaemia only. Lower weight-for-age, heart rate, respiratory rate, inability to feed and apnoea were not risk factors for severe or very severe hypoxaemia.

Children identified as being cyanosed had a median SpO₂ (IQR) of 68% (51–76%), and those not seen to be cyanosed had a SpO₂ of 76% (70–80%). Cyanosis was detected in 88% of children with a SpO₂ <50%; in 81% of children with SpO₂ 50–69%; and in 44% of children with SpO₂ 70–84%.

Duration of hypoxaemia

The median duration of hypoxaemia after admission was 4 days (2–8 days). After 5 days of completed treatment the median SpO₂ was 90% (IQR 80–93). At 10, 20 and 30 days after beginning treatment, respectively 102 (14.5%), 38 (5.4%) and 19 (2.7%) of children remained hypoxaemic (Figure 1). Longer duration of hypoxaemia was related to lower weight-for-age, longer duration of cough, and lower SpO₂ at the time of admission. The odds ratio for hypoxaemia longer than 20 days was 1.92 (95% CI 1.10–3.38) if the cough had been present for more than 7 days, 3.72 (95% CI 2.09–10.8) if the weight was <60% of expected for age, and 3.37 (95% CI 1.95–5.83) if the SpO₂ was <50% at admission (all *P* < 0.01). Longer duration of hypoxaemia was not predicted by temperature, respiratory rate, heart rate or presence of cyanosis or hepatomegaly, all of which were measured at the time of admission.

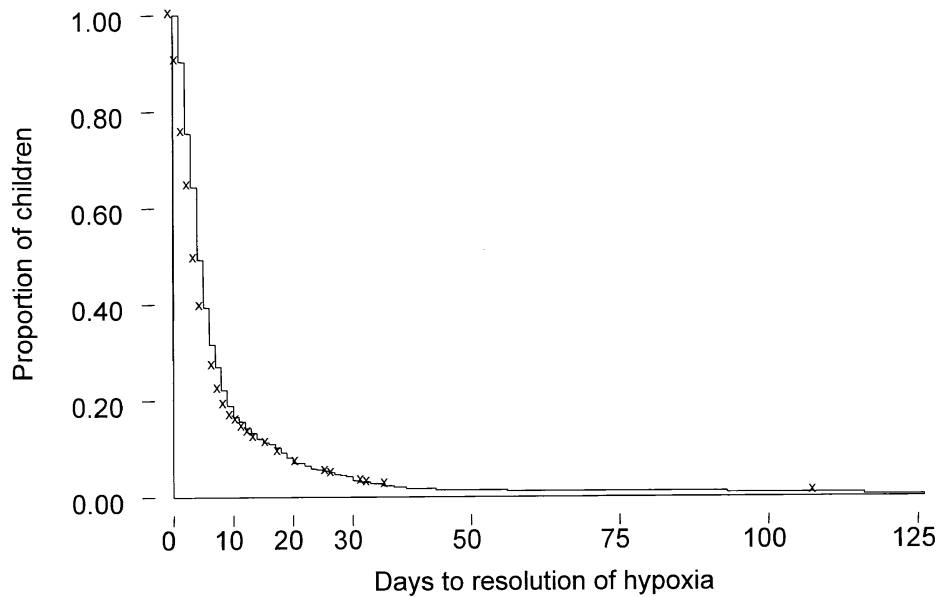


Figure 1 Kaplan-Meier curve showing the time to resolution of hypoxaemia ($\text{SpO}_2 > 89\%$). The crosses indicate deaths, which are censored.

Mortality

Forty-six children died (6.5%), and there were three additional late deaths. The median (IQR) admission SpO_2 in those who survived was 71% (57–77%), compared with 59% (40–71%) in those who died ($P < 0.0003$); 126 (18%) children had a $\text{SpO}_2 < 50\%$ at the time of presentation, of whom 15.4% died. Compared to children with only moderate hypoxaemia (SpO_2 70–84%, $n = 367$), the group with severe hypoxaemia at admission (SpO_2 between 50–69%,

$n = 202$) had only a trend towards lower survival (OR 1.75, 95%CI 0.83–3.70, $P = 0.14$). Figure 2 shows the predicted probability of mortality for a given level of SpO_2 at admission.

Fifteen deaths occurred in the first 5 days of treatment, and 31 children survived to day 5 but subsequently died. Day 5 SpO_2 for subsequent non-survivors was 62% (40–75%), and for survivors it was 90% (82–93%). Eighty children had measles and severe pneumonia, 11 of whom died (13.8%).

Using logistic regression analysis for admission

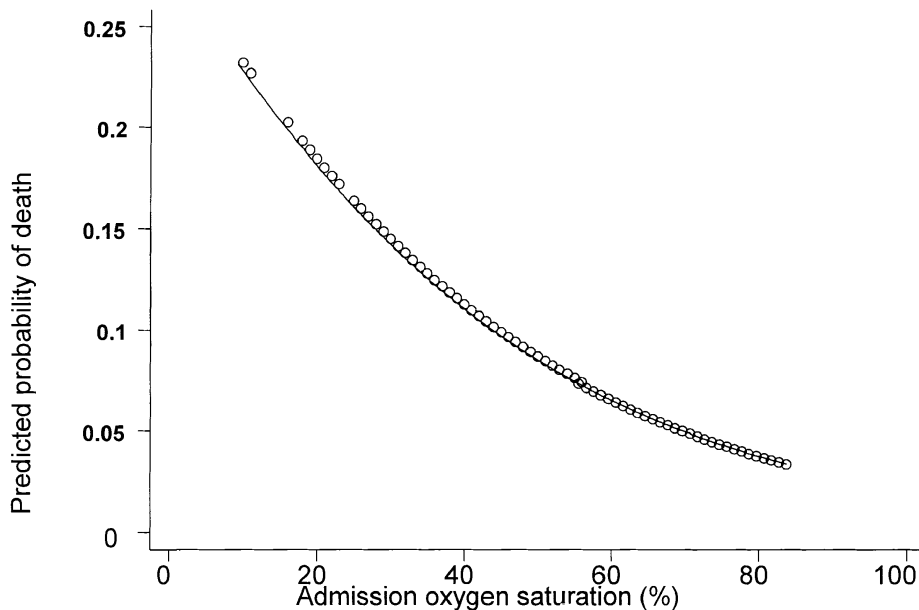


Figure 2 Log likelihood plot of predicted probability of death according to oxygen saturation, measured at admission in 703 children with very severe pneumonia. Probability of mortality must be seen in the context of the current treatment protocol of oxygen administration. Without oxygen the mortality from pneumonia with severe hypoxaemia will be much higher.

Table 1 Summary of the predictive power of variables measured at the time of presentation for death. Univariable analysis is shown; in a multivariable model, duration of cough was not significant

| Variable | OR for death (95%CI) | OR P value | Sens. | Spec. | PPV | NPV |
|---------------------------------|----------------------|------------|-------|-------|------|------|
| Weight <60% (n = 33) | 6.32 (2.74–14.57) | <0.001 | 20.0 | 96.2 | 27.3 | 95.1 |
| Cough >7 days (n = 143) | 3.99 (2.17–7.36) | <0.001 | 48.0 | 81.3 | 18.2 | 95.6 |
| SpO ₂ <50% (n = 125) | 2.93 (1.56–5.52) | 0.001 | 37.0 | 83.3 | 13.6 | 94.9 |
| SpO ₂ <70% (n = 327) | 2.46 (1.30–4.65) | 0.001 | 67.4 | 54.3 | 9.4 | 95.9 |
| Measles (n = 80) | 2.18 (1.05–4.53) | 0.04 | 26.1 | 86.0 | 13.8 | 94.4 |
| Hepatomegaly (n = 338) | 1.68 (0.92–3.08) | 0.09 | 60.9 | 52.3 | 9.2 | 94.9 |
| Cyanosis (n = 451) | 1.46 (0.79–3.45) | 0.19 | 80.0 | 29.6 | 8.1 | 98.3 |
| Not feeding (n = 520) | 0.99 (0.56–1.74) | 0.96 | 84.1 | 17.4 | 7.1 | 93.6 |

OR = odds ratio; CI = confidence interval; Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value.

data, duration of cough >7 days, SpO₂ at presentation, weight-for-age, and presence of measles were statistically significant predictors of death. The area under the ROC curve to predict death for admission SpO₂ was 0.66, weight-for-age 0.59, and duration of cough 0.67 (as continuous variables). Table 1 summarises the predictive power of these and other variables for death. Presence of apnoea, cyanosis or hepatomegaly, respiratory rate and temperature did not predict death. In a multivariable logistic regression model using all the significant variables, SpO₂ at admission, % weight-for-age and measles remained independently significant predictors of mortality (all $P < 0.05$), but the duration of cough was no longer a significant predictor of mortality ($P = 0.52$).

Recurrent pneumonia in survivors

Within one month of the date of discharge, 59 (9.7%) of the children who had been discharged apparently well were readmitted with recurrent pneumonia and hypoxaemia. Fifty-five (8.3%) children absconded before completion of treatment; however, only nine of these were still hypoxaemic at the time of leaving hospital.

Comparison of mortality before and after pulse oximetry use at Goroka Hospital

In the 12 months prior to using pulse oximetry at Goroka Hospital, 258 children were admitted with severe pneumonia, of whom 26 (10.0%) died. In this earlier

group, oxygen administration was based on the detection of clinical signs, particularly the presence of cyanosis. The mortality rate ratio between this retrospective control group and the 703 children managed with the above pulse oximetry protocol was 0.65 (95% CI 0.41–1.02, Fisher's exact test, $P = 0.07$).

A previous study of 748 children with severe pneumonia based at Goroka Hospital, which used standard antibiotics and similar entry criteria but clinical signs rather than pulse oximetry to administer oxygen, had a mortality of 14.7%.⁷ In the published literature six papers report mortality for children who fulfil the WHO criteria for very severe pneumonia (Table 2).^{7–12} These include 1666 children, of whom 213 died (case fatality 12.8%).

Complications of the oxygen administration protocol

During daily trials of supplemental oxygen several children were observed to have brief apnoea or oxygen desaturation to SpO₂ <70%. These corrected when restarted on oxygen, and there were no respiratory arrests and no prolonged complications from the trials on room air. No child deteriorated or died in the first hours after a trial of supplemental oxygen.

DISCUSSION

This study found that in children with severe pneumonia in Papua New Guinea 1) hypoxaemia is often

Table 2 Published reports of mortality from very severe pneumonia, according to current WHO criteria. Some studies referred to pneumonia with cyanosis or inability to feed as 'severe' rather than 'very severe' pneumonia (reflecting the previous WHO classification and local definitions of pneumonia severity)

| Study, author and country | Patients (n) | Deaths | Case fatality (%) | Comments |
|--|--------------|--------|-------------------|----------------------------------|
| Shann et al. 1985, PNG ⁷ | 748 | 110 | 14.7 | 53% cyanosed or too sick to feed |
| Mishra et al. 1993, India ⁸ | 39 | 3 | 7.7 | 10.3% cyanosed |
| Bahl et al. 1995, India ⁹ | 53 | 6 | 11.3 | 7.7% cyanosed |
| Sehgal et al. 1997, India ¹⁰ | 201 | 21 | 10.4 | Severe or very severe pneumonia |
| Banajeh et al. 1997, Yemen ¹¹ | 529 | 52 | 9.8 | 56% cyanosed |
| Smyth et al. 1997, Zambia ¹² | 96 | 21 | 21.8 | |
| Total | 1666 | 213 | 12.8 | |

severe and prolonged, 2) cyanosis does not reliably detect moderate hypoxaemia, 3) the severity of hypoxaemia on presentation is a predictor of mortality even when supplemental oxygen is given, and 4) a protocol of relatively liberal oxygen therapy that is guided by pulse oximetry may reduce mortality. Other studies of children with acute respiratory infection have shown that the presence of hypoxaemia is a risk factor for mortality.^{13,14} This cohort of children is the largest with very severe pneumonia where the severity and duration of hypoxaemia has been studied.

Hypoxaemia in pneumonia is due to alveolar consolidation causing marked increases in intrapulmonary shunting^{15,16} and ventilation-perfusion mismatching, and increased respiratory secretions causing airflow obstruction. Other factors include respiratory muscle fatigue (in respiratory failure, severe sepsis and malnutrition); pulmonary hypertension and heart failure,¹⁷ and reduced central respiratory centre response to hypoxaemia and hypercarbia (in very young infants and those with coexistent brain injury, including hypoxic brain injury or coexistent meningitis). Hypoxaemia may be more frequent and more severe in children with pneumonia who live at higher altitude, because of reduced partial pressure of atmospheric oxygen—Goroka is at an altitude of 1600 m above sea level. We showed that the lower limit of SpO₂ among normal children was 90.3% (mean minus 2 SD). Other observations in normal children from places where the altitude is between 1000–2000 m above sea level show a lower limit of SpO₂ (mean minus 2 SD) of between 88.7% and 96.9%.^{14,18–20} Therefore the severe hypoxaemia seen in Highlands Papua New Guinea is unlikely to be strongly influenced by low baseline levels due to the altitude, although the effect of higher altitude on the duration of hypoxaemia is uncertain.

Factors associated with an increased risk of severe or very severe hypoxaemia were cyanosis, hepatomegaly and longer duration of cough. The predictive power of these clinical features was low, but these signs may identify children who should preferentially receive oxygen when supplies are limited.

Cyanosis was an unreliable indicator of moderate hypoxaemia: more than half of the children with SpO₂ 70–84% were assessed not to be cyanosed. Because the current study did not include children with mild or no hypoxaemia, it is not possible to determine the signs that distinguish those with any degree of hypoxaemia from those without hypoxaemia. It has previously been shown that clinical algorithms may fail to detect 30–40% of children with hypoxaemia.^{13,21,22}

Although there was a moderately strong relationship between the severity of hypoxaemia and risk of death, given appropriate provision of oxygen and standard antibiotic treatment almost 85% of the children presenting with even very severe hypoxaemia (SpO₂ <50%) survived long-term. It is likely that

many of these children would not have survived a further 24 hours without supplemental oxygen and antibiotic treatment. The area under the ROC curve of 0.66 (SpO₂ as a predictor of mortality) represents low predictive power, but this must be seen in the context of the protocol of oxygen administration. Without supplemental oxygen the mortality from pneumonia with severe hypoxia will be much higher, and therefore the predictive power of hypoxaemia for death greater. In addition to mortality, the burden of morbidity and consumption of health care resources from pneumonia are enormous. One month after admission 49 children had died or died subsequently, 19 had persistent hypoxaemia, and 59 had been readmitted with hypoxaemic pneumonia, representing medium-term morbidity or mortality of 18%. A late mortality of 10% among hospital survivors has been reported in Gambian children with hypoxaemic pneumonia who were followed up within their community.²³ We did not follow up children within the community after discharge, so 18% will be an underestimate of the medium to longer term sequelae.

Several authors have recommended administration of supplemental oxygen if the SpO₂ is <90%.^{13,24} Although this is consistent with the level of SpO₂ that is abnormal, a threshold SpO₂ of 90% will be impractical in most settings in developing countries. There were two reasons why we decided to give oxygen only to children with a SpO₂ <85%. First, we treat a large number of patients with respiratory disease, as well as other diseases complicated by hypoxia, and there are a limited number of oxygen outlets and oxygen supplies in the hospital. Second, the level of hypoxaemia that will limit survival or delay recovery has not been established, but many children with cyanotic heart disease survive untreated for years with SpO₂ <80% (although they often have compensatory polycythaemia). The only groups of children in our ward who always receive oxygen below the threshold level of SpO₂ 90% are those with acute brain injury (most commonly bacterial meningitis), those with heart failure or septic shock, and those with severe anaemia prior to blood transfusion. In pneumonia, impaired oxygen delivery to tissues that would be predicted to result from low blood oxygen content is likely to be compensated for by increased cardiac output. Our data suggest that children with severe pneumonia can be managed safely, in almost all cases, by giving oxygen to all those with an SpO₂ <85%. Without further evaluation this threshold should not be applied directly to children living at lower altitude, where baseline SpO₂ will be >95%. Even though SpO₂ 85% is a lower SpO₂ threshold than that recommended by some authors, it will be higher than if the administration of supplemental oxygen were based on clinical signs. With a SpO₂ threshold of 85%, oxygen would have been given far earlier, and to far more children, than if clinical signs were used, as cyanosis was only

reliably detected when the SpO₂ was < 70%. Our data support the need to administer oxygen earlier in the course of the disease.^{11,25}

The long duration of hypoxaemia has not previously been reported. More than 10% of children required supplemental oxygen for longer than the duration of antibiotic therapy. It is likely that if these children had been discharged at the completion of antibiotic treatment they would have deteriorated at home without supplemental oxygen. The causes of prolonged hypoxaemia are uncertain, but may be due to persistent inflammation impairing gas exchange, secretions or constriction of bronchi or bronchioles causing airflow obstruction; the inflammatory response in the lung may persist long after bacterial killing occurs. Pneumonia due to viruses, mycobacteria or other atypical organisms may persist for longer periods. Bronchiolitis may be associated with prolonged hypoxaemia, and we could not do viral cultures or immunofluorescence testing to exclude this, but we did exclude children from the study who had wheeze or other clinical signs such as hyperinflation. Other potential factors causing prolonged hypoxaemia include acquired pulmonary hypertension and cardiac insufficiency,¹⁷ and lung scarring. Recognition of the small but important proportion of children with severe pneumonia who have a prolonged need for supplemental oxygen may be one reason for the lower mortality, compared with results from previous series in the highlands of PNG and from other centres.

The analysis of mortality before and after introduction of the oxygen administration protocol using pulse oximetry at Goroka Hospital is not in itself convincing evidence of a benefit of the monitoring technology. We think it would be unethical to do a study randomising children with severe pneumonia to monitoring with or without pulse oximetry; however, the comparison using a retrospective control group has many confounding factors. First, the prospective cases were enrolled in a randomised antibiotic trial where close attention was given to following a strict management protocol; second, there was a change of staff 5 months into the 12-month retrospective period; and third, new oxygen outlets were installed during the study. These and other uncontrolled variables may introduce bias towards a lower mortality in the prospective cohort, and the difference in mortality was a trend, rather than being statistically significant. The analysis of published mortality in very severe pneumonia combines studies where several aspects of treatment (including oxygen and antibiotic availability) or patient selection may have differed from the present study.⁷⁻¹² In addition, at least two studies have used pulse oximetry at least at the time of admission and have reported mortality rates (15.2%²⁴ and 12.3%¹³) similar to those in published series where oximetry was not used. Although the evidence is far from conclusive, it seems likely that there is a survival

benefit using a protocol for the more liberal use of supplemental oxygen, based on pulse oximetry monitoring.

The protocol for oxygen administration and the technique of pulse oximetry monitoring can be easily learnt by nurses. Modern portable oximeters are robust, and sensor attachments are well tolerated by young infants. If a 35% reduction in pneumonia mortality could be achieved in a hospital admitting 250 children annually with severe pneumonia and a baseline case fatality of 10%, over 3 years a US\$5000 oximeter would cost US\$190 per life saved (in children with severe pneumonia alone). Oximetry may help ration the use of oxygen, which is an expensive resource, as the use of clinical algorithms for oxygen administration results in oxygen being given to at least 20% of children who do not have hypoxaemia.^{13,22} However, total oxygen use may not decrease with more precise monitoring, as the recognition of moderate hypoxaemia and the longer duration of hypoxaemia will necessitate increased use of oxygen in some children. The initial cost of an oximeter is substantial, recurrent expenses include the cost of the digital probes and oximeter maintenance, and it is essential to have ongoing training of staff in the correct technique of measurement and interpretation of results. Most importantly, such technology will be of no assistance to children who cannot access health care *and* oxygen; these are the majority of children world wide who die from pneumonia.

Further studies are needed to prospectively validate the use of retrospectively derived algorithms for the detection of hypoxaemia,^{13,21,22} as retrospective fitting of models to data maximises the predictive power of the variables. The precision of these signs should be field-tested in very young infants, who make up a large proportion of the world wide pneumonia mortality burden. Studies might best focus on defining the precision, and use, of clinical signs for SpO₂ < 85%.

In developing countries the highest priorities in pneumonia control must be 1) immunisation against *Streptococcus pneumoniae*, *Haemophilus influenzae* and measles; 2) increased availability of good quality primary health services, and 3) the universal use of standard treatment (including supplemental oxygen based on empirical recommendations). In medium-sized hospitals, protocols for the more liberal use of supplemental oxygen based on monitoring oxygen saturation may substantially reduce the case fatality of severe pneumonia.

Acknowledgements

We are very grateful to the following people who assisted in the collection of pulse oximetry data and in the care of the children in the study: Drs Harry Poka, Charlie Turharus, Jonah Karubi, Siwi Wau, Sam Maima, Sioni Sialis, and Simon Konae. We thank Drs Anne Blaschke and Josh Bonkowsky for collecting the oximetry values in normal children. We gratefully acknowledge the work of the nursing staff of the Goroka Hospital Children's Ward for their

excellent care of the patients in this study. We thank Dr Simon Young from the Royal Children's Hospital, Melbourne, and Dr John Reeves for assistance in the donation of pulse oximeters, Bradley Carter for oximeter repairs, and Datex-Ohmeda Pty Ltd, Australia, for the donation of several sensor probes. TD is indebted to Prof Frank Shann and Dr Martin Weber for invaluable advice, and Alison Duke for her constant support.

Contributors

TD designed the study and the oxygen administration protocol, arranged study funding and ethical approval, was in charge of enrolling and managing patients, collection of oximetry and outcome data, data entry and analysis, and wrote the paper. JM and DF enrolled and managed patients, collected oximetry data, and made revisions to drafts of the paper.

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RÉSUMÉ

OBJET : Investiguer la gravité et la durée de l'hypoxémie chez 703 patients atteints de pneumonie grave ou très grave et consultant à l'Hôpital Goroka dans les régions montagneuses de la Papouasie-Nouvelle Guinée. Étudier également la valeur prédictive des signes cliniques vis à vis de la sévérité de l'hypoxémie, ainsi que la valeur prédictive pour la mortalité de la mesure de la saturation d'oxygène par voie transcutanée (SpO₂) et celle d'autres variables.

MÉTHODE : Évaluation prospective des enfants atteints de pneumonie grave ou très grave. La SpO₂ fut mesuré au moment de l'admission et tous les jours jusqu'à la résolution de l'hypoxémie. Les enfants avec une SpO₂ de

moins de 85% ont reçu des suppléments d'oxygène. En comparaison avec un groupe contrôle rétrospectif chez lequel l'administration d'oxygène dépendait des signes cliniques, nous avons évalué dans quelle mesure il y avait avantage en matière de survie à utiliser un protocole pour l'administration d'oxygène basé sur l'oxymétrie de pouls. Nous avons déterminé les valeurs normales de saturation d'oxygène pour les enfants vivant dans les régions montagneuses.

RÉSULTATS : Chez 151 enfants bien normaux dans les régions montagneuses, la SpO₂ est de 95,7% (DS 2,7%). La SpO₂ médiane parmi les enfants atteints de pneumonie grave ou très grave est de 70% (56–77) ; chez 376

(53,5%), l'hypoxémie est modérée (SpO_2 70–84%) ; chez 202 (28,7%), elle est marquée (SpO_2 50–69%) et chez 125 (17,3%), elle est très marquée ($SpO_2 < 50\%$). Une durée plus longue de la toux ou la présence d'hépatomégalie ou de cyanose permettent de prédire des degrés plus marqués d'hypoxémie. Après 10, 20 ou 30 jours de traitement, respectivement, une hypoxémie persistait chez 102 (14,5%), 38 (5,4%) et 19 (2,7%) des enfants. Le décès est survenu chez 46 enfants (6,5%). Les facteurs prédictifs du décès sont une SpO_2 basse lors de l'admission, une malnutrition sévère, la rougeole et des antécédents d'une toux durant plus de 7 jours. Le ratio de risque de mortalité entre les 703 enfants traités

où l'administration d'oxygène a été guidée par l'utilisation de l'oxymétrie de pouls et le groupe contrôle rétrospectif qui avait reçu des suppléments d'oxygène sur base de signes cliniques est de 0,65 (IC95% 0,41–1,02 ; test exact bilatéral de Fisher, $P = 0,07$).

CONCLUSIONS : Il est nécessaire d'augmenter l'accessibilité à des suppléments d'oxygène dans les plus petites institutions de soins des pays en développement et d'entraîner les travailleurs de la santé à reconnaître les signes cliniques et les facteurs de risque pour l'hypoxémie. Dans les hôpitaux de taille moyenne, un protocole concernant une administration d'oxygène basée sur l'oxymétrie de pouls peut améliorer la survie.

RESUMEN

OBJETIVO : Investigar la gravedad y duración de la hipoxemia en 703 niños con neumonía grave o muy grave atendidos en el Hospital Goroka en las tierras altas de Papua Nueva Guinea. También, estudiar el valor predictivo de los signos clínicos para la severidad de la hipoxemia y el valor predictivo de la saturación de oxígeno transcutánea (SpO_2) y otras variables, para la mortalidad. **DISEÑO :** Evaluación prospectiva de niños con neumonía grave o muy grave. La SpO_2 fue medida al inicio y todos los días hasta la resolución de la hipoxemia. Los niños con una SpO_2 de menos de 85% han recibido oxígeno suplementario. Comparando con un grupo control, retrospectivo, en quienes la administración de oxígeno fue guiada por signos clínicos, evaluamos si había ventajas en la sobrevivencia al usar un protocolo para la administración de oxígeno basada en la oximetría del pulso. Determinamos los valores normales de la saturación de oxígeno en los niños que vivían en las alturas.

RESULTADOS : En 151 niños normales, que vivían en la altura, la SpO_2 media fue de 95,7% (SD 2,7%). La SpO_2 media en los niños con neumonía grave o muy grave fue de 70% (56–77) ; 376 (53,5%) tenían hipoxemia moderada (SpO_2 70–84%); 202 (28,7%) tenían hipoxemia

severa (SpO_2 50–69%) ; y 125 (17,8%) tenían hipoxemia muy severa ($SpO_2 < 50\%$). La duración más prolongada de la tos o la presencia de hepatomegalia o la cianosis predecían un mayor grado de hipoxemia. Después de 10, 20 y 30 días desde el inicio del tratamiento, 102 (14,5%), 38 (5,4%) y 19 (2,7%) de los niños, respectivamente, tenían hipoxemia persistentes. Cuarenta y seis niños (6,5%) murieron. Los factores predictivos de la muerte fueron una SpO_2 muy baja al inicio, severa malnutrición, sarampión y una historia de tos de más de siete días. La relación del riesgo de mortalidad entre los 703 niños atendidos cuya administración de oxígeno estaba guiada por el uso del oxímetro de pulso y el respectivo grupo control que recibió oxígeno suplementario sobre la base de los signos clínicos fue de 0,65 (IC95% 0,41–1,02 ; test exacto bilateral de Fisher, $P = 0,07$).

CONCLUSIONES : Es necesario aumentar el suministro de oxígeno suplementario en los pequeños establecimientos sanitarios en los países en desarrollo y entrenar a los trabajadores de la salud para reconocer los signos clínicos y los factores de riesgo de la hipoxemia. En los hospitales medianos, un protocolo de administración de oxígeno basado en la oximetría del pulso puede mejorar la sobrevivencia.