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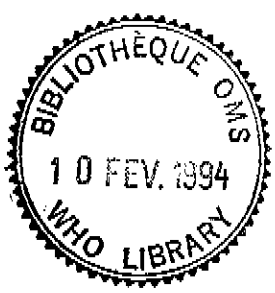
Oxygen therapy for acute respiratory infections in young children in developing countries



Programme for the Control of Acute Respiratory Infections

World Health Organization
Geneva

OXYGEN THERAPY FOR ACUTE RESPIRATORY INFECTIONS IN YOUNG CHILDREN IN DEVELOPING COUNTRIES

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1. REVIEW OF THE USE OF OXYGEN THERAPY

Anoxaemia not only stops the machine but wrecks the machinery.
JS Haldane, 1919

Oxygen was first isolated by Priestley in 1744 and used therapeutically by Beddoes in 1798.[1] However, for many years oxygen was not given properly and most doctors thought it was ineffective; it was administered to patients who were not hypoxaemic, and who would therefore not benefit from it; it was delivered by ineffective means, usually at a very low flow rate through a funnel held near the patient's face, but also by nasogastric tube, subcutaneously and even intravenously; and it was given only intermittently, for example, for 10 minutes every four hours.[1]

Oxygen therapy was first used in a logical way by JS Haldane, who treated soldiers affected by toxic chlorine gas during the First World War.[2] Haldane stressed that the body has practically no stores of oxygen, so that therapy needs to be continuous,[3] and he developed equipment that delivered oxygen cheaply and effectively.

1.1 DOES OXYGEN THERAPY REDUCE MORTALITY IN PNEUMONIA?

For a patient with severe or very severe pneumonia who is dying from lack of oxygen, it seems logical to give oxygen to keep the patient alive until the body defences and antibiotics have had time to kill the pathogens causing the infection. Unfortunately, no randomized controlled trials were conducted when oxygen therapy was first introduced into clinical practice in about 1920; however, there is indirect evidence of its effectiveness.

1.1.1 An animal study (pre-antibiotics), 1928

Binger and associates[4] at the Mayo Clinic anaesthetized guinea-pigs with ether, and then injected into their lungs streptococci cultured from the throats of healthy humans. Of 70 guinea-pigs kept in air, 66 (94%) died within 2 weeks, while of 45 guinea-pigs kept in 50% oxygen for 24 to 48 hours only 22 (49%) died within this period; the mortality was 45% lower with oxygen (95% confidence limit 30% to 61%).

1.1.2 Retrospective controls in humans (pre-antibiotics), 1919-1929

The case-fatality rate for pneumonia varies greatly from year to year, so retrospective controls can be used only if details are available about the severity of the disease. Mortality from pneumonia has been shown to be related to the oxygen saturation of arterial blood,[5,6] the presence of bacteraemia, the serotype of the organism (in pneumococcal pneumonia) and the age of the patient.[7]

Measurement of the oxygen saturation of arterial blood became possible at just about the time when oxygen therapy began to be used routinely, so few patients with pneumonia had oxygen saturation measured without receiving oxygen therapy. Stadie reported such measurement in 33 adults who did not receive oxygen;[8] however, since he did not report the age of his subjects, age could not be included in the analysis. The mortality in Stadie's patients can be compared with the mortality in five early studies of oxygen therapy in which oxygen saturation was measured[9-13] and one large series of patients for which oxygen saturation can be estimated because the degree of cyanosis was carefully recorded.[5] All these reports were from the Rockefeller Institute Hospital[8,10,11,13] and the Presbyterian Hospital[5,12] in New York, or the Massachusetts General Hospital[9] in Boston. The results of the analysis are shown in Table 1. Adjusted for the severity of illness, mortality was 39% with oxygen and 74% without oxygen. No effective chemotherapeutic treatment was then available.

Table 1

Effect of oxygen therapy on mortality from pneumonia[5,8-13]

	Died/total (% died)	
	Without oxygen	With oxygen
Saturation[a] <80%, bacteraemia:	2/2 (100)	15/21 (71)
Saturation <80%, no bacteraemia:	12/13 (92)	19/52 (37)
Saturation >=80%, bacteraemia:	2/4 (50)	3/8 (38)
Saturation >=80%, no bacteraemia:	2/15 (13)	2/12 (17)
Total, adjusted for severity of illness:	74% died	39% died

[a] Saturation represents oxygen saturation of arterial blood.

1.1.3 Concurrent controls in humans (with antibiotics, 1966-1967)

It is expensive and difficult to transport oxygen cylinders to rural areas. In Papua New Guinea, from mid-1976 to mid-1977 at Tari in the Southern Highlands, oxygen was available for only about two out of every four weeks. Treatment was given according to a standard protocol. When oxygen was available, it was given at 0.5 l/min via nasopharyngeal catheter to any child who was cyanosed or restless. For eight children, oxygen therapy was begun but supplies of oxygen ran out before clinical cyanosis or restlessness had resolved. The outcome of treatment was recorded by Dr David Smith (unpublished data), and the results are presented in Table 2. A clear trend towards a reduction in mortality with oxygen therapy is seen, but the number of children studied was small and the effect does not reach statistical significance.

Table 2

Oxygen therapy and mortality from pneumonia in children with cyanosis or restlessness, Tari, Papua New Guinea, 1976-1977 (n=32)

	No oxygen	Some oxygen	Ample oxygen
Number who survived	9	6	8
Number who died (%)	6 (40.0)	2 (25.0)	1 (11.1)

Conclusion

The evidence presented here has to be interpreted cautiously. The results of the guinea-pig study may not apply to humans, and few details were given in the report. There are two problems with the analysis of mortality from pneumonia in humans just before and just after the introduction of oxygen therapy: we do not know what differences there were in treatment other than oxygen therapy, and we cannot be certain that the two groups of patients were comparable, although it was possible to adjust for known risk factors, with the exception of age. Interpretation of the study of the effect of oxygen therapy on mortality from pneumonia in children in Papua New Guinea is hampered by the small number of patients in each group; the trend towards a lower mortality with oxygen therapy does not reach statistical significance. However, despite these shortcomings, the evidence presented here suggests that there is a substantial reduction in mortality when oxygen is given to

patients with very severe pneumonia who are hypoxaemic. It must also be borne in mind that considerable morbidity, including brain damage, may result from prolonged hypoxaemia in children who survive.

It is clear that the above-mentioned studies and analyses have serious methodological inadequacies. They represent, however, the best information which can be found in the literature. What is relevant is the consensus among scientists and clinicians about the life-saving benefits of oxygen therapy for pneumonia patients with signs of decreased oxygen saturation. On the basis of the general consensus it is therefore important to develop inexpensive and reliable ways of providing oxygen to children with very severe pneumonia or severe pneumonia with cyanosis, and to advise health workers at small hospitals in developing countries on the minimum set of signs that can be reliably used to institute oxygen therapy.

1.2 INDICATIONS FOR THE USE OF OXYGEN

There are relatively few published studies that have explored the relationship between individual clinical signs and hypoxaemia. The strength of the published evidence for each of the clinical signs recommended in 1990 by WHO[14] is summarized below.

1.2.1 Central cyanosis

There is no doubt that central cyanosis is the best clinical sign of hypoxaemia.[7,15] However, cyanosis is a late and therefore relatively insensitive sign (particularly in the presence of anaemia), it may be difficult to detect in pigmented races or in poor lighting,[16] and observers often disagree about whether cyanosis is present.[17] Of six studies that measured pO_2 (partial pressure of oxygen) or oxygen saturation in children with cyanosis caused by an acute respiratory infection (almost all the patients studied had bronchiolitis),[18-23] all but one concluded that cyanosis was the best sign of hypoxaemia. The exception[19] was a small study of 18 children with bronchiolitis which measured pO_2 in "arterialized" capillary blood; this technique is inaccurate. Two recent studies[6,24] confirmed that cyanosis is a very specific but insensitive sign of hypoxaemia, measured by pulse oximetry, in children. Both studies were, however, conducted at high altitudes, in the Peruvian Andes (3750 m)[24] and in Nairobi, Kenya, (1670 m)[6]; in these situations, where children have an increased risk of hypoxaemia and may be less able to compensate, many more children than those presenting with central cyanosis would require oxygen therapy. In the Kenyan study, Onyango et al.[6] found that a mother's report of cyanosis ("blueness") was the best

single predictor of hypoxaemia in young infants less than 3 months of age.

1.2.2 Inability to drink

None of the studies referred to above[6,18-24] provided data relating inability to drink (or to feed in young infants) when caused by an acute respiratory infection, to hypoxaemia. Mulholland et al. (unpublished) collected data about inability to feed and oxygen saturation: they found no difference between the saturation levels of children who fed poorly and children who fed well. However, the study involved children with bronchiolitis rather than pneumonia,[20] and only 2 of 48 children were unable to feed (26 of the 48 fed poorly). Two studies in Papua New Guinea[16,25] found a relationship between inability to feed and mortality from pneumonia, but pO_2 and oxygen saturation were not measured in these studies.

1.2.3 Severe chest indrawing

Hall et al.[18] found no relationship between hypoxaemia and chest indrawing in children with bronchiolitis. Mulholland et al.[20] reported that chest indrawing was present in 7 (58%) of 12 children with bronchiolitis and less than 90% saturation, compared with only 13 (30%) of 44 with saturation of 90% or more; although this difference is not statistically significant, there was a significant difference between the oxygen saturation levels of children with and without severe chest indrawing (unpublished data). The relationship between chest indrawing and saturation disappears when cyanosis is included in the model; that is, once cyanosis has been taken into account, chest indrawing does not help in the prediction of hypoxaemia. Reynolds[22] studied 10 infants with bronchiolitis. Analysis of his data shows a statistically significant relationship between hypoxaemia and chest indrawing but, as in the previous study,[20] this relationship disappears when cyanosis is included in the model. Berman et al.[26] measured oxygen saturation