Anemia, nutrition and ambulatory oxygen weaning in a cohort of oxygen-dependent premature infants.

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Abstract

Background: In Bogotá, Colombia, oxygen-dependent (OD) preterm infants are home discharged in Kangaroo Position, to a Kangaroo Mother Care program (KMCP) with ambulatory oxygen, strict follow-up and oxygen weaning protocols. Objectives: 1) to describe growth and morbimortality up to 6 months of an OD preterm infants' cohort. 2) to explore the association between oxygen requirement, perinatal history, Hb levels, transfusions, feeding patterns and growth. Methods: Prospective cohort study. Descriptive and multivariate analysis. Results: 445 patients were recruited with 33 weeks median gestational age (GA). 21% of mothers had preeclampsia, 50% infections and 77% received antenatal corticosteroids. Upon KMCP admission, median GA, chronological age and hospital stay were 36 weeks, 19 and 17 days, respectively; 55.6% of patients had neonatal sepsis and 66.6% were admitted to Neonatal Intensive Care Unit. Patients had on average 52 days with oxygen, a median of 3200g and 42 weeks GA at oxygen weaning. Median follow-up oxygen saturation was 94% with 0.016-0.5 l/min of oxygen. One-year mortality was 0.2% and attrition 20%. At 6 months, all patients had appropriate growth and 66% were breastfeeding. Multiple regression analysis showed that higher GA, Hb levels, weight gain, and exclusive breastfeeding decreased oxygen requirement whilst invasive ventilation and transfusions had the opposite effect (R2=0.48). Conclusions: In OD preterm infants, there is a close relationship between days of oxygen requirement and GA, mechanical ventilation, Hb levels at discharge, transfusions, exclusive breastfeeding and weight gain. Strict monitoring with established protocols in an ambulatory KMCP allows adequate growth and safe oxygen weaning.

Title: Anemia, nutrition and ambulatory oxygen weaning in a cohort of oxygen-dependent premature infants.

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Abbreviated title: Anemia, nutrition and ambulatory oxygen weaning in BPD.

Structured Abstract (250/250)

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Objectives: 1) to describe growth and morbimortality up to 6 months of an OD preterm infants' cohort. 2) to explore the association between oxygen requirement, perinatal history, Hb levels, transfusions, feeding patterns and growth.

Methods: Prospective cohort study. Descriptive and multivariate analysis.

Results: 445 patients were recruited with 33 weeks median gestational age (GA). 21% of mothers had preeclampsia, 50% infections and 77% received antenatal corticosteroids. Upon KMCP admission, median GA, chronological age and hospital stay were 36 weeks, 19 and 17 days, respectively; 55.6% of patients had neonatal sepsis and 66.6% were admitted to Neonatal Intensive Care Unit. Patients had on average 52 days with oxygen, a median of 3200g and 42 weeks GA at oxygen weaning. Median follow-up oxygen saturation was 94% with 0.016-0.5 l/min of oxygen. One-year mortality was 0.2% and attrition 20%. At 6 months, all patients had appropriate growth and 66% were breastfeeding. Multiple regression analysis showed that higher GA, Hb levels, weight gain, and exclusive breastfeeding decreased oxygen requirement whilst invasive ventilation and transfusions had the opposite effect (R^2=0.48).

Conclusions: In OD preterm infants, there is a close relationship between days of oxygen requirement and GA, mechanical ventilation, Hb levels at discharge, transfusions, exclusive breastfeeding and weight gain. Strict monitoring with established protocols in an ambulatory KMCP allows adequate growth and safe oxygen weaning.

Introduction

Currently in Colombia, preterm infants are discharged home once they are stable and adapted to the Kangaroo Mother Care (KMC) method, without taking into consideration their weight or gestational age (GA), and are followed up through high-risk ambulatory programs called Kangaroo Mother Care Programs (KMCP). Home discharge is carried out in Kangaroo Position (KP) (permanent skin-to-skin contact) for thermoregulation, with a feeding strategy based on exclusive breastfeeding (EBF) wherever possible, and a strict, multidisciplinary ambulatory follow-up.

KMC was created in 1978 at the Instituto Materno Infantil of Bogotá, Colombia, by Dr. Rey- Sanabria and has gone through multiple modifications to become a routine tool for the care of premature or low birth weight (LBW) infants. It is evidence-based and has been partially or fully implemented, in most neonatal units around the world[1–3].

Starting in 1999, as the survival of preterm infants improved, ambulatory management of oxygen-dependent (OD) babies began in the KMCPs of Bogotá (2600m above sea level), mostly due to bronchopulmonary dysplasia (BPD). These programs seek to fulfill three main goals: 1) to achieve and maintain a good nutritional status that promotes growth, based on EBF and eventually supplemented with preterm formula. 2) to monitor oxygen-therapy (OT), in order to achieve adequate oxygen saturation (SpO2), correcting anemia in a timely manner, if necessary, and 3) to carry out a strict multidisciplinary follow-up that reduces neurodevelopmental as well as morbimortality problems, inherent to this population.

Currently, although ambulatory OT in premature infants has increased, little is known about how it should be monitored[4]. While SpO2 limits have been extensively investigated during hospitalization with studies such as SUPPORT, BOOST and COT[5], there is little evidence on monitoring the minimum acceptable limits of SpO2 after hospital discharge, and optimal titration of OT at home in children with BPD[4]. Furthermore,

there is not enough information on the ideal hemoglobin (Hb) value to guarantee adequate oxygenation and growth in children with BPD who are followed-up in the KMCPs of Bogotá.

With regards to nutrition, it is known that malnutrition in children with BPD is an early phenomenon and continues throughout childhood. Preterm OD patients have a lower caloric reserve in the neonatal period contrasted to their high energy requirements, due to increased breathing work, as well as a difficulty in oral nutrition[6–8]. It is important to learn about the best nutritional strategy that promotes adequate growth.

The objectives of this study are 1) to describe the monitoring of SpO2, feeding pattern, somatic growth and morbimortality during the first 6 months, of a cohort of OD infants followed-up in 2 centers of excellence in KMC in Bogotá, Colombia. 2) to establish the relationship between these variables, Hb level upon KMCP admission, and time required to reach oxygen weaning.

Materials and Methods

445 patients were recruited from a prospective cohort of 452 preterm OD neonates, cared for in two ambulatory KMCPs in Bogotá, Colombia, between July 25, 2017 and May 7, 2018, and followed during the first 6 months of corrected age. Patients with a contraindication to breastfeeding due to HIV and those with major congenital malformations, genetic problems, intestinal malabsorption and hemolytic diseases were excluded.

Procedures

Once eligible patients were identified at the KMCPs admission, informed consent was requested from parents. Babies' perinatal data and levels of the last Hb measured within last 7 days were obtained from the hospitalization clinical history and recorded. In case of no Hb recent measurement, a capillary blood sample was taken in the KMCP with Hemocue®.

Children were controlled daily in the first days of follow-up, monitoring their weight gain until reaching 15-20 g/kg/day. Afterwards, weekly controls of anthropometric measurements, clinical evaluation and dynamic oximetry were carried out until oxygen weaning (Figure 1). This constitutes the ambulatory equivalent of minimal inpatient care. The objective of OT was to achieve an SpO2 between 90-94% with an adequate heart rate. At the time of oxygen weaning, the nurse would take a capillary Hb sample and record SpO2.

Upon admission to KMCPs, parents were provided with comprehensive education on OT at home and received an explanatory brochure. Only infants with OT $<$ 1 l/min were admitted, because parents are living in average at one hour of transportation and oxygen tank capacity is limited.

Medical care of these patients included routine prophylactic treatments such as oral iron, vitamins and prophylaxis for apnea of prematurity with xanthine. The follow-up program included detection of ophthalmological, auditory, cardiovascular and neurological conditions, including echocardiography and brain ultrasound.

During follow-up, anthropometric data were carefully collected and adjusted to the Fenton reference charts[9], until child reached term (40 weeks GA) and then, to the WHO corrected age charts[10].

Babies remained in a permanent skin-to-skin contact, 24 hours a day, in a strict vertical position between mother's breasts and clothing, supported by an elastic wrap. The baby could be fed at any time, staying in KP until the child showed clear signs of intolerance (profuse sweating or discomfort with the position). Nutrition was based on EBF to the extent possible. If the goal of obtaining a weight gain at least equal to intrauterine was not achieved despite receiving intensive breastfeeding counseling and having ruled out pathological conditions such as anemia, infection or hypothermia related to poor adherence to KP, supplementation with preterm formula (24 Kcal/30cc) with a dropper or spoon was initiated. The amount was calculated based on 30% of the recommended daily caloric intake, and after at least one week of adequate growth, a progressive reduction of the supplement was attempted, so as to reach 40 weeks GA with EBF.

At each follow-up, rehospitalizations, feeding patterns and administration of iron, vitamins or erythropoietin (EPO) with exact dose received were recorded, as well as a physical examination by the pediatrician, and

neurosensory and psychomotor development evaluations using standardized formats. At the end of these multidisciplinary evaluations, a certified nurse recorded the dynamic oximetry (rest, sleep, suction), together with the required oxygen flow in liters per minute.

After oxygen weaning, monthly controls were carried out during the first 6 months of life with nutritional and multidisciplinary assessment.

Ethical Considerations

This study was adjusted to comply with the national and international standards for research in human beings, in accordance with the provisions of the Declaration of Helsinki and the resolution of good clinical practices in the country[11,12]. Informed consent was requested from parents. The study had approval by the scientific and ethics committees of the institutions.

Analysis

The STATA14 program was used for statistical analysis. To characterize the population, descriptive analysis with means and standard deviations (SD) or medians and range, according to the variable distribution, were done; subsequently, a multiple linear regression analysis was performed to establish variables that could be associated with OT time.

Results

452 patients were eligible, of which parental consent was not given in 7 cases. 445 patients were recruited. With regards to the socio-demographic background, most of the parents had jobs, were stable couples, and had a secondary education, with a monthly income corresponding to the Colombian minimum wage (229 USD). Between mothers, more than 50% had a history of urinary tract or gynecological infection, 21% had toxemia and 77% received prenatal corticosteroids (Table 1).

Patients' average GA at birth was 33 weeks, 58.4% were male and 25% had Intrauterine Growth Restriction (IUGR). The average GA at recruitment was 36.5 weeks, with a median of 19 days. The median total hospital and Neonatal Intensive Care Unit (NICU) stay were 17 days and 3 days, respectively; 49% of patients required invasive ventilation (median 2 days) and 16% CPAP only (median 2 days); 56% had early or late sepsis (Table 2).

Median oxygen requirement was 51 days. Mean SpO2 during follow-up was 94% (SD 2.1). Oxygen volume upon admission had a median of 0.06 (1/16) l/min with a range between 0.02-0.5 (1/64-1/2) l/min. Median weight at oxygen weaning was 3200g with a mean GA of 42 weeks (Table 3). At the time of weaning, 99.8% of patients were [?]36 weeks GA, 66.3% [?]40 weeks, 94.3% had $>$ 28 days with oxygen, and 84.9% were [?]36 weeks and had $>$28 days with oxygen.

Concerning hematological parameters, 20% of patients had been transfused at least once prior to entering the study (1-8 transfusions). Between KMCP admission and 40 weeks, only 4.5% required additional transfusions, being minimal after oxygen weaning (0.5%). During follow-up, a very low proportion of patients received EPO (0.5-1%).

Iron replacement was 51.7% at 40 weeks, 82.8% at 3 months, and 80.6% at 6 months. The mean Hb value upon entering the study was 14.1 g/dl (SD 3.2) and at weaning 11.4 g/dl (SD 1.9).

Regarding growth and feeding pattern, Table 3 shows how at 6 months, all patients had adequate anthropometric measurements and 66% of patients received some breast milk at 6 months, while only 34% received exclusive formula.

With respect to neuromotor examination at follow-up (INFANIB), 19.5% and 20.8% reported a non-normal examination at 3 months and at 6 months, respectively; 20.2% had a Griffiths scale score$<$85 at 6 months. Additionally, refractive errors were found in 82% of the patients, (68% with hypermetropic astigmatism), Retinopathy of Prematurity (ROP) in 7.9% (1.2% required surgery) and hearing problems in 1.2%.

Rehospitalizations between KMCP admission and 40 weeks occurred in 9.6% of the cohort (17.4% of them were for transfusions), 4.8% of patients were rehospitalized between 40 weeks and 3 months and after 3 months there were no rehospitalizations.

At 40 weeks, 442 patients were followed up (99.3%), at 3 months 395 (88.8%) and at 6 months 356 (80%), with an attrition up to 20%, due mostly to problems with the health insurer. Only one patient out of the total cohort died (0.2%).

Multiple linear regression analysis showed that, adjusting for control variables, for each week of gestational age, 2.9 fewer days of supplemental oxygen are required; for each additional gram of Hb on admission at KMCP, 1.8 fewer days of oxygen are needed; for each day of invasive ventilation, 1.4 more days of oxygen are required; for each g/k/d of weight gain until oxygen weaning, 1.6 less days of oxygen are required; for each transfusion received, 4.8 more days of oxygen are required. Moreover, with EBF, the oxygen requirement tends to decrease by up to 10 days (Table 4).

Discussion

On account of the availability of the ambulatory KMCP in Bogota, Colombia (2600m), the OT at home is frequent due to two main reasons: 1. The early discharge of these OD infants has made it possible to reduce hospital stay with a low mortality during the first year of follow-up[13] and, 2. The cost of one month of ambulatory care in babies who receive oxygen is as low as a single day of hospitalization in the neonatal unit, reducing the burden on the health system, as well as on the families.

The Kangaroo Foundation developed a care protocol for these OD children which has made it possible to have follow-up data on 10,452 children between 1999 and 2019. In the 2003-2007 period, more than 40% of children cared for were OD, decreasing progressively to 17% between 2018 and 2019.

The history of the OD preterm cohort in this study is similar to that found in the literature, with predominance of male patients and a history of maternal infection in more than 50% of the cases, followed by toxemia (21%) and premature rupture of membranes (6.7%)[14–17].

Regarding postnatal history, almost half of our patients received invasive ventilation (49%), although with a low median duration (2 days). This highlights the need to avoid this type of ventilatory support as much as possible, favoring strategies such as CPAP and/or nasal ventilation from the delivery room[8,18,19].

Additionally, in this cohort, 56% of patients had a history of early or late sepsis, that can be acquired from the prenatal stage, as mentioned above, or during hospitalization, and is associated with BPD[20].

It is noteworthy that all patients in this study met the diagnostic criteria for BPD defined as the requirement of respiratory support at 36 weeks of GA, which better predicts morbimortality at 18-26 months of corrected age in this population[21]. They required OT for a median of 51 days and at the time of weaning, they had a mean corrected GA of 42 weeks (SD 5.3).

The two ambulatory KMCPs where the study was carried out, have performed strict and multidisciplinary follow-up of OD children in KMC, with the possibility of ambulatory OT for the past 21 years, following technical guidelines updated in 2017 by the Ministry of Health of the country[22]. There is evidence in the literature on the OT at home for OD children, a practice still scarce worldwide, but that has increased in recent years[23]. With this method, prolonged separation from parents is avoided, improving the probability of exclusive breastfeeding and reducing morbimortality from infections due to prolonged hospitalizations, all widely cited benefits of the KMC method[13].

All of our OD patients had adequate anthropometric measurements at 6 months, and 66% of the cohort received some breast milk. Moreover, when assessing neurodevelopment, approximately 21% had a non-normal neuromotor examination (INFANIB), which coincides with the frequency of patients with a Griffiths scale $<$85 at 6 months (20.2%), a relatively low percentage. By having a strict follow-up by a multidisciplinary

team, we allow for the timely treatment of neurodevelopment and neurosensory problems, reducing alterations that occur long term[17]. Another outstanding fact is the low frequency of ROP in our cohort; 6.7% (28/421) of patients had autoregressive ROP and only 1.2% (5/421) required surgery. Furthermore, only 1.2% of the patients assessed presented hearing problems (5/409).

Rehospitalizations were low: 9.6% between KMCP admission and 40 weeks, and 4.8% between 40 weeks and 3 months, as opposed to 40-50% of rehospitalizations reported in other studies[8,17]. There was no record of hospitalizations occurring between 3 and 6 months and the mortality was of only 1 patient (0.2%).

It is important to take into account that we had 20% attrition, mostly due to problems with the health insurers. All patients who did not continue the program were contacted by the KMCP social worker to verify their health status and the reason for leaving the program.

As to the monitoring of home OT, the KMCP has an ambulatory monitoring protocol that guarantees maintaining an adequate SpO2 until weaning. In order to do this, a progressive, stress-free and dynamic weaning is carried out with the baby asleep, awake and during feeding, with a gradual decrease in oxygen flow, and a monitoring of both weight gain and other causes of weaning failure such as anemia or infections. The average saturation at follow-up was 94% (SD 2.1). There are other oxygen weaning techniques reported, such as that described by Hussain et al. in Connecticut, USA, where stress oximetry is performed while monitoring heart rate and dynamic oximetry with total suspension of supplemental oxygen. The authors report that the test has a specificity of 97.4% and a predictive positive value of 99.6% in determining oxygen weaning success[24]. We prefer a staggered weaning, to reduce stress and safety issues caused by total oxygen suspension. Various guidelines from USA, England and Australia have been published on ambulatory management of OD preterm infants, and how to reach a low-risk weaning in these past 10 years[25–27], all of them are in agreement with our guidelines implemented since 1999.

Multivariate analysis showed that the risk factors for a longer OT are low GA at birth, invasive ventilation, low Hb levels at KMCP admission, number of transfusions received, and the protective factors, weight gain and exclusive breastfeeding up to weaning. Concerning risk factors, the relation between prematurity, invasive ventilation and BPD is widely known[17,20,28,29]. In recent years invasive ventilation has been reduced; yet, even a relatively low median duration of ventilation in our cohort, two days, was associated with a higher risk of BPD.

Another interesting aspect to keep in mind is the link between anemia, transfusions and a higher frequency of BPD. In our study, for each additional gram of Hb upon KMCP admission, oxygen dependency would decrease by 1.8 days and for each transfusion received, 4.8 more days of oxygen would be required. In this regard, Hellstrom et al., in a retrospective cohort study with records of 149 extremely premature babies born in Sweden between 2013 and 2018, found that blood sampling produced a 58% depletion of blood volume between days 1-14, which was correlated with the number of adult blood transfusions (r=0.87); blood loss from sampling during the first 7 days of life was related to higher BPD (adjusted OR 2.4; 95% CI 1.1-5.4)[30]. Similarly, Duan et al. in a prospective cohort with 243 children <32 weeks GA in China, found early anemia significantly associated with the development of BPD (adjusted OR 4.89; 95% CI 1.57 -15.26)[31]. This leads us to think that laboratory methods that minimize blood sampling during hospitalization in the NICU should be implemented, hopefully using the micro method technique, which would allow for better Hb levels at discharge and minimize transfusions. Subsequently, in ambulatory management, transfusions should depend on established protocols where the oxygen requirement, weight gain and hemodynamic status of the patient are assessed, rather than an isolated Hb level.

In our cohort, adequate weight gain in g/k/d and EBF were associated with a decrease in OT days, findings supported by studies such as those carried out by Wemhoner et al., and Ehrenkranz et al[32,33], and that emphasize the fundamental role of nutrition in reducing the risk of BPD. There are also other studies that emphasize the benefits of EBM, preferably from the mother, or if this is not possible, from a donor, to reduce BPD. In a recent meta-analysis by Villamor et al. in 2016, 31 randomized controlled trials (RCTs) and observational studies were analyzed, and the results showed that the administration of donor milk

conferred protection against BPD in very low birth weight preterm infants[34]. In 2019 another systematic review published by this author, showed that EBF was associated with a significant reduction in the risk of BPD (RR 0.74; 95% CI 0.57-0.96; 5 studies)[35]; contrastingly, when comparing children who received mixed feeding and those who received exclusive formula, there was no significant difference in the risk of BPD (RR 1.0; 95% CI 0.78-1.27; 6 studies). The authors hypothesize that EBF can reduce the incidence of BPD thanks to its bioactive and nutritional components that counteract oxidative stress, inflammation and nutritional failures involved in the pathogenesis of BPD. On the other hand, EBF could also reduce the risk of BPD by reducing the incidence of Necrotizing Enterocolitis and late sepsis.

Part of the kangaroo care is EBF to the extent possible, supplemented with liquid formula in case of not achieving the weight gain goals for GA. Supplement is never administered with a bottle or nipple, but with a syringe, and the calculated amount is distributed over the intakes that the child receives in 24 hours. The liquid preterm formula avoids manipulations. This technique allows for adequate growth by supplementing without jeopardizing breastfeeding.

It is noteworthy that supplemental iron was administered between hospital discharge and 40 weeks in only approximately 52% of our patients, and in 81% at 6 months. This may be due in part to the fact that iron is temporarily suspended when patients have had previous transfusions; other causes are that the children had not yet reached one month, when KMCP starts iron by protocol, or received milk formula with iron.

The results obtained in this cohort of OD preterm infants managed in ambulatory KMCPs show that it is possible to reduce mother-child separation and hospital stay and to perform strict ambulatory and multidisciplinary follow-up. The goals of ambulatory OT would be a safe oxygen administration and progressive weaning protocol with intense parents education, SpO2 monitoring, supporting EBF to the extent possible, supplementing with formula in case of not having an adequate weight gain, monitoring Hb levels hopefully with a micro-method, having clear transfusion indication protocols and achieving a multidisciplinary follow-up to minimize neurodevelopmental problems and morbimortality.

Currently, there are 53 KMCPs in Colombia to care for premature or LBW children. This ambulatory management of OD children allows to reduce health system costs, which are a burden for public health in middle-income countries such as ours. With regards to the latter, there is evidence which showed how the median hospitalization costs per child with BPD was $377,871 USD compared to $175,836 USD per child without BPD (adjusted cost ratio 1.54; 95% CI 1.49-1.59)[36].

One weakness of this study is its observational design, without a comparison to another kind of ambulatory follow-up, which could support the differences in the outcomes obtained in the KMCPs. However, measures of effectiveness can be established indirectly, by comparing results with what is reported in the literature.

On the other hand, selection biases due to mortality prior to hospital discharge, that could be suspected with average GA at birth of 33 weeks, and moderate follow-up attrition of 20%, indicate that the data obtained should be interpreted with caution.

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List of abbreviations

BPD: Bronchopulmonary Dysplasia.

EBF: Exclusive Breastfeeding.

GA: Gestational Age.

Hb: Hemoglobin.

IUGR: Intrauterine Growth Restriction.

KMC: Kangaroo Mother Care.

KMCP: Kangaroo Mother Care Program.

KP: Kangaroo Position.

LBW: Low Birth Weight.

NICU: Neonatal Intensive Care Unit.

OD: Oxygen Dependent.

OT: Oxygen Therapy.

RCT: Randomized Controlled Trial.

ROP: Retinopathy of Prematurity

SpO2: Oxygen saturation.

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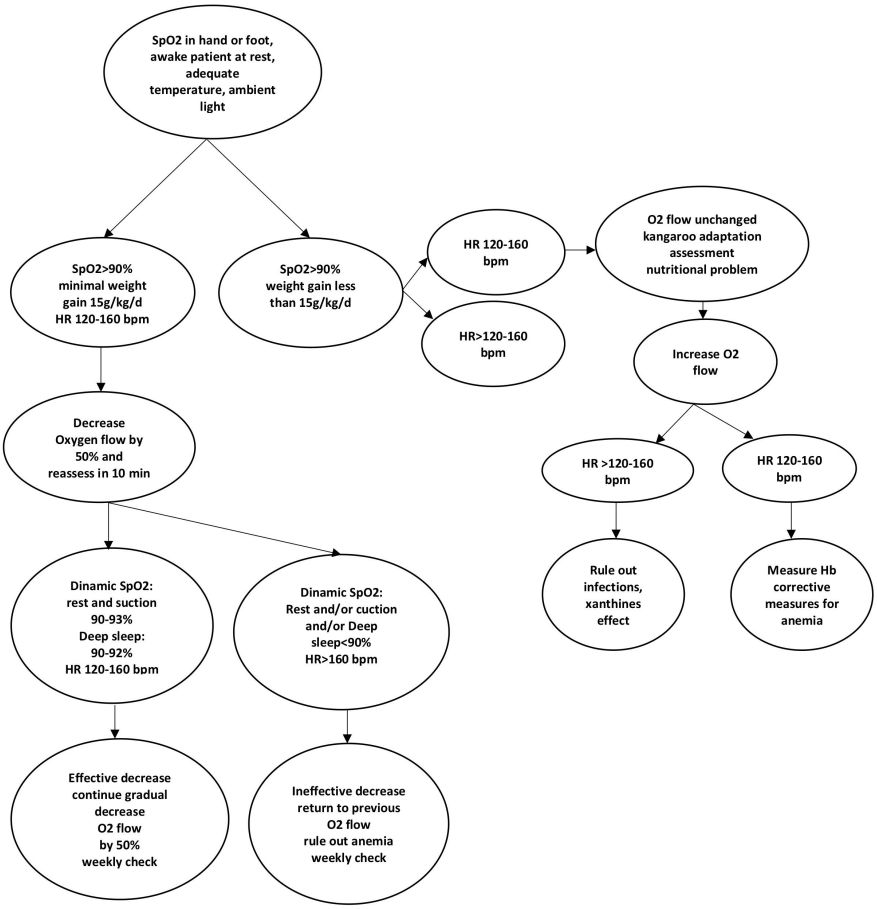

Oxygen weaning flow chart at KMCP