Hypoxaemia in children: “abnormal” values may be misleading

Duke et al are to be commended for their interesting report aimed to determine normal oxygen saturation values in healthy infants and children and to assess the performance of clinical signs for predicting hypoxaemia in sick neonates and children with and without acute lower respiratory infections (ALRI).1 Acute lower respiratory infections (ALRI) account for a substantial burden of disease in children and adults, pneumonia being the leading cause of deaths in children under five, particularly in developing countries. Tachypnoea and chest retraction have been shown to be the most useful clinical signs for determining which cut off values for supplementary oxygen are related to better outcomes in sick children living at high altitude. Moreover, our study at 4100 m revealed that SpO2 values may be different according to different ethnic group and history of exposure to high altitude. Higher SpO2 values in Quechua children suggest a better degree of adaptation to high altitude in native populations with a longer time to exposure to high altitude. This latter finding has obvious practical implications, as high altitude native children, with higher baseline oxygen saturation levels than newcomers or resident non-native children, need oxygen at higher cut off SpO2 values when they are sick.

Singhi is justifiably concerned on the cost of giving oxygen to children who may not need it. Oxygen may be unacceptably expensive for health services in developing countries, particularly at primary level, where most sick children seek health care. However, hypoxaemia may be a serious, life threatening problem in sick children, particularly at high altitude, and thus we recommend that the study of Duke et al for different altitudes, in healthy and sick infants and children, to determine normal values of SpO2, and to identify highly predictive clinical signs for hypoxaemia. The potential aggravating role of co-existing prevalent childhood diseases other than ALRI, namely diarrhoea, malnutrition, malaria, and HIV/AIDS, is also an area that warrants more attention. This data will allow providing both good quality and cost effective health care to sick children with and without ALRI. Millions of children and adults live at high altitude. Developing a medicine based on scientific evidence that can be applicable to this setting is a major public health challenge for all of us working in those parts of the world.

L Huicho
Department of Paediatrics, Universidad Nacional Mayor de San Marcos and Instituto de Salud del Niño, Lima, Peru; huicho@viabcp.com

References

Response to Duke et al

We read with interest the article by Duke et al regarding hypoxaemia in acute respiratory and non-respiratory illnesses in infants and children in developing countries published recently in Archives.1 The authors have rightly pointed out the limited availability of published data on the incidence, significance or clinical signs predicting hypoxaemia in infants less than three months of age. With similar concerns we had conducted a study in infants less than two months, a part of which was published in the Archives.2 We found that tachypnoea, defined as RR>60/min, predicted hypoxia with 80% sensitivity and 68% specificity.3 In that study we also examined functional and behavioural responses as predictors of hypoxemia (table 1). Five of these six variables had a very good sensitivity to detect hypoxaemia.

A very high prevalence of hypoxaemia in the population studied by Duke et al is rather intriguing. Out of total 257 sick neonates and children 52%, were hypoxic. Among children with acute lower respiratory infection (ALRI) 73% and those with non-ALRI 32% were hypoxic. In an ongoing study we have measured oxygen saturation (by Nellcor® oximeter) in a prospective cohort of 683 children 2–59 months brought to paediatric emergency department (ED) with any respiratory symptom. Oxygen saturation using a fingertip sensor in these children at the time of arrival to ED ranged from 78–99%. The overall prevalence of hypoxaemia defined as SpO2 <90% was 4.5% (table 2).

An additional 5.1% children had borderline hypoxaemia, i.e. a SpO2 value of 90%. This is similar to a prevalence of 5.9% hypoxaemia defined as SpO2 <90% in Gambian children, 2–33 months of age, reported by Usen et al.4 Even in our previous study of 200 infants less than two months, only 38.5% of the sick infants attending ED were hypoxic.5 A systematic review of studies on prevalence and predictors of hypoxemia in children by Lozano et al found that the prevalence of hypoxia was dependent upon a number of factors including the setting of the study. The prevalence ranged from 6–9% in outdoor setting to 31–43% in emergency departments to a maximum of 47% in hospitalised children.

Yet, in our study, which represents the situation at high sea level (Chandragiri-Topographically) and the setting of an emergency department, the prevalence of hypoxaemia is much lower than that reported at heights. In light of our data and published literature we believe that either the definition of hypoxia used by Duke et al is too liberal or the children with respiratory symptoms living at high altitude compensate more frequently to develop hypoxia. More information is needed in this respect to formulate...
referral and selection biases are likely. Hypoxaemia will be more common in emergency departments of referral hospitals than at primary care settings, and more common still among children requiring hospital admission. The prevalence of hypoxaemia in the hospitals studied depended on thresholds for admission and case-mix. The 491 children in our study constituted about 20% of all the children admitted during the course of the study. A specialist paediatrician, whose practice was to oversee the care of sicker children, enrolled many of the patients, so this was a further source of selection bias. The much lower overall prevalence of hypoxaemia seen by Drs Singhi and Bharti in their emergency department population is therefore understandable. Of note the prevalence of hypoxaemia among sick neonates admitted to Goroka Hospital (43%) was similar to the prevalence among young infants (<2 months of age) attending the emergency department in Chandiagh (38.5%).

It is interesting to consider the effects of altitude on hypoxaemia in children with pneumonia. Some populations living at higher altitudes have a greater tendency to pulmonary hypertension; this susceptibility may be genetically determined and supports Dr Huicho's statement that ethnic differences in SpO2 at the same altitude are important. At altitude in response to hypoxaemia, pulmonary blood flow is shunted to the lung apices associated with an exaggerated vasoconstriction in the basilar lung. This may have an adverse effect on ventilation perfusion match in the supine position. In addition cardiac expression of natriuretic peptides increases in parallel with pulmonary artery pressure. These and other pathophysiological changes may account for the greater severity and prolonged duration of hypoxaemia seen at higher altitudes. It is thus essential to evaluate the simple intervention of nursing children with pneumonia and hypoxaemia at high altitude in an inclined head-up position, rather than supine, to determine if this reduces the severity of hypoxaemia. There is a need for more evidence about the prevalence of hypoxaemia at sea level and different altitudes; which children benefit from oxygen; for how long to deliver oxygen in remote settings. Controlled trials of oxygen in mild hypoxaemia may not be justified for ethical reasons, but other evidence will be informative. Before the introduction of pulse oximetry in Goroka we used a supine, to determine if this reduces the severity of hypoxaemia. We found that even after excluding children with moderate or severe hypoxaemia at baseline, who were more likely to benefit from additional oxygen, the group receiving supplementary oxygen had a significantly higher oxygen saturation after 1 hour of resuscitation compared to the group receiving no oxygen.

In children with severe hypoxaemia at baseline, who were more likely to benefit from oxygen, the group receiving supplementary oxygen had a significantly higher oxygen saturation after 1 hour of resuscitation compared to the group receiving no oxygen. It is noteworthy that the children who received oxygen had a significantly higher survival rate compared to those who did not receive oxygen. This finding is consistent with previous studies that have shown the benefit of oxygen therapy in children with severe hypoxaemia. It is important to note that oxygen therapy should be started early in the treatment of children with severe hypoxaemia, as delayed oxygen therapy has been associated with poorer outcomes. The use of pulse oximetry in remote settings is crucial to identify children who require oxygen therapy, and to determine the duration and intensity of treatment. Further research is needed to determine the optimal use of oxygen therapy in children with severe hypoxaemia in remote settings.
Pharmacogenomic can give children safer medicines

I read with great interest Clarkson and Choonara’s paper on the fatal suspected adverse drug reactions (ADRs) in the UK and I strongly agree with their conclusions, namely that an evidence-based approach to drug treatment is needed to minimise fatalities due to drug toxicity in children. However, recent evidence also suggests that we are now ready for a gene-based approach to drug treatment allowing to further minimise the occurrence and the severity of adverse drug reactions.

In a recently published systematic review, the authors found that more than half of the drugs cited in ADR studies are metabolised by at least one enzyme with a variant allele known to cause poor metabolism, suggesting that genetic variability in drug metabolising enzymes is likely to be an important contributor to the incidence and severity of ADRs. In

Ketoad levels may alter osmoticity in diabetic ketoacidosis and precipitate cerebral edema

In a study of DKA we found that the mean osmolality at admission was 318 (SD 12.9; range 291–337). Further, we also found that the calculated osmolality (calculated osmolality = 1.86(Na+ + K+ + Urea + Glucose) was only 289 (range 282–304). This suggests hypertonicity is common in DKA and that calculated osmolality underestimates true osmolality. The mean osmolar gap was 29 (range 14–48). The osmolar gap between true and the calculated osmolality, is made up of unmeasured substances like ketoads. The osmolality of ketoads have been ignored in the past, as they are considered to be physiologically inactive and not contributing to osmoticity. A study done by us (submitted for publication) has demonstrated that ketoads (acetoads) are osmotically active. (Aceto)acetad can influence fluid shifts across a semipermeable membranes. This is in contrast to urea, which is not osmotically active. Osmolal, osmolar gap, and ketoad bodies are not measured routinely during the management of DKA. A rapid fall in ketoad body levels can result in a fall in osmolality and osmoticity of the serum and lead to cerebral edema. In a recent paper looking at the risk factors for development of cerebral edema in DKA the authors noted that since none of the “relevant variables” (serum glucose concentration at presentation, osmolality, osmoticad concentration during therapy, rate of fluid and sodium administration) were associated with the risk of cerebral edema, their data did not support the theory that a rapid decrease in extra cellular osmolality did not occur. In summary we suggest that changes in ketoad body levels be considered, as a factor that can be partially responsible for the cerebral edema often seen during treatment of DKA. We will be glad to share our data at any summit of experts convened to study the enigma of cerebral edema in DKA.

References

The Lazarus case, Life and Death Issues in Neonatal Intensive Care


When things go badly wrong in the perinatal period there has developed a culture in many “advanced societies” that demands a search for someone to blame. This search for guilt, accountability, punishment, and recompense often results in litigation.

In this thought provoking book John D Lantos describes such lawsuits as “our public morality plays” and uses his experience as a neonatologist, expert witness, and ethicist to create, debate, and crystallise relevant issues of ethics related to the neonatal intensive care of a fictional preterm infant who should have died but did not—The Lazarus Case.

A fictitious neonatologist, Dr Miller, decides to stop resuscitation of a very preterm infant who seems past reasonable care. The baby who might have died survived with severe neurological problems and the parents sue Dr Miller, alleging that stopping treatment was negligent. John Lantos places himself in the role of expert witness and uses questions put by the plaintiff’s lawyers to explore the moral, ethical, legal, and social factors and to illustrate the ambiguities, misunderstandings, responsibilities, and evasions highlighted by the perinatal care of a 25 week gestation infant.

A key question put to Dr Lantos by one lawyer was “Can studying philosophy tell you whether what a doctor does in a particular case is right or wrong?” Probably not is the final conclusion reached by Dr Lantos, but it was just as unlikely that definitive guidance would come from sociology, religious doctrine, strict medical protocols, or any other single source.

There have been many attempts over the past half century to face and explain the moral dilemmas associated with our attempts to save the lives, prevent damage, and encourage optimal development of critically ill preterm infants. The Lazarus Case reviews in a most effective, compelling, erudite, and compassionate way the enormous complexity of these issues. It is highly recommended to all who are concerned with the care of preterm infants and their families and is essential reading for those required to provide medico-legal advice on life and death issues in neonatal intensive care.

Forrester Cockburn

Problems in Paediatric Drug Therapy, 4th edn


There is increasing interest in both the clinical and scientific aspects of drug therapy in paediatric patients. This text book by the American Pharmaceutical Association is aimed at the North American market.

It is a reference book aimed at paediatric pharmacists. It covers a wide range of the problems associated with paediatric drug therapy, with chapters on the administration of drugs, fetal toxicity, drugs in breast milk, and both poisoning and drug toxicity, and also specific clinical areas, for example chemotherapy. There did not appear to be any order in the chapters. It would seem more appropriate to put chapter 13 on neonatal doses after chapter 3 on drugs in breast milk than after a chapter on chemotherapy.

There are several chapters with information on the dosage of medicines and it is of interest that these are divided into three separate chapters, one for neonates, one for infants/children and adolescents and one specifically for intravenous drugs. Despite having a chapter specifically on intravenous drugs, the chapters on drug dosing on both neonates and infants/children and adolescents contains details on the doses required for intravenous administration. This makes the book far more difficult to use. The dosage guidance is far less user friendly than publications such as Medicines for Children or the Neonatal Formulary.

It is for this reason I would not therefore recommend Paediatric Pharmacy departments to buy a copy of the book.

I Choonara
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